

Progression-free survival after next line of treatment (PFS2) and subsequent therapies (subs tx) in the ASCENT-04 study of participants (pts) with previously untreated PD-L1+ metastatic triple-negative breast cancer (mTNBC) treated with sacituzumab govitecan (SG) plus pembrolizumab (pembro) vs chemotherapy (chemo) plus pembro.

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Progression-free survival after next line of treatment (PFS2) and subsequent therapies (subs tx) in the ASCENT-03 study of participants (pts) with previously untreated metastatic triple-negative breast cancer (mTNBC) treated with sacituzumab govitecan (SG) vs chemotherapy (chemo).

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Background: In ASCENT-03, first-line (1L) SG led to a clinically meaningful improvement in PFS vs chemo (median, 9.7 vs 6.9 months [mo]; hazard ratio [HR], 0.62; 95% CI, 0.50–0.77; $P < .0001$) in previously untreated pts with mTNBC who were not candidates for PD-(L)1 inhibitors. Since overall survival data are immature, PFS2 can be used to assess long-term benefit as it accounts for the impact of initial and subs tx, including trial crossovers. We report PFS2 and subs tx from ASCENT-03. **Methods:** Pts ($N = 558$) were randomized 1:1 to SG (10 mg/kg IV, days 1 & 8 in 21-day cycles) or chemo (paclitaxel, nab-paclitaxel, or gemcitabine + carboplatin); primary end point was PFS by blinded independent central review (BICR). Eligible pts in the chemo group could receive 2L SG provided on study via crossover following BICR-verified progressive disease or in any subs line commercially; other subs txs per local practice were also permitted. PFS2 was defined as the time from randomization to the first documented progression on next-line therapy per investigator assessment or death due to any cause, whichever occurred first. **Results:** Median follow-up for OS was 13.2 mo; 75 (27%) pts remained on study treatment in the SG group ($n = 279$) and 39 (14%) in the chemo group ($n = 279$). Of the 204 pts in the SG group who discontinued tx, 126 received any subs tx, the most frequent of which were platinum chemo (40%), taxanes (29%), and gemcitabine (19%). Of 240 pts in the chemo group who discontinued tx, 179 received any subs tx, the most frequent of which were SG (82%), capecitabine (16%), platinum chemo (9%), and trastuzumab deruxtecan (9%). Median (95% CI) PFS2 was 18.2 mo (15.9–not reached [NR]) in the SG group and 14.0 mo (12.5–17.4) in the chemo group (stratified HR, 0.70; 95% CI, 0.55–0.90). PFS2 rates are in the Table. Median (95% CI) time to first subs tx was 11.2 mo (10.0–13.0) and 7.9 mo (7.2–9.0) for SG and chemo, respectively; median (95% CI) time to second subs tx was 17.3 mo (15.2–NR) and 16.6 mo (13.6–18.5). **Conclusions:** PFS2 was improved in the SG group compared with the chemo group despite crossover tx, with most pts who initiated subs tx in the chemo group receiving SG. The benefit of first-line SG is clinically relevant and sustained until the next line of therapy, which further supports SG as a potential new standard of care in pts with previously untreated mTNBC who are not candidates for PD-(L)1 inhibitors. Clinical trial information: NCT05382299. Research Sponsor: Gilead Sciences, Inc.

	SG	Chemo
Pts with PFS2 events, n/N (%)	114/279 (41)	143/279 (51)
Median PFS2 (95% CI), mo	18.2 (15.9–NR)	14.0 (12.5–17.4)
Stratified HR ^a (95% CI)	0.70 (0.55–0.90)	
Stratified log-rank nominal P-value ^a	.0051	
PFS2 rate (95% CI), %		
12 mo	71 (65–76)	59 (53–65)
18 mo	52 (45–59)	41 (33–48)

^aSG vs chemo.

First-line datopotamab deruxtecan (Dato-DXd) vs chemotherapy in patients with locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC) for whom immunotherapy was not an option: Additional efficacy endpoints from the TROPION-Breast02 study.

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Background: In the primary analysis of the phase 3 TROPION-Breast02 study (NCT05374512), first-line Dato-DXd demonstrated statistically significant and clinically meaningful improvements in overall survival (OS; hazard ratio [HR]: 0.79 [95% confidence interval [CI]: 0.64–0.98]; $p = 0.0291$) and progression-free survival (PFS; HR: 0.57 [95% CI: 0.47–0.69]; $p < 0.0001$) compared with investigator's choice of chemotherapy (ICC) in patients with locally recurrent inoperable or metastatic TNBC for whom immunotherapy was not an option. Both median OS and PFS by blinded independent central review (BICR) were ≥ 5 months longer with Dato-DXd compared with ICC. Moreover, with Dato-DXd vs ICC, the confirmed objective response rate was more than double and median duration of response was > 5 months longer. The Dato-DXd safety profile was manageable and generally consistent with the known profile. Here we report additional efficacy endpoints. **Methods:** Adult patients with previously untreated locally recurrent inoperable or metastatic TNBC, for whom immunotherapy was not an option, were randomized 1:1 to Dato-DXd (6 mg/kg IV every 3 weeks) or ICC ([nab]-paclitaxel/capecitabine/eribulin mesylate/carboplatin). Dual primary endpoints were OS and PFS by BICR per RECIST 1.1; secondary endpoints included time to second progression or death (PFS2), time to first subsequent therapy or death (TFST), and time to second subsequent therapy or death (TSST). The planned sample size was approximately 600 randomized patients. A stratified log-rank test was used to analyze PFS2, TFST, and TSST. HRs and 95% CIs were estimated from a stratified Cox proportional hazards model. **Results:** A total of 644 patients were randomized (Dato-DXd: 323; ICC: 321). At data cutoff (25 Aug 2025), median study follow-up was 27.5 months and 53 (8.4%) patients remained on treatment (Dato-DXd: 45 [14.1%]; ICC: 8 [2.6%]). PFS2 was longer with Dato-DXd vs ICC: median 15.6 vs 11.8 months (HR: 0.61 [95% CI: 0.50–0.74]). Both TFST and TSST were prolonged in the Dato-DXd vs ICC arm: median TFST was 10.9 vs 5.6 months with Dato-DXd vs ICC (HR: 0.49 [95% CI: 0.41–0.59]) and median TSST was 16.7 vs 12.6 months (HR: 0.67 [95% CI: 0.55–0.81]). **Conclusions:** In TROPION-Breast02, improvements in the secondary endpoints of PFS2, TFST, and TSST were observed for patients receiving Dato-DXd compared with ICC, consistent with the dual primary endpoints of OS and PFS by BICR. Alongside the manageable safety profile for Dato-DXd, these data further support Dato-DXd as the new first-line standard of care in this setting. Clinical trial information: NCT05374512. Research Sponsor: This trial is sponsored by AstraZeneca. In July 2020, Daiichi Sankyo entered into a global development and commercialisation collaboration with AstraZeneca for datopotamab deruxtecan (Dato-DXd).

Izalontamab brengitecan (iza-bren) versus physician's choice of chemotherapy in patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC): A randomized phase III study.

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Prevalence of symptomatic skeletal events (SSE) with reduced denosumab (Dmab) dose density (every 12 weeks versus every 4 weeks): A randomized phase III non-inferiority trial SAKK 96/12 REDUSE.

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Background: Clinical guidelines recommend Dmab 120 mg every 4 weeks (Q4W) for patients (pts) with bone metastases. While dosing every 12 weeks (Q12W) is established for zoledronic acid based on phase III trials, prospective trials with Dmab evaluating the efficacy endpoint of skeletal-related events (SRE) for a Q12W schedule are missing. The results of an early dose-finding study of Dmab demonstrated a similar suppression of bone-turnover markers for 60 mg Q12W as for 120 mg Q4W at weeks 13 and 25, suggesting that Q12W dosing might be sufficient. The SAKK 96/12 REDUSE trial investigated whether a de-escalated Dmab schedule is non-inferior to the standard Q4W regimen in preventing symptomatic skeletal related events (SSEs; symptomatic pathological fracture, radiation or surgery to bone, or spinal cord compression).

Methods: In this international, multicenter, randomized, phase III trial, pts with metastatic breast cancer (BC) or castration-resistant prostate cancer (CRPC) and at least three bone metastases were randomized 1:1. Arm A (standard) received Dmab 120 mg Q4W. Arm B (reduced) received 4 loading doses Q4W, followed by Q12W dosing. The primary endpoint was time to first on-trial SSE. The sample size of 1,380 pts was calculated to demonstrate non-inferiority using a log-rank test with a non-inferiority margin of 1.20 (80% power, 5% type I error). Secondary endpoints included time to first and subsequent on-trial SSE, and toxicity focusing on hypocalcemia and osteonecrosis of the jaw (ONJ). A health economic analysis is ongoing.

Results: 1,380 pts were enrolled between 7/2014 and 3/2024 (784 and 596 with BC and CRPC, respectively). Median follow-up time was 37 months (mo) (42 mo for BC and 29 mo for CRPC). The trial met its primary endpoint, demonstrating that denosumab Q12W is non-inferior to Q4W. Median time to first on-trial SSE for arm A was 56.6 mo (95% CI (40.7, not reached [NR])) and for arm B 56.5 mo (95% CI 47.7, NR). The stratified HR and 90% CI calculated using a Cox regression model is 1.023 (0.874, 1.197) with the upper limit remaining below 1.20. Also, for time to first and subsequent on-trial SSE, non-inferiority was shown with a stratified HR 1.043 (90% CI 0.907, 1.198). Safety analysis showed less toxicity for the Q12W arm: Hypocalcemia occurred in 46% (Arm A) vs 30% (Arm B), and ONJ was reported in 8.5% vs 6.9% of pts, respectively.

Conclusions: The SAKK 96/12 REDUSE trial demonstrates that a Dmab Q12W schedule, following a 3-month loading phase, is non-inferior to the Q4W regimen in pts with bone-metastatic BC or CRPC. The observed lower rates in ONJ and hypocalcemia indicate a more favorable safety profile for the Q12W schedule. These data indicate that Dmab Q12W represents the new standard of care in pts with bone metastasis from BC or CRPC, offering comparable efficacy while reducing toxicity, treatment burden, and costs. Clinical trial information: NCT02051218. Research Sponsor: Santesuisse; CSS and Helsana health insurance; Swiss Cancer Institute, Switzerland.

Efficacy and safety of tucatinib (TUC) vs placebo (PBO) combined with trastuzumab and pertuzumab (HP) as maintenance therapy for HER2+ metastatic breast cancer by stratified subgroups.

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Background: In the phase 3 HER2CLIMB-05 study (NCT05132582), TUC + maintenance HP demonstrated a statistically significant improvement in progression-free survival (PFS) vs control treatment (Tx) (hazard ratio: 0.641, $P < 0.0001$) in patients (pts) with HER2+ locally advanced or metastatic breast cancer (MBC). Here we report additional efficacy and safety outcomes by stratified subgroups. **Methods:** Pts with centrally confirmed HER2+ MBC without evidence of progression following chemotherapy-based induction Tx (taxane + HP) were randomly assigned 1:1 to TUC (300 mg) or PBO BID + HP. Randomization was stratified by diagnosis (*de novo*/recurrent), hormone receptor (HR) status (positive/negative), and presence or history of brain metastases (BM; yes/no). Endocrine therapy (ET) is permitted for pts with HR+ disease. The primary endpoint is investigator-assessed PFS. Confirmed objective response rate (cORR), duration of response (DOR), and safety were evaluated in stratified subgroups. **Results:** Among pts assigned to TUC + HP (n = 326) or PBO + HP (n = 328), ~69% had *de novo* MBC, ~53% had HR+ status with ~45% having received concurrent ET, and ~12% had baseline BM. At data cutoff (Sep 5, 2025), median PFS was longer with TUC than PBO + HP in all stratified subgroups; TUC + HP consistently improved cORR vs PBO + HP (Table). Safety outcomes in subgroups aligned with the overall population. **Conclusions:** TUC + HP demonstrated clinically meaningful efficacy vs PBO + HP in pts with *de novo* or recurrent disease, HR+ or HR– disease, and baseline BM or not, with no new safety signals identified. Results were consistent with the overall population and support TUC + HP as a potential new maintenance therapy across pts with HER2+ MBC. Clinical trial information: NCT05132582. Research Sponsor: Pfizer Inc.

Efficacy outcomes.														
	Overall TUC+HP (n=326)	PBO+HP (n=328)	De novo TUC+HP (n=227)	PBO+HP (n=226)	Recurrent TUC+HP (n=99)	PBO+HP (n=102)	HR+ (± ET) ^a TUC+HP (n=168)	PBO+HP (n=176)	HR– TUC+HP (n=158)	PBO+HP (n=152)	BM (yes) TUC+HP (n=41)	PBO+HP (n=40)	BM (no) TUC+HP (n=285)	PBO+HP (n=288)
Median PFS, mos (95% CI)	24.9 (21.3–NE)	16.3 (12.6–18.7)	28.9 (22.7–NE)	16.8 (12.9–19.2)	21.3 (15.6–27.2)	12.7 (8.3–18.1)	25.0 (16.5–NE)	18.1 (13.0–20.8)	24.9 (19.4–NE)	12.6 (9.4–16.8)	8.5 (4.2–16.5)	4.2 (2.2–8.1)	27.2 (24.3–NE)	18.1 (14.8–20.7)
cORR, % (95% CI)	22.6 (18.0–27.8)	15.2 (11.3–19.7)	26.1 (20.2–32.7)	18.5 (13.5–24.4)	15.1 (8.5–24.0)	7.0 (2.6–14.6)	20.1 (14.0–27.5)	12.9 (8.2–19.0)	25.2 (18.4–33.0)	17.9 (11.8–25.5)	15.0 (6.7–29.8)	8.3 (1.8–22.5)	23.8 (18.7–29.5)	16.1 (11.9–12.1)
Median DOR ^a , mos (95% CI)	20.9 (16.4–NE)	16.9 (12.3–NE)	NR (16.4–NE)	16.3 (10.4–NE)	17.9 (8.3–NE)	NR (7.2–NE)	20.9 (12.6–NE)	18.7 (7.8–NE)	NR (8.6–NE)	14.5 (10.4–NE)	12.6 (8.1–NE)	16.3 (12.6–NE)	20.9 (16.4–NE)	18.7 (10.4–NE)

^aORR and DOR were assessed in patients with target or non-target lesions at baseline.
^bData on HR+ w/ ET will be presented.

Giredestrant (GIRE) + palbociclib (PALBO) vs letrozole (LET) + PALBO as first-line (1L) therapy in patients (pts) with estrogen receptor–positive, HER2-negative locally advanced or metastatic breast cancer (ER+, HER2– LA/mBC): Primary analysis of the phase III persevERA BC trial.

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First-line (1L) camizestrant (CAMI) for emergent *ESR1* mutations (*ESR1m*) in advanced breast cancer (ABC): Final progression-free survival 2 (PFS2) from the phase III SERENA-6 trial.

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Efficacy and safety of camrelizumab combined with docetaxel and carboplatin as neoadjuvant therapy for triple-negative breast cancer: The HELEN-Trio 011 randomized clinical trial.

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Background: The KEYNOTE-522 trial demonstrated that adding a PD-1 inhibitor to neoadjuvant chemotherapy significantly improves pathological complete response (pCR) rates, albeit with notable toxicity. The phase III Camrelief trial further confirmed that camrelizumab combined with sequential neoadjuvant chemotherapy significantly improved pCR compared with placebo in early-stage triple-negative breast cancer (TNBC). This study aimed to evaluate the efficacy and safety of camrelizumab plus neoadjuvant docetaxel and carboplatin in previously untreated stage II–III TNBC. **Methods:** This multicenter, randomized, open-label, phase III trial (ClinicalTrials.gov identifier: NCT05475678) enrolled eligible female patients aged 18–70 years with previously untreated stage II–III TNBC. Patients were randomized (2:1) to receive six 21-day cycles of docetaxel (75 mg/m²) and carboplatin (area under the curve=6) on day 1, with or without camrelizumab (200 mg intravenously on day 3). The primary endpoint was pCR (ypT0/Tis ypN0), assessed in the modified intention-to-treat (mITT) population, which included all patients who received at least one dose of the trial treatment. **Results:** Between December 2022 and June 2025, 369 patients from fourteen hospitals in China were enrolled and randomized to the camrelizumab-chemotherapy group (n=245) or the chemotherapy-alone group (n=124), of whom 352 comprised the mITT population. The pCR rate was 57.5% (134 of 233) in the camrelizumab-chemotherapy group versus 45.4% (54 of 119) in the chemotherapy-alone group (absolute difference, 12.2 percentage points; 95% CI, 1.4–22.9; one-sided P= 0.014). In the prespecified exploratory subgroup (CPS ≥1), pCR rates were 69.8% (97/139; 95% CI, 62.2%–77.4%) with camrelizumab-chemotherapy and 51.9% (41/79; 95% CI, 40.9%–62.94%) with chemotherapy-alone (absolute difference, 17.9%; 95% CI, 5.3%–30.5%; one-sided P = 0.004). In the PD-L1-negative subgroup (CPS <1), pCR rates were 37.8% (31/82; 95% CI, 27.4%–48.2%) and 28.1% (9/32; 95% CI, 12.5%–43.7%), respectively (absolute difference, 9.7%; 95% CI, -10.5%–29.9%; one-sided P = 0.165). Grade 3 or higher treatment-related adverse events occurred in 24.8% (58/233) of patients in the camrelizumab-chemotherapy group, and 21.8% (26/119) in the chemotherapy-alone group. No treatment related deaths were reported. **Conclusions:** The addition of camrelizumab to neoadjuvant docetaxel and carboplatin significantly improved pCR rates in patients with stage II–III TNBC with a manageable safety profile. This anthracycline-free regimen represents a promising neoadjuvant treatment option for early TNBC. Clinical trial information: NCT05475678. Research Sponsor: None.

Time-of-day administration of immunotherapy in early-stage triple-negative breast cancer: Immune-dependent chronotherapy effects in the phase III A-BRAVE trial.

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Background: Circadian rhythms regulate immune functions, and morning (AM) administration of immunotherapy (IO) is associated with survival in several solid tumors. However, whether time-of-day (ToDa) of IO delivery influences outcomes in early-stage triple-negative breast cancer (TNBC), and whether this effect depends on immune biomarkers, remains unknown.

Methods: A-BRAVE randomized patients with high-risk early-stage TNBC to 1 year of adjuvant avelumab or observation. Infusion time of avelumab was retrieved from eCRF. AM-rate was calculated for each patient as the proportion of the first 4 infusions occurring before 12:30 PM (cohort median ToDa) and patients categorized as AM-dominant (AM-rate $\geq 50\%$) or PM-dominant. Tumor-infiltrating lymphocytes (TILs) and PD-L1 (Dako 73-10) were centrally assessed on treatment-naïve tumor samples. We analyzed distant disease-free survival (DDFS) and overall survival (OS) by adjusted Cox models. **Results:** ToDa data were available for 221 avelumab-treated patients (94.0%); TILs and PD-L1 were evaluable in 188 (85%) and 195 (88%) of these, respectively. AM-rate was not associated with outcomes. However, ToDa effects were strongly immune-dependent. Increasing AM-rate was associated with improved DDFS and OS in immune-hot tumors (TILs $\geq 20\%$ or PD-L1 ≥ 21 high), but with worse outcomes in immune-cold tumors (TILs or PD-L1 low) (AM-rate*TILs interaction: DDFS $p=0.008$, OS $p=0.001$; AM-rate*PD-L1 interaction: DDFS $p=0.030$, OS $p=0.039$). These findings were concordant using AM-dominant vs. PM-dominant categorization (Table). Patients receiving immune-aligned treatment (immune-hot/AM-dominant OR immune-cold/PM-dominant) had superior survival compared with immune-misaligned (immune-hot/PM-dominant OR immune-cold/AM-dominant) and the observational arm (TILs-based: 3-year OS 95.7% vs 75.2% vs 78.0%; $p<0.001$; PD-L1-based: 3-year OS 93.4% vs 79.4% vs 76.1; $p=0.035$).

Conclusions: In early-stage TNBC, time of IO administration may be a driver of efficacy, with opposing effects according to baseline immune milieu. Immune-informed circadian alignment may represent a previously unrecognized determinant of IO efficacy in TNBC. Clinical trial information: NCT02926196. Research Sponsor: Merck KGaA; CrossRef Funder ID: 10.13039/100009945.

		AM-dominant 3-yr Rate % (95% CI)	PM-dominant 3-yr Rate % (95% CI)	Log-rank p	AM vs PM dominant HR (95% CI)
TILs High	DDFS	90.1 (81.3–99.8)	72.0 (56.4–91.9)	0.064	0.39 (0.13–1.21)
	OS	97.5 (92.8–100)	76.0 (61.0–94.7)	0.019	0.35 (0.10–1.20)
TILs Low	DDFS	63.1 (52.6–75.7)	84.7 (75.5–95.1)	0.003	2.61 (1.23–5.55)
	OS	74.9 (65.2–86.0)	94.3 (88.3–100)	0.003	3.84 (1.30–11.29)
PD-L1 high	DDFS	100 (100–100)	61.5 (40.0–94.6)	0.015	0.11 (0.01–0.94)
	OS	100 (100–100)	76.9 (57.1–100)	0.008	0.11 (0.01–1.03)
PD-L1 low	DDFS	66.4 (57.3–77.0)	83.0 (74.7–92.2)	0.026	1.82 (1.00–3.31)
	OS	79.8 (71.9–88.6)	91.5 (85.3–98.2)	0.025	2.05 (0.95–4.43)

Primary results from the triple-negative cohort of TBCRC-053 (P-RAD): A randomized trial of no, low, or high dose preoperative radiation with pembrolizumab and chemotherapy in node-positive breast cancer.

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Background: Approximately one-quarter of patients with node-positive, triple-negative breast cancer (TNBC) did not experience a complete nodal response to neoadjuvant chemo-immunotherapy in KEYNOTE-522. We conducted a randomized trial to evaluate whether no-, low-, or high-dose preoperative radiotherapy (RT) to the breast primary tumor combined with pembrolizumab (pembro) enhances tumor T-cell infiltration (TCI) and pathologic response in non-irradiated lymph node (LN) metastases (NCT04443348). **Methods:** Between 2021–2025, 55 patients with cT1c–T4c, cN1–3, cM0, ER/PR < 10%, HER2-negative breast cancer and biopsy-proven, clipped axillary LN metastasis were randomized to no RT (0 Gy), low-dose RT (9 Gy) or high-dose RT (24 Gy) to the primary tumor with concurrent pembro, followed by an on-treatment tumor biopsy at 2 wks. Stratification factors included cT stage (T1c vs. T2–4) and cN stage (N1 vs. N2–3). Patients subsequently received pembro (200 mg q3w or 400 mg q6w) with 12 wks of paclitaxel/carboplatin, followed by four cycles of doxorubicin-cyclophosphamide (q2w or q3w) with pembro, surgery and adjuvant therapy. Primary endpoints were 2-wk tumor TCI and nodal pathologic complete response (ypNo) at surgery. TCI was assessed by multiplexed immunofluorescence (panCK/CD3/CD8) using a rank-based Immunoscore. 2-wk TCI for each treatment arm was compared to a common reference cohort of pretreatment TCI measurements. The study was powered to detect an increase in upper-quartile TCI from 25% to 55%. Statistical comparisons used two-tailed Fisher's exact tests. ypNo and secondary endpoints pCR (ypTo/TisNo) and Residual Cancer Burden (RCB) 0/1 were underpowered for a statistical test. **Results:** Among 55 enrolled patients, 48 were evaluable for TCI and 51 for ypNo. Median age was 50 years (range 28–77). 81.8% had cT2–4 disease, 20% had cN2–3, and 87.3% had grade 3 tumors. The proportion of tumors with upper-quartile TCI was significantly increased with RT plus pembro, but not pembro alone, when compared to the pretreatment cohort: 44% (0Gy; $p = \text{NS}$), 80% (9Gy, $p < 0.0001$), and 82% (24Gy; $p < 0.0001$). ypNo rates were 73.3% (0Gy), 88.2% (9Gy) and 78.9% (24Gy). pCR/RCB 0–1 rates were 66.6%/66.6% (0Gy), 76.5%/82.4% (9Gy) and 68.4%/84.2% (24Gy). Tumors with upper-quartile TCI at the 2-wk timepoint had a significantly higher ypNo rate relative to tumors without upper-quartile TCI (94% [31/33] vs. 46% [6/13]; $p = 0.0009$). **Conclusions:** The addition of preoperative RT to pembro significantly increased 2-wk TCI and yielded high rates of ypNo and pCR after chemo-immunotherapy, with the numerically highest ypNo rate observed in the 9Gy arm. 2-wk TCI correlated strongly with surgical ypNo status. A larger study that tests whether preoperative RT and pembro increases pCR should be conducted in node-positive TNBC. Clinical trial information: NCT04443348. Research Sponsor: Breast Cancer Research Foundation; Translational Breast Cancer Research Consortium; U.S. National Institutes of Health; Merck, Inc.; Natera, Inc.

Trastuzumab deruxtecan (T-DXd) + durvalumab (D) in patients (pts) with previously untreated HER2+ unresectable/metastatic breast cancer (mBC): Final analysis from DESTINY-Breast07.

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Background: T-DXd is approved for adult pts with HER2+ mBC who received a prior anti-HER2–based regimen, or as 1L therapy when given in combination with pertuzumab (P). DESTINY-Breast07 (NCT04538742) is a Phase 1b/2, open-label, platform study exploring the safety, tolerability, and antitumor activity of T-DXd ± other anticancer agents in HER2+ mBC. 1L T-DXd ± P recently showed encouraging clinical activity and safety profiles consistent with previous reports. D, an anti-PD–L1 antibody, has shown efficacy in combination with T-DXd in HER2–low, hormone receptor (HR)–negative mBC. As part of the DESTINY-Breast07 final analysis, here we report the dose-expansion phase for T-DXd + D as a 1L treatment in HER2+ mBC. **Methods:** Pts had locally assessed HER2+ (IHC 3+ or IHC 2+/ISH+) mBC. A disease-free interval of ≥12 months (mo) from (neo)adjuvant therapy was required; no prior therapy for mBC was allowed. Pts were stratified by HR (positive vs negative), disease (recurrent vs de novo), and PD–L1 status (positive vs negative; positive defined as ≥1% IHC). Pts received T-DXd 5.4 mg/kg IV, in combination with D 1120 mg IV, every 3 weeks. Primary endpoints were safety and tolerability; secondary endpoints included confirmed ORR (cORR), duration of response (DOR) and progression-free survival (PFS) per RECIST 1.1 by investigator, time to progression on subsequent therapy or death (PFS2) by investigator, and overall survival (OS). **Results:** At data cutoff (DCO) (January 31, 2025), 64 pts were randomized to the T-DXd + D module, and 63 received treatment. Median follow up was 30.1 mo; median total treatment duration was 26.7 mo for T-DXd and 24.6 mo for D. Efficacy results are given in the Table. The most common adverse events (AEs) were nausea (79.4%), vomiting (46.0%), neutropenia (46.0% by grouped term [GT]), anemia (44.4% by GT), and fatigue (38.1%). Grade ≥3 AEs occurred in 58.7% (n=37/63) and serious AEs in 30.2% (n=19/63) of pts. There were two deaths due to AEs (3.2%): one pt with neutropenia and septic shock and one pt with sepsis. Adjudicated drug-related interstitial lung disease (ILD)/pneumonitis events occurred in 11 (17.5%; Grade 1, n=1; Grade 2, n=8; Grade 3, n=2) pts. Additional data by subgroups (stratification factors and biomarkers) will be presented. **Conclusions:** Encouraging clinical activity was seen for T-DXd + D as a 1L treatment for HER2+ mBC. Safety profiles were consistent with the known profiles for each therapy, with no fatal ILD events. These promising results provide a rationale for further investigation of this treatment combination. Clinical trial information: NCT04538742. Research Sponsor: AstraZeneca.

	T-DXd + D (n=64)
cORR (80% CI), %	82.8 (75.2, 88.8)
mDOR* (Q1–Q3), mo	36.1 (23.3, NE)
mPFS* (80% CI), mo	37.7 (35.1, NE)
PFS rate at 24 mo (80% CI), %	75.5 (67.2, 82.0)
mOS (80% CI), mo	NE (NE, NE)
mPFS2 (80% CI), mo	NE (NE, NE)

*Most pts were censored at DCO; m, median; NE, not evaluable; Q, quartile.

ASCENT-04: Analysis of efficacy by biomarker subgroups with sacituzumab govitecan (SG) + pembrolizumab (pembro) vs chemotherapy (chemo) + pembro in participants (pts) with previously untreated PD-L1+ metastatic triple-negative breast cancer (mTNBC).

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Background: In the phase 3 ASCENT-04/KEYNOTE-D19 study (NCT05382286) SG + pembro showed significant and clinically meaningful progression-free survival (PFS) improvement vs chemo + pembro in pts with previously untreated PD-L1+ mTNBC. SG + pembro exhibited a manageable safety profile consistent with prior studies for each agent. We present preplanned exploratory efficacy analyses in ASCENT-04 by biomarker subgroups. **Methods:** 443 pts received (1:1 ratio) SG + pembro in 21-day cycles or chemo (gemcitabine + carboplatin; taxane) + pembro. From centrally tested fresh or archival tumor samples, Trop-2 expression was determined by immunohistochemistry (IHC), tumor BRCA (tBRCA) status by whole exome sequencing, and HER2 expression by in situ hybridization (ISH) + IHC. Pts were grouped by Trop-2 expression quartiles, tBRCA status (wild-type [WT] or mutant [mut] in *BRCA1/BRCA2/both*), and HER2 status (IHC 0 vs Low [IHC 1+ or IHC 2+/ISH-]). Biomarker subgroups were analyzed descriptively for association with PFS by blinded independent central review (BICR); other outcomes by biomarker status are forthcoming. **Results:** Median Trop-2 H-score was 280, ranges: quartile 1 (Q1) 0-224, Q2 225-279, Q3 280-298, Q4 299-300. SG + pembro demonstrated longer PFS by BICR in Q3/Q4 vs Q1/Q2, and benefit was observed for SG + pembro vs chemo + pembro in all quartiles (Table). Hazard ratios (HR; 95% confidence interval [CI]) were: Q1, 0.81 (0.48-1.36); Q2, 0.73 (0.44-1.22); Q3, 0.46 (0.27-0.80); Q4, 0.57 (0.33-0.99). Proportion of pts with tBRCA mutations (~20%) was similar between treatment groups. Longer PFS was observed with SG + pembro with HR (95% CI) of 0.67 (0.49-0.91) in the tBRCA WT and 0.88 (0.45-1.74) in the tBRCA mut subgroups. PFS was longer with SG + pembro vs chemo + pembro in the HER2 IHC 0 and HER2 low subgroups, HR (95% CI) 0.69 (0.46-1.04) and 0.67 (0.48-0.92), respectively. **Conclusions:** SG + pembro demonstrated longer PFS vs chemo + pembro across all Trop-2, tBRCA, and HER2 subgroups. These analyses strengthen support for the significant, clinically meaningful benefit of SG + pembro as first-line treatment for mTNBC across subgroups. Clinical trial information: NCT05382286. Research Sponsor: Gilead Sciences, Inc.

Efficacy, BICR		N		Median PFS (95% CI), mo		
Biomarker	Subgroup	SG + pembro	Chemo + pembro	SG + pembro	Chemo + pembro	HR (95% CI)
Trop-2 (n = 400)	Q1	48	47	9.3 (7.4-19.4)	9.0 (6.0-10.9)	0.81 (0.48-1.36)
	Q2	50	50	9.6 (7.3-16.7)	7.4 (6.9-9.7)	0.73 (0.44-1.22)
	Q3	55	50	13.5 (9.3-NR)	8.4 (5.6-10.8)	0.46 (0.27-0.80)
	Q4	51	49	16.6 (8.1-NR)	9.2 (5.5-11.3)	0.57 (0.33-0.99)
tBRCA (n = 332)	WT	130	131	9.6 (7.6-16.7)	7.4 (6.9-9.2)	0.67 (0.49-0.91)
	Mut	39	32	16.6 (7.5-NR)	12.9 (7.1-NR)	0.88 (0.45-1.74)
HER2 (n = 435)	IHC 0	84	82	16.6 (9.1-21.2)	9.0 (7.2-10.8)	0.69 (0.46-1.04)
	Low	133	136	11.2 (9.1-16.6)	7.7 (7.0-9.4)	0.67 (0.48-0.92)

ASCENT-03: Efficacy by biomarker subgroup with sacituzumab govitecan (SG) vs chemotherapy (chemo) in participants (pts) with previously untreated advanced triple-negative breast cancer (TNBC) who are not candidates for PD-(L)1 inhibitors (PD-[L]1i).

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Background: SG demonstrated significant and clinically meaningful progression-free survival (PFS) improvement vs chemo in pts with previously untreated, locally advanced unresectable or metastatic TNBC who were not candidates for PD-(L)1i in ASCENT-03 (NCT05382299). We report preplanned exploratory efficacy analyses in ASCENT-03 by Trop-2 expression, BRCA status, and HER2 expression. **Methods:** 588 pts randomized 1:1 to SG or chemo (taxane or gemcitabine + carboplatin). Trop-2 expression was measured by immunohistochemistry (IHC), tumor BRCA (tBRCA) status by whole exome sequencing, and HER2 expression by in situ hybridization (ISH) and IHC, all in centrally tested tumor samples (fresh or archival; 43% from metastatic sites). Pts were subgrouped by Trop-2 expression quartile, tBRCA wild-type (WT) or mutant (mut; mut in *BRCA1*, *BRCA2*, or both) status, and HER2 status (IHC 0 vs Low [IHC 1+ or IHC 2+/ISH-]). Biomarker status was analyzed to determine association with PFS by blinded independent central review (BICR). Other efficacy outcomes by biomarker status will be presented. **Results:** Median Trop-2 H-score: 240; H-scores by quartile (Q): Q1 0-184, Q2 185-239, Q3 240-283, Q4 284-300. Trop-2 expression was available in 499 pts. PFS by BICR was longer with SG vs chemo in all Trop-2 expression quartiles (Table). Hazard ratio (HR; 95% confidence interval [CI]) was 0.54 (0.35-0.84) in Q1, 0.62 (0.40-0.97) in Q2, 0.84 (0.54-1.31) in Q3, and 0.60 (0.38-0.95) in Q4. tBRCA status was available in 423 pts; proportion of pts with tBRCA mutations was comparable between treatment groups (~18%). PFS was longer with SG vs chemo in tBRCA WT and mut subgroups, with HR (95% CI) 0.70 (0.54-0.92) in tBRCA WT and 0.59 (0.32-1.09) in tBRCA mut. HER2 status was available in 551 pts; PFS was longer with SG vs chemo in both HER2 subgroups. HR was 0.63 (0.46-0.85) in the IHC 0 subgroup and 0.74 (0.55-1.01) in the HER2 Low subgroup. **Conclusions:** PFS was longer with SG vs chemo across all Trop-2 categories, tBRCA genotypes, and HER2 subgroups. These results reinforce the significant, clinically meaningful benefit of SG as first-line treatment for pts in this population across multiple biomarker subgroups. Clinical trial information: NCT05382299. Research Sponsor: Gilead Sciences, Inc.

Efficacy, BICR Biomarker	Subgroup	N		Median PFS (95% CI), months		HR (95% CI)
		SG	Chemo	SG	Chemo	
Trop-2 (n = 499)	Q1	68	55	8.5 (5.6-12.7)	5.5 (4.2-8.1)	0.54 (0.35-0.84)
	Q2	60	62	8.3 (5.6-12.4)	6.8 (4.2-9.0)	0.62 (0.40-0.97)
	Q3	50	74	9.7 (7.6-11.3)	7.0 (5.3-8.5)	0.84 (0.54-1.31)
	Q4	74	56	9.9 (6.9-NR)	8.1 (4.4-8.5)	0.60 (0.38-0.95)
tBRCA (n = 423)	WT	177	169	8.8 (7.2-9.9)	6.9 (5.4-8.3)	0.70 (0.54-0.92)
	Mut	40	37	12.7 (7.2-18.7)	8.3 (5.6-11.2)	0.59 (0.32-1.09)
HER2 (n = 551)	IHC 0	115	138	8.3 (6.9-10.3)	5.6 (4.3-7.0)	0.63 (0.46-0.85)
	Low	159	139	9.8 (8.3-12.4)	8.3 (5.7-9.7)	0.74 (0.55-1.01)

Impact of food access and poverty on somatic genomic profiles and clinical outcomes in metastatic breast cancer.

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Background: Patients living in food deserts or experiencing food insecurity have higher cancer mortality rates. While neighborhood poverty correlates with more aggressive tumor biology, including higher OncotypeDX scores and rates of *TP53* mutations, the associations among food access, somatic genomic profiles, and clinical outcomes in metastatic breast cancer (MBC) remain understudied. **Methods:** This multi-institutional retrospective cohort study included patients with MBC and circulating tumor DNA (ctDNA) testing through the Guardant360 assay from Washington University in St. Louis (N = 651), Massachusetts General Hospital (N = 349), Weill Cornell Medicine (N = 187), and Northwestern University (N = 86). Patient census tracts were linked with the USDA Food Access Research Atlas, which provides data on census-level food access throughout the United States. Deidentified data were shared across sites. We categorized patients by: Food access: Low access (LA) if $\geq 33\%$ of the census tract lived > 1 mile (urban) or > 10 miles (rural) from a food store Income and food access: Low-income and low access (LILA) if the census tract was both LA and poverty rate was $\geq 20\%$ We assessed descriptive differences and determined associations between LA/LILA and ctDNA profiles using multivariate analysis adjusted for race, stage, and subtype. **Results:** Of the 851 patients with census tract data, 46.8% lived in LA and 8.0% lived in LILA areas. Although White patients were more likely to live farther from food stores than Black patients (48.9% vs 34.4%, $p = 0.003$), Black patients were significantly more likely to live in LILA areas (19.2% vs 6.1%, $p = < 0.001$). On multivariate analysis, patients in the overall cohort living in LA areas were more likely to have *RTK/RAS* pathway mutations (Odds ratio [OR] 2.05, 95% confidence interval [CI] 1.36–3.09, $p = 0.001$), confirmed in the hormone receptor positive, HER2 negative (HR+/HER2-) cohort (OR 2.18, 95% CI 1.34–3.55, $p = 0.002$). Patients in the overall cohort living in LILA areas were more likely to have *CCNE1* copy number variants [cnv] (OR 2.81, 95% CI 1.18–6.73, $p = 0.02$). Patients in LA areas had significantly shorter overall survival (OS) after first ctDNA test (24 months [mos] vs 31 mos, $p = 0.01$). In HR+/HER2- MBC, Black patients in LA areas had the shortest OS (11 mos) compared to those in high access areas (38 mos) and White patients in either setting (27–33 mos, $p = 0.02$). **Conclusions:** Patients with MBC living in food deserts appear to have distinct ctDNA profiles, including higher rates of *RTK/RAS* pathway mutations, which drive tumor growth, and *CCNE1* cnv, associated with poor prognosis. We also found a significant survival disadvantage associated with living in LA areas, particularly among Black patients. These findings demonstrate the necessity of considering the intersection of tumor biology and social determinants of health in understanding and treating MBC. Research Sponsor: None.

Post-progression treatment (tx) analyses of evERA Breast Cancer (BC): A phase III trial of giredestrant (GIRE) + everolimus (E) in patients (pts) with estrogen receptor–positive, HER2-negative advanced BC (ER+, HER2– aBC) previously treated with a CDK4/6 inhibitor (i).

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Background: evERA BC (NCT05306340) is the first Phase III trial to demonstrate a statistically significant and clinically meaningful improvement in investigator-assessed progression-free survival (INV-PFS) with an all-oral, selective ER degrader and full ER antagonist combination (GIRE + E) compared with standard-of-care endocrine therapy combinations (SOC ET + E) in pts with ER+, HER2– aBC post-CDK4/6i + ET (Mayer ESMO 2025). Improvement in INV-PFS was seen in all pts (hazard ratio [HR], 0.56) and in pts whose tumors had a detectable *ESR1* mutation (*ESR1*m; HR, 0.38), with no unexpected safety findings. We report exploratory post-progression tx analyses. **Methods:** Pts with ER+, HER2– aBC who had disease progression (PD) or relapse during/post-CDK4/6i + ET were randomized 1:1 to once-daily oral 30 mg GIRE + 10 mg E or SOC ET (exemestane/ fulvestrant/tamoxifen) + E until PD/unacceptable toxicity. Exploratory analyses included PFS2 (time from randomization to PD on next-line tx, or death), chemotherapy-free survival (CFS; time to first subsequent chemotherapy and/or antibody-drug conjugate [ADC], or death), and types of cancer tx following discontinuation from study tx. **Results:** Median PFS2 and CFS were longer with GIRE + E vs SOC ET + E in all pts (PFS2 HR, 0.69; CFS HR, 0.61), including in the *ESR1*m (PFS2, 0.61; CFS, 0.46) and *ESR1*m not detected populations (PFS2, 0.77; CFS, 0.80; Table). Of those receiving follow-up cancer therapy in all pts, and in the *ESR1*m and *ESR1*m not detected populations, 69.1%, 63.3%, and 73.8%, respectively, received chemotherapy in the GIRE + E arm vs 71.5%, 65.3%, and 79.0% in the SOC ET + E arm; 24.5%, 18.4%, and 29.5% received an ADC in the GIRE + E arm vs 31.4%, 25.3%, and 38.7% in the SOC ET + E arm. **Conclusions:** Delaying chemotherapy improves clinical and quality of life outcomes in ER+ aBC. These analyses further support the superior INV-PFS of GIRE + E over SOC ET + E observed in all pts and in the *ESR1*m population. Improvements in PFS2 and CFS, regardless of *ESR1*m status, suggest that the clinical benefit of GIRE + E is sustained beyond initial progression. Clinical trial information: NCT05306340. Research Sponsor: F. Hoffmann-La Roche Ltd.

	All pts		<i>ESR1</i> m		<i>ESR1</i> m not detected	
	GIRE + E (n = 183)	SOC ET + E (n = 190)	GIRE + E (n = 102)	SOC ET + E (n = 105)	GIRE + E (n = 81)	SOC ET + E (n = 85)
PFS2						
Event, n (%)	81 (44.3)	108 (56.8)	39 (38.2)	57 (54.3)	42 (51.9)	51 (60.0)
Median, mo (95% CI)	19.0 (15.5, not evaluable [NE])	13.2 (11.7, 15.9)	19.0 (15.5, NE)	12.9 (11.8, 17.6)	17.3 (13.0, NE)	12.9 (9.8, 20.8)
Stratified HR (95% CI)	0.69 (0.51, 0.92)		0.61 (0.40, 0.93)		0.77 (0.51, 1.17)	
CFS						
Event, n (%)	111 (60.7)	146 (76.8)	51 (50.0)	78 (74.3)	60 (74.1)	68 (80.0)
Median, mo (95% CI)	11.1 (9.6, 12.7)	7.9 (6.9, 9.5)	12.6 (10.9, 18.7)	8.5 (7.1, 10.0)	9.5 (7.4, 11.6)	7.2 (6.1, 9.5)
Stratified HR (95% CI)	0.61 (0.47, 0.78)		0.46 (0.32, 0.66)		0.80 (0.57, 1.14)	

Effectiveness of first-line ET+CDK4/6i continuation beyond disease progression in a large cohort of patients with HR+/HER2– advanced breast cancer: Results from the multicenter, real-world, Italian study PALMARES-2.

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Background: Endocrine therapy (ET) plus Cyclin-Dependent Kinase 4/6 inhibitors (CDK4/6i) is the standard 1st line treatment for patients (pts) with Hormone Receptor-positive, Human Epidermal growth factor Receptor 2-negative, advanced Breast Cancer (HR+/HER2– aBC). ET+CDK4/6i continuation beyond progressive disease (PD) detection, plus/minus locoregional therapies, is often used in clinical practice for selected pts with oligoprogressive disease or minimal PD. However, the effectiveness of this approach has never been investigated in large studies. **Methods:** In this analysis of the multicenter, real-world study PALMARES-2 (NCT06805812), we evaluated clinical characteristics and outcomes in HR+/HER2– aBC pts who continued 1st line ET+CDK4/6i after detection of PD, as defined by physicians based on clinical-radiological assessment. The primary endpoint was real-world progression-free survival (rwPFS) beyond PD, defined as the time between the detection of the first PD event during 1st line ET+CDK4/6i and the occurrence of subsequent PD leading to definitive ET+CDK4/6i discontinuation, or patient death. We used multivariable Cox regression models to explore the association of 15 covariates with rwPFS beyond PD. We also assessed real-world overall survival (rwOS), as defined as the time between 1st line ET+CDK4/6i initiation and patient death. **Results:** Of 4,236 consecutive pts who initiated ET+CDK4/6i between January 2016 and September 2024 in 27 Italian Institutions, 2,434 pts experienced a PD event. Of these pts, 454 (18.7%) continued the same ET+CDK4/6i beyond PD and underwent radiotherapy (n = 306; 67%), surgery (n = 39; 9%), other locoregional treatments (n = 28; 6%) or no local therapies (n = 81; 18%). Pts continuing ET+CDK4/6i beyond PD were more likely to be younger and premenopausal, to have higher tumor estrogen receptor (ER) and/or progesterone receptor (PgR) expression, to have bone/lymph node metastases, and less likely to have liver metastases (p < 0.05 for all covariates). Median rwPFS beyond PD was 10.5 months (95% CI: 9.7–12). At multivariable analysis, higher tumor ER (p = 0.031)/PgR (p = 0.001) or lower Ki-67 (p < 0.001) expression, better ECOG Performance Status (p = 0.009) and the use of locoregional treatments (p < 0.001) were associated with longer rwPFS beyond PD. Pts continuing ET+CDK4/6i therapy beyond PD had better median rwOS than those discontinuing it after first PD detection (71.3 and 44.7 months, respectively; p < 0.001). **Conclusions:** This is the largest real-world study to show the effectiveness of 1st line ET+CDK4/6i continuation beyond PD in HR+/HER2– aBC pts. Our findings support the use of this well-tolerated and effective approach in selected pts, such as those with less biologically aggressive tumors and/or amenable to locoregional therapies. Clinical trial information: NCT06805812. Research Sponsor: Italiana Ministry of Health; AIRC, the Italian Association of Cancer Research; Scientific Directorate of Fondazione IRCCS Istituto Nazionale dei Tumori.

Palbociclib plus tamoxifen $\pm$ goserelin in women with hormone receptor (HR)-positive, HER2-negative advanced breast cancer (BC): PATHWAY, an Asian international double-blind randomized phase 3 trial—Final overall survival (OS) analysis.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

Paclitaxel plus bevacizumab with or without atezolizumab for hormone receptor-positive/HER2-negative advanced breast cancer: JCOG1919E (AMBITION) phase III trial.

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Background: Hormone receptor-positive/HER2-negative (HR+/HER2-) advanced breast cancer (aBC) is immunologically “cold,” with limited clinical benefit from immune checkpoint inhibitors. Since VEGF-mediated angiogenesis promotes an immunosuppressive tumor microenvironment, we hypothesize that inhibiting VEGF could reverse immunosuppressive state thereby augmenting response to immunotherapy. The JCOG1919E (AMBITION) phase III trial evaluates whether adding the anti-PD-L1 antibody: atezolizumab (ATZ) to paclitaxel (PTX) plus anti-VEGF antibody: bevacizumab (BEV) improves outcomes in patients (pts) with HR+/HER2- aBC. **Methods:** This multicenter, open-label, randomized phase III trial enrolled pts with HR+/HER2-aBC who had no prior chemotherapy for aBC and were endocrine-resistant or visceral crisis. Pts were randomized in a 1:1 ratio to PTX plus BEV (Arm A) or PTX plus BEV with ATZ (Arm B). Randomization was stratified by disease status (de novo stage IV vs. recurrent), liver metastasis (presence vs. absence), and PD-L1 expression (SP142 assay; negative [$<1\%$ on immune cells (ICs)] vs. positive [$\geq 1\%$]). PTX was administered on days 1, 8, and 15 of a 28-day cycle, BEV on days 1 and 15, and ATZ on days 1 and 15 in Arm B. The primary endpoint was investigator-assessed progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), PFS by blinded independent central review, and safety. Clinical trial information: NCT04732598. **Results:** From Sep 2021 to Sep 2023, 281 pts were randomized. At baseline, 33.1% were de novo stage IV, 68.0% had liver metastases, and 16.0% were PD-L1 positive. At a median follow-up of 30 months, median investigator-assessed PFS was 11.2 months in Arm A and 12.4 months in Arm B (hazard ratio [HR] 0.88; 95% CI, 0.67–1.15; $p=0.17$). Median OS was immature, but numerically longer in Arm B than in Arm A (39.1 vs. 31.2 months; HR 0.80, 95% CI, 0.58–1.11). The ORR was high and comparable between arms (71.9% vs. 73.0%). Grade ≥ 3 adverse events (AEs) were similar between arms. The most common immune related AEs (any grade) with ATZ were rash (17.3%), adrenal insufficiency (11.5%) and hypothyroidism (10.8%). No treatment-related deaths were observed, and no new safety signals emerged. **Conclusions:** PTX plus BEV with ATZ did not demonstrate a statistically significant improvement in PFS compared to PTX plus BEV as a frontline treatment for HR+/HER2- aBC, although a numerical extension in OS was observed. The safety profile of PTX plus BEV with ATZ was consistent with the known profiles. Clinical trial information: NCT04732598. Research Sponsor: None.

	ARM A PTX+BEV (n=140)	ARM B PTX+BEV+ATZ (n=141)
PFS events, n	117	109
Median PFS (95% CI), months	11.2 (9.6-13.5)	12.4 (10.3-15.2)
HR (95% CI)		0.876 (0.670-1.145)
P-value		0.168
OS events, n	81	71
Median OS (95% CI), months	31.2 (23.9-34.7)	39.1 (30.0-47.8)
HR (95% CI)		0.804 (0.584-1.108)
ORR, %	71.9%	73.0%

Impact of bevacizumab on the efficacy of antibody–drug conjugates as later-line treatment of basal-like immune-suppressed triple-negative breast cancer.

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Background: Basal-like immune-suppressed (BLIS) triple-negative breast cancer (TNBC) is associated with a poor prognosis; however, prior analyses from the FUTURE and FUTURE-SUPER clinical trials indicated clinical responsiveness to anti-angiogenic therapy. We conducted this study to evaluate the safety and efficacy of combining bevacizumab with antibody–drug conjugates (ADCs) in patients with the BLIS subtype. **Methods:** The FUTURE 2.0 study (NCT05749588) is an ongoing, open-label, multi-arm phase II platform trial evaluating novel molecularly targeted agents in patients with histologically confirmed TNBC who progressed after ≥1 line of systemic therapy for recurrent or metastatic disease. This report presents results from the BLIS arms: arm C (HER2-low) and arm D (HER2-zero). In arm C, patients received either SHR-A1811 (anti-HER2 ADC, 4.8 mg/kg IV q3w) alone (C1) or with bevacizumab (15 mg/kg IV q3w) (C2). In arm D, patients received either SHR-A1921 (Trop2-targeted ADC, 3.0 mg/kg IV q3w) alone (D1) or with bevacizumab (7.5 mg/kg IV q3w) (D2). The primary endpoint was confirmed objective response rate (ORR). Safety was assessed in all treated patients with available safety data. **Results:** From April 2022 to October 2025, 100 women were enrolled: 60 assigned to bevacizumab–combination arms (C2 and D2) and 40 to ADC monotherapy arms (C1 and D1). All 100 patients completed at least one post-baseline assessment. Confirmed ORR was 40.0% (8/20; 95% CI: 21.9–61.3%) in C1, 86.7% (26/30; 95% CI: 70.3–94.7%) in C2, 40.0% (8/20; 95% CI: 21.9–61.3%) in D1, and 83.3% (25/30; 95% CI: 66.4–92.7%) in D2. All four arms met the protocol-specified ORR success criterion with high posterior probability. Median PFS was 9.2 months in the combination group versus 4.6 months in the monotherapy group (HR = 0.47; 95% CI: 0.30–0.74), indicating a clinically meaningful improvement. Grade ≥3 treatment-related adverse events occurred in 27.5% (11/40) of monotherapy patients and 33.3% (20/60) of combination patients. No treatment-related deaths occurred. **Conclusions:** This study provides preliminary evidence of synergy between bevacizumab and ADCs, supporting a promising new strategy—especially for basal-like, immune-suppressed TNBC. Phase III trials are ongoing to confirm the efficacy and safety of this combination. Clinical trial information: NCT05749588. Research Sponsor: National Natural Science Foundation of China; 82403912.

The efficacy table.						
	ADC monotherapy			ADC combined with bevacizumab		
	A1811 N=20	A1921 N=20	Total N=40	A1811+ Bev N=30	A1921+ Bev N=30	Total N=60
ORR, n (%, 95% CI)	8 (40.0) 21.9 – 61.3	8 (40.0) 21.9 – 61.3	16 (40.0) 26.4 – 55.4	26 (86.7) 70.3 – 94.7	25 (83.3) 66.4 – 92.7	51 (85.0) 73.9 – 91.0
mPFS (mo, 95% CI)	4.9 4.1 – 5.7	4.4 3.7 – 5.1	4.6 3.9 – 5.3	9.1 7.2 – 11.1	9.3 8.2 – 10.5	9.2 7.3 – 11.0
HR in PFS, 95% CI	0.47 0.30 – 0.74 (P=0.001)					

A DESTINY-Breast09 analysis of treatment duration and clinical outcomes by best response to trastuzumab deruxtecan (T-DXd) + pertuzumab (P).

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Background: In DESTINY-Breast09 (NCT04784715), first-line (1L) T-DXd + P demonstrated durable responses, a near doubling of complete response (CR) rates, and significantly improved progression-free survival (PFS) vs taxane + trastuzumab + pertuzumab for patients (pts) with HER2+ advanced/metastatic breast cancer (a/mBC). Pts had a median treatment duration of 21.7 months (mo) with T-DXd + P. Safety was consistent with the known profiles of each treatment. These results led to US approval in Dec 2025. Here, we report an exploratory analysis of efficacy and safety outcomes by pts' best confirmed response to T-DXd + P. **Methods:** Pts had no prior systemic therapy for a/mBC (1 line of endocrine therapy was allowed). Endpoints included PFS and duration of response (DOR), both by blinded independent central review per RECIST 1.1, and safety. Best response subgroups included CR, partial response (PR), and stable disease / progressive disease (SD/PD). **Results:** Of 377 evaluable pts assigned to T-DXd + P, 58 (15.4%) had a CR, 268 (71.1%) had a PR, and 51 (13.5%) had SD/PD at interim data cutoff (Feb 26, 2025). Median time to PR was 1.5 mo (95% CI 1.4, 1.5), and median time to CR was 8.4 mo (95% CI 5.6, 11.1). Additionally, median time to achieve maximum tumor reduction (nadir) in the overall population (n=383) was ~11 mo (~16 cycles). Pts with a CR or PR had favorable PFS (see Table) and a longer median treatment duration (CR, 28.0 mo [range 4.8–44.5]; PR, 22.2 mo [range 2.8–42.7]) vs those with SD/PD (4.4 mo [range 0.3–37.2]). Exposure-adjusted incidence rates (EAIRs) of drug-related Grade ≥3 adverse events (AEs) were 0.30, 0.30, and 0.57 per pt-year, respectively. EAIRs of any AEs leading to discontinuation were 0.14, 0.11, and 0.16 per pt-year. Rates of adjudicated drug-related interstitial lung disease (ILD)/pneumonitis by CR, PR, or SD/PD were similar: 12.1% (n=7, all Grade 1/2), 11.9% (n=32, all Grade 1/2), and 12.2% (n=6, two Grade 5), respectively. Pts with a CR had a longer median time to first onset of ILD/pneumonitis (484 days [d] [range 84–967]) than those with a PR (227 d [17–1028]) or SD/PD (99 d [37–211]). **Conclusions:** In this exploratory analysis of DESTINY-Breast09, achieving a durable CR or PR was associated with favorable PFS outcomes and prolonged treatment duration. Complete response or maximum tumor reduction (nadir) was achieved with sustained T-DXd + P treatment. Safety findings were consistent with previously reported profiles of T-DXd and P. Clinical trial information: NCT04784715. Research Sponsor: AstraZeneca in collaboration with Daiichi Sankyo.

	CR (n=58)	PR (n=268)	SD/PD (n=51)
Median DOR, mo (95% CI)*	NC	39.2 (34.8, NC)	–
Median PFS, mo (95% CI)*	NC	40.7 (36.0, NC)	13.0 (4.0, 25.7)
6-mo PFS rate, % (95% CI)	100 (100, 100)	97.7 (95.0, 99.0)	57.2 (41.2, 70.4)
12-mo PFS rate, % (95% CI)	94.8 (84.8, 98.3)	89.8 (85.4, 92.9)	51.9 (35.9, 65.7)
24-mo PFS rate, % (95% CI)	85.1 (72.2, 92.3)	72.9 (66.6, 78.2)	35.5 (21.1, 50.2)

*Calculated by Kaplan-Meier technique. NC, not calculable.

Identifying patients with human epidermal growth factor receptor 2 (HER2)–low and –ultralow breast cancer (BC): Use of digital, artificial intelligence (AI)–based computational algorithms to assist HER2 scoring by pathologists.

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Background: Trastuzumab deruxtecan is approved in HER2–low (IHC 1+ or 2+/ISH negative) or –ultralow (IHC 0 with membrane staining in $\leq 10\%$ of tumor cells) metastatic BC per DESTINY–Breast04 and –06 trials. Manual HER2 IHC scoring can be time–consuming and subjective. This retrospective, real–world study assessed manual scoring (ground truth) vs standalone AI–computational pathology–assisted (CPa) tools for scoring. **Methods:** Whole slide images (WSIs; N = 600, scanned with Aperio AT2) of BC samples stained with PATHWAY HER2 (4B5) assay, originally scored as HER2 IHC 0 (n = 400) or 1+ (n = 200), were rescored by 3 pathologists and using 4 CPa/AI tools in development as either IHC 0 absent membrane staining, 0 with membrane staining in $\leq 10\%$ of cells, 1+, or 2+. Using 2023 ASCO/CAP guidelines, each pathologist performed 2 blinded readings per WSI; a reconciled score was used if the 2 readings differed. Manual consensus required $\geq 2/3$ agreement. Concordance between pathologist manual consensus vs standalone CPa scoring was measured by positive and negative percentage agreement (PPA; NPA), overall percentage agreement (OPA), and Cohen κ , with review time recorded. **Results:** Of 600 WSIs, 586 (97.7%) had manual consensus. CPa tools were faster (Table) than manual scoring (manual median review time: 7.0 min; range, 3.0–11.5). PPA was high ($\geq 92.5\%$) between manual consensus scoring and CPa tools; NPA across the tools was 79.1%, 68.9%, 67.4%, and 23.1%. Overall concordance varied across CPa tools; OPA ranged from 48.5% to 75.4% and Cohen κ from 0.26 to 0.61. **Conclusions:** Integrating CPa/AI tools as decision support aids for pathologists may reduce pathologist review time and augment pathologist inter–observer reproducibility, especially in HER2–ultralow identification. Refinement of CPa/AI algorithms in development may improve scoring to an even greater extent. **Research Sponsor:** This study was sponsored and led by AstraZeneca.

DP tool (N = 586 ^a)	Review time, median (range), min	PPA, ^{b,c} % (95% CI)	NPA, ^{b,d} % (95% CI)	OPA, ^{b,e} % (95% CI)	Cohen κ ^e (95% CI)
RV73X	2.7 (0.3–56.8)	94.9 (92.5–96.7)	79.1 (70.6–85.7)	75.4 (71.7–78.9)	0.61 (0.56–0.66)
MQ52G	0.7 (0.1–8.5)	93.4 (90.9–95.4)	68.9 (60.5–76.2)	73.0 (69.3–76.6)	0.57 (0.52–0.63)
KL84Q	3.1 (0.5–84.4)	92.5 (89.8–94.6)	67.4 (59.1–74.8)	69.5 (65.6–73.2)	0.54 (0.48–0.59)
ZX19P	2.5 ^f (Not available)	99.1 (97.6–99.6)	23.1 (16.4–31.5)	48.5 (44.4–52.6)	0.26 (0.22–0.31)

^aPrimary and metastatic samples from biopsies, effusions, fine needle aspirations, and surgical resection; due to the inbuilt pre-QC module, a few WSI outputs were not processed by RV73X and ZX19P.

^bRounded to 1 decimal.

^cAgreement for consensus-positive cases (IHC 0 with membrane staining, 1+, or 2+).

^dAgreement for consensus-negative cases (IHC 0 absent membrane staining).

^eAgreement across all IHC scores.

^fMean review time; median not available.

Biology-informed predictive modeling and resistance monitoring in trastuzumab deruxtecan–treated metastatic breast cancer.

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Background: The antibody–drug conjugate (ADC), trastuzumab deruxtecan (T-DXd), produces meaningful responses in metastatic breast cancer (mBC), yet current biomarkers inadequately identify likely responders or elucidate resistance mechanisms. We developed a biology-informed survival model to predict T-DXd benefit in real-world data, assess treatment specificity, and characterize resistance evolution at time of progression. **Methods:** We analyzed RNA-seq and clinical outcomes from 150 de-identified T-DXd–treated mBC patients in the Tempus real-world multimodal database. Baseline expression profiles were embedded into biology-structured biomodules using a large molecular foundation model trained on over 1-million transcriptomes, capturing processes relevant to ADC activity: DNA damage response (DDR), intracellular trafficking, cellular stress adaptation, and tumor microenvironment signaling. These biomodules informed a survival model trained to predict T-DXd–specific clinical benefit. Predictive specificity was evaluated in a matched cohort of T-DXd–eligible mBC patients treated with taxane-based chemotherapy and HER2–targeting therapy. Longitudinal tumor profiling from 15 patients with progressive disease were analyzed to monitor resistance evolution. **Results:** The survival model predicted and identified biologically distinct benefit groups within the T-DXd cohort, with minimal separation observed in a control standard-of-care cohort, confirming treatment-specific predictive value (HR 2.22 [95% CI 1.14–4.35], $p = 0.017$). Predicted-benefit patients had longer rwTTNT (median=345 vs 245 days), and no prognostic signal appeared in control cohorts (C-index = 0.51), suggesting predictive specificity. Longitudinal analysis of progressed patients revealed reproducible biological shifts at progression, including attenuation of programs associated with effective ADC engagement and upregulation of adaptive stress-response pathways. These molecular transitions correlated with clinical deterioration and earlier transition to subsequent therapy. **Conclusions:** This study delineates the biology associated with durable T-DXd benefit and captures resistance evolution at progression in real-world patients. These findings highlight opportunities to refine patient selection and identify therapeutically actionable biology driving acquired resistance to T-DXd in the mBC setting. Research Sponsor: None.

Organ- and histology-specific molecular and immune landscape of metastatic breast cancer.

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Background: Invasive lobular carcinoma (ILC) is a distinct breast cancer (BC) subtype with dissemination patterns differing from invasive breast carcinoma of no special type (IBC-NST). While genomic differences between ILC and IBC-NST have been described, the extent to which molecular and immune profiles vary by metastatic organ and histology is poorly characterized.

Methods: We conducted a retrospective analysis to evaluate organ- and histology-specific molecular features of metastatic BC (mBC). Patients with metastatic IBC-NST or pure ILC underwent NGS (592, NextSeq; WES/WTS, NovaSeq; Caris Life Sciences). Tumor mutational burden (high ≥ 10 mut/Mb), PD-L1 expression (22C3), and immune cell fractions (RNAseq deconvolution, quanTIseq) were assessed. Analyses were restricted to sites with ≥ 10 biopsies per histology. Comparisons used chi-square or Mann-Whitney U tests with multiple testing correction ($q < 0.05$). **Results:** A total of 2645 mBC biopsies (605 ILC; 2040 IBC-NST) were analyzed (Table). In ILC, *ERBB2* mut frequency differed by metastatic site ($q < 0.01$), with higher prevalence in liver (32.7%) and lower in gastrointestinal (GI) lesions (3.7%). In IBC-NST, *ESR1* and *GATA3* mut and *FGFR1* amplification were enriched in liver metastases, whereas PD-L1 expression was highest in skin (20.7%) and lowest in liver (5.0%). No organ-specific differences were observed for *PIK3CA*, *AKT*, *PTEN*, *BRCA1/2* or *RB1*. Across metastatic sites, both ILC and IBC-NST showed differences in B cells, macrophages (M1/M2), neutrophils, NK cells, dendritic cells, CD8+ T cells, and Tregs (all $q < 0.05$); CD4+ T-cell differences were observed only in IBC-NST ($q = 0.002$). In organ-specific ILC vs IBC-NST comparisons, *CDH1* mut were more frequent in ILC across sites, along with higher *PIK3CA* mut in skin (ILC 51.3% vs IBC-NST 34.4%) and higher *ERBB2* mut in liver (32.7% vs 3.3%), whereas a higher *TP53* mut frequency was observed in IBC-NST in skin (28.5% vs 52.3%) and lymph nodes (LND) (23.5% vs 55.5%) (all $q < 0.01$). **Conclusions:** mBC exhibits marked organ-specific molecular and immune heterogeneity that differs by histology. These findings support histology- and site-aware interpretation of metastatic biopsies and may inform biomarker assessment and treatment decisions in advanced disease. Research Sponsor: None.

	BC-NST								ILC									
	Skin	LND	Bone	Breast	Liver	Perit.	CNS	q-value	Skin	LND	Bone	Breast	GI	Liver	GYN	Perit.	CNS	q-value
N (specimens)	785	401	109	361	220	15	44	-	172	84	62	56	56	54	43	37	11	-
<i>ERBB2</i> mut (%)	3.2	3.1	3.2	2.3	3.3	7.1	2.5	1.0	7.1	7.4	16.4	15.4	3.7	32.7	2.4	5.7	11.1	<0.01
<i>ESR1</i> mut (%)	9.4	5.2	8.3	16.0	28.2	7.1	2.4	0.0	7.8	7.2	8.9	9.8	16.7	26.0	4.9	20.0	0.0	0.9
<i>FGFR1</i> amp (%)	10.1	6.6	5.6	12.8	16.5	0.0	9.7	0.02	4.4	3.4	6.7	6.1	2.4	5.6	7.7	18.5	0.0	1.0
IHC-PD-L1 (%)	20.7	-	5.3	16.0	5.0	11.1	10.3	0.02	8.9	-	5.0	5.7	6.1	0.0	0.0	0.0	14.3	1.0
TMB-High (%)	10.7	10.1	8.8	8.8	8.5	14.3	21.4	0.8	27.6	11.0	19.6	28.0	11.3	19.6	9.8	32.4	22.2	0.8

Perit: peritoneum; CNS: central nervous system; GYN: genital tract.

Using ML to predict rapid progression for patients (pts) with HR+/HER2- metastatic breast cancer (mBC) treated with frontline (1L) CDK 4/6 inhibitors (CDK 4/6i).

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Background: CDK4/6i ± aromatase inhibitors is a preferred tx for pts with HR+/HER2- mBC in the 1L setting. While a subset of pts experience rapid progression on standard tx, addressing the unmet need remains challenging due to difficult pt identification. While multimodal data have predicted fast progressors in prior work, routinely collected electronic health record (EHR) variables may be more practical for clinical trial design and enrichment use cases. Thus, we performed a feasibility assessment to determine if EHR data can adequately predict fast progressors. **Methods:** Models were trained on pts in the Flatiron Health Research Database with 1L CDK4/6i start on February 3, 2015, or later and an event ≤12 months (mos) or follow-up ≥12 mos after tx start. Fast progression was defined as real-world progression or death ≤12 mos after tx start. Baseline demographics, clinical characteristics, and laboratory/vital signs were used to train a logistic regression (LR) and a full-feature XGBoost (XGB) model. A feature-reduced XGB model was also developed by sequentially removing least important features until area under the curve (AUC) declined. Hyperparameters were optimized by grid search. Performance was evaluated via AUC, with feature importance assessed via LR coefficients and SHapley Additive exPlanations. Test-set analyses included rwPFS comparisons between predicted fast progressor (pFPs) and predicted non-fast progressors (pNFPs) using Kaplan-Meier methods. **Results:** Among 10,811 included pts, 3,782 were identified as fast progressors, split 80/20 for train/test datasets. The 3 models had comparable performance for predicting fast progression and effectively stratified pts into risk groups (Table). LR and XGB models used 48 and 76 features, respectively, while a feature-selected XGB model retained 30 features with minimal performance loss. Top LR predictors included advanced age, BRCA/ESR1/AKT positivity, and de novo stage IV disease. Important XGB features were consistent across models and emphasized continuous measures, including shorter time to metastatic diagnosis, greater metastatic burden, elevated AST and alkaline phosphatase, and bone-only metastases. **Conclusions:** While these models are not optimized as point-of-care clinical risk scores, their ability to identify high- and low-risk groups using scalable, routinely captured variables highlights their potential utility for clinical trial design, enrichment strategies, and cohort stratification. These findings establish a real-world benchmark and support the feasibility of practical, EHR-only approaches to rapid progression prediction. Research Sponsor: None.

Model	AUC	pFP rwPFS, median (95% CI), mos	pNFP rwPFS, median (95% CI) mos
LR	0.67	10.8 (9.8–12.4)	25.6 (23.3–27.9)
XGB	0.67	10.8 (9.8–12.4)	25.4 (22.9–27.3)
XGB (feature selected)	0.66	11.3 (10.2–13.2)	25.6 (23.0–27.9)

Development and evaluation of a novel digital pathology image analysis pipeline for prediction of clinical outcomes with the TROP2-directed antibody-drug conjugate (ADC) sacituzumab tirumotecan (sac-TMT) in triple-negative breast cancer (TNBC).

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Background: Digital pathology (DP), including artificial intelligence (AI)-based image analysis methods, enables IHC biomarker assessment on a continuous scale, potentially improving precision and accuracy versus conventional IHC scoring. DP may also capture features relevant to ADC response that traditional methods miss. As proof of concept, we developed and evaluated an AI-assisted DP image analysis pipeline to explore the association between target antigen expression and clinical outcomes of sac-TMT, a TROP2-directed ADC with a unique bifunctional linker, in TNBC. **Methods:** We analyzed whole-slide images of IHC-stained tumor samples from participants with TNBC enrolled in the phase 1/2 MK-2870-001 study (NCT04152499) evaluating sac-TMT in pretreated advanced solid tumors. We established a set of prespecified human-interpretable features (HIFs), including IHC signal intensity, sub-cellular localization, and spatial patterns of cell and signal distribution. To mitigate overfitting, we prioritized a subset of 35 HIFs based on correlation structure and biological hypotheses, and in a blinded fashion, assessed their association with clinical outcomes (BOR; PFS) in a development cohort (DC) (n = 58). After unblinding clinical outcome data, additional HIFs and a multivariate model trained to predict clinical outcomes in the DC were prioritized for validation. Both sets of HIFs (identified from blinded and unblinded analyses) were assessed for their relationship to clinical outcomes in an independent validation cohort (IVC) from the same study (n = 34). In both cohorts, DP HIFs were compared with conventional TROP2 H-scores (on paired slides) for prediction of clinical outcome using the area under the receiver operating characteristic curve (AUROC) and Harrell C-index. **Results:** The blinded approach identified a HIF that was positively associated with BOR (multiplicity-adjusted $P = 0.023$), with an AUROC higher than TROP2 H-scores (0.76 vs 0.70). After unblinding, 5 additional HIFs and a multivariate model were selected for their associations with BOR (AUROC, 0.70–0.80). In the IVC, the 6 prioritized HIFs and 1 multivariate model were associated with response to sac-TMT (AUROC, 0.60–0.69); each outperformed TROP2 H-scores with respect to association with BOR (H-score AUROC, 0.57) and demonstrated incrementally better association with PFS than TROP2 H-scores (Harrell C-index, 0.64–0.66 vs 0.62). **Conclusions:** In this proof-of-concept study, DP-derived HIFs were associated with response to sac-TMT in TNBC and showed incrementally better nominal performance than conventional TROP2 H-scores. While the sample size was small, data from this study suggest that DP-based image analysis can identify novel biomarkers of response to sac-TMT in TNBC. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Antibody-drug conjugate (ADC) after ADC: Predicting survival in patients with HER2-low metastatic breast cancer with lung metastasis using artificial intelligence (AI) and radiomics.

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Background: With the approval of multiple antibody drug conjugates (ADCs) for HER2-low metastatic breast cancer (MBC), defining which patients (pts) will benefit from an ADC after ADC approach is essential. No reliable biomarker exists to predict overall survival (OS) in the ADC after ADC setting. This study investigates whether AI informed radiomic texture features derived from CT scans prior to ADC therapy in pts with lung metastases who received both trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) are associated with OS in HER2-low MBC. **Methods:** A single-institution retrospective study was conducted including pts with HER2-low MBC treated with both T-DXd and SG at Winship Cancer Institute of Emory University between 2020 and 2024. Among 44 pts reviewed (median age, 55 years), 21 pts with evaluable lung lesions were included. Radiomic texture features characterizing tumor heterogeneity were extracted from baseline pre-treatment CT scans of lung metastases before ADC initiation. A least absolute shrinkage and selection operator Cox regression model was applied within a 50-fold cross-validation framework to identify prognostic features associated with OS. OS was defined as the interval from initiation of first ADC therapy to death from any cause and was censored at the date of last follow-up for patients who were alive. A radiomic risk score (RRS) was calculated as a linear combination of the selected features weighted by their corresponding coefficients. Pts were stratified into high- and low-risk groups based on the median RRS. Cox proportional hazards regression was used to evaluate associations with OS. **Results:** Among the total 44 pts, the median duration of response was 6.1 months for the first ADC and 2.7 months for the subsequent ADC. 59.1% received SG as ADC1. For the 21 pts with lung metastasis, mOS was 20.8 months (95% CI: 14.33–30.8). In univariable analysis, the RRS was significantly associated with OS (HR = 2.5, 95% CI: 1.3–4.8; P = 0.006). In multivariable analysis adjusting for clinicopathologic factors including race, ER status, number of prior lines of therapy before ADC treatment, and relapsed vs de novo metastatic disease, RRS remained the only variable independently associated with OS (HR = 2.6, 95% CI: 1.2–5.5; P = 0.01). **Conclusions:** These preliminary findings suggest that CT-derived radiomic features may serve as a non-invasive biomarker to identify pts at higher risk of poor OS in the ADC after ADC setting for HER2-low MBC, for whom we need better, novel therapeutics after resistance develops to initial ADC therapy. This radiomics approach has the potential to inform treatment sequencing and risk stratification. Future work will include prospective validation in a larger cohort which includes other sites of metastatic disease. Research Sponsor: None.

Cross-modality AI modeling of histopathology images to stratify outcomes among patients treated with hormonal or chemo-hormonal therapy in ER+/HER2– breast cancer.

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Background: Oncotype DX (ODX) is widely used to guide adjuvant treatment decisions in early-stage ER+/HER2– breast cancer. However, ODX provides limited stratification of residual metastatic risk within patients receiving hormonal therapy (HT) alone or hormonal therapy following chemotherapy (HT+CT). We developed a cross-modality AI approach that derives risk scores directly from routine H&E-stained whole-slide images (WSIs) to stratify metastatic outcomes among patients receiving standard adjuvant therapies. **Methods:** Using a cross-modality transfer learning framework, we first developed genomic biomarkers by mapping RNA-seq data to distant metastatic outcomes by integrating thousands of genes and signaling pathway activities in the publicly available ScanB dataset. Deep learning models were then trained to infer these biomarkers directly from WSI of breast tumors using the TCGA dataset. External validation was performed in an independent cohort of 287 early-stage ER+/HER2–, node-negative patients from MD Anderson Cancer Center. Among these, 147 patients with ODX<25 received HT alone, while 140 patients with ODX>25 were included, 121 of whom received HT+CT. Kaplan–Meier survival analysis, log–rank tests, and Cox proportional hazards models were used to evaluate outcome stratification within each treatment group. **Results:** Among patients treated with HT alone, AI score stratified metastatic outcomes (HR=2.75; $p < 0.01$), identifying patients who developed distant recurrence despite low ODX scores. Among patients treated with HT+CT, AI score also stratified outcomes (HR=3.94; $p < 0.03$), identifying patients who experienced metastasis despite combination therapy. Across treatment groups, AI score provided prognostic information beyond ODX and clinicopathologic variables. In multivariable analyses adjusting for ODX and clinical covariates, AI score remained independently associated with metastatic risk and demonstrated consistent stratification across clinically relevant subgroups. Validation of these findings in an expanded cohort is ongoing. **Conclusions:** This AI-based approach further stratifies outcomes among patients receiving HT or HT+CT as guided by ODX, directly from routine histopathology images in early-stage ER+/HER2– breast cancer. Thus, integration of AI-derived outcome stratification with ODX scores may improve individualized treatment decision-making and support consideration of alternative therapies. Research Sponsor: PATHOMIQ.

Integrating artificial intelligence to evaluate outcomes and disparities in young-onset breast cancer: A SEER-based retrospective cohort study.

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Background: Young-onset breast cancer (YOBC), defined as breast cancer diagnosed in women <40 years, is associated with aggressive tumor biology and affects patients differently depending on race, ethnicity, and socioeconomic status (SES). Traditional risk models may insufficiently predict disease severity and survival in this population. Artificial intelligence (AI) can integrate multidimensional clinical and demographic data to improve outcome prediction and identify high-risk subgroups. We evaluated AI-based prediction of advanced-stage disease and 5-year survival in a large U.S. cohort over two decades. **Methods:** We conducted a retrospective study using the SEER database, identifying women aged <40 years diagnosed with invasive breast cancer from 2000–2021. Variables included age, race, ethnicity, marital status, tumor stage, grade, receptor status, treatment, and county-level SES. A machine learning model was trained to predict advanced-stage disease (stage III–IV) and 5-year overall survival. Model performance was compared with multivariable logistic regression using area under the receiver operating characteristic curve (AUC). We also explored differences by race, ethnicity, and SES to understand disparities. **Results:** Our cohort included 97,462 women—38.9 percent non-Hispanic White, 26.7 percent non-Hispanic Black, 22.3 percent Hispanic, 11.1 percent Asian/Pacific Islander, and 1 percent American Indian/Alaska Native. Overall, 33 percent presented with advanced-stage disease, with higher rates among non-Hispanic Black (42 percent) and Hispanic (37 percent) patients compared with non-Hispanic White patients (26 percent, $p<0.001$). Women living in the lowest SES areas were 30 percent more likely to have advanced-stage disease than those in the highest SES areas. The AI model predicted advanced-stage disease (AUC 0.81) and 5-year survival (AUC 0.84) better than traditional regression (AUC 0.67 and 0.71, respectively). Importantly, 23 percent of high-risk patients identified by AI would have been missed by conventional criteria. Survival disparities persisted: 5-year survival was 77 percent for non-Hispanic Black women versus 89 percent for non-Hispanic White women, and 75 percent for women in the lowest SES areas versus 91 percent in the highest. The AI model's predictions were consistent across all subgroups. **Conclusions:** As per the study AI-based models improved prediction of advanced-stage disease and survival while highlighting persistent racial, ethnic and socioeconomic disparities. These findings suggest AI-driven risk assessment can help identify high-risk young women and support equity-focused interventions to improve outcomes in YOBC. Research Sponsor: None.

Association between HER family expression and clinical outcomes with trastuzumab deruxtecan (T-DXd) in patients with hormone receptor–positive/HER2–negative (HR+/HER2–) metastatic breast cancer (mBC).

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Background: T-DXd improves outcomes in HR+/HER2– mBC, yet response remains heterogeneous. Treatment selection is based on HER2 IHC. Preclinical models suggest signaling from HER family dimerization partners like EGFR drive resistance; specifically, *EGFR* overexpression impairs T-DXd internalization by favoring EGFR/HER2 heterodimerization. Because clinical data linking HER dimerization partners to T-DXd outcomes are limited, investigation is warranted to understand how expression of these partners may serve as predictive biomarkers.

Methods: The Tempus Lens Platform was used to identify and analyze a cohort of patients (pts) with HR+/HER2– mBC treated with T-DXd (n = 224) and sacituzumab govitecan (SG) (n = 81, comparator) who underwent RNA (Tempus xR) and DNA (Tempus xT) sequencing within one year of treatment initiation. HER family gene expression (*EGFR/ERBB1*, *ERBB2/3/4*) was quantified as transcripts per million (TPM) and reported as $\log_2(\text{TPM}+1)$. High vs low groups were defined using median expression. Median real-world time to next treatment (rwTTNT) with T-DXd and real-world overall survival (rwOS) were calculated using Kaplan–Meier curves and compared using log-rank tests. Hazard ratios (HR) were calculated using Cox proportional hazards models. **Results:** The cohort (n = 305) had a median age of 60; 83% of pts' race was reported as White, 9.6% Black or African American, 2.7% Asian, 7.6% Hispanic or Latino, and 4.3% unknown. Median HER family gene expression values were: *ERBB1* (*EGFR*): 3.92; *ERBB2* 7.75; *ERBB3* 7.65; *ERBB4* 4.72. *EGFR* RNA expression was negatively correlated with *ERBB2/3/4* ($p < 0.0001$). *ERBB2/3/4* RNA expression was positively correlated with one another ($p < 0.0001$). Among pts treated with T-DXd, the *EGFR*-high group had shorter median rwTTNT (7.76 vs 13.25 months; HR = 2.17 95% CI 1.42–3.34, $p < 0.001$) and rwOS (13.71 vs 22.55 months, HR = 2.21; 95% CI 1.50–3.24, $p < 0.001$) compared to the *EGFR*-low group. In contrast, increased RNA expression of other HER family members was not associated with a significant difference in rwTTNT or rwOS. Among pts treated with SG, the *EGFR*-high group did not have significantly different rwTTNT (median 4.34 vs 5.56 months; HR = 1.30 95% CI 0.72–2.36, $p = 0.4$) or rwOS (median 14.47 vs 11.28 months; HR = 0.86, 95% CI 0.47–1.55, $p = 0.6$) compared with the *EGFR*-low group. **Conclusions:** Among pts with HR+/HER2– mBC treated with T-DXd, elevated *EGFR*, but not *ERBB2/3/4*, RNA expression was associated with worse outcomes. *EGFR* overexpression did not modulate outcomes in pts treated with SG, highlighting a potential differential impact based on antibody target rather than payload. Further research is needed to confirm the utility of pre-treatment *EGFR* expression as a predictive biomarker for T-DXd treatment. Research Sponsor: None.

Concordance between circulating tumor DNA and tissue biopsy in patients with newly diagnosed recurrent breast cancer.

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Background: Accurate determination of tumor origin and molecular subtype are recommended for patients with suspected recurrent breast cancer (BC). Circulating tumor DNA (ctDNA) provides a non-invasive alternative to tissue biopsy that offers identification of molecular tumor type (MTT) and molecular breast cancer subtype (MBS). This study aimed to assess the concordance between ctDNA and tissue biopsy in participants with suspected distant BC recurrence. **Methods:** This cross-sectional study evaluated patients with a previous history of primary BC who presented with suspected distant BC recurrence at least six months after initial BC diagnosis and underwent both tissue and liquid biopsy at enrollment. Blood samples were collected within 30 days before, or within 7–28 days after tissue biopsy and before any systemic or radiation treatment. Objectives were to assess concordance between tissue biopsy of the suspicious distant recurrent sites and liquid biopsy MTT and MBS (hormone receptor (HR)+/HER2–, HER2+ and triple negative BC (TNBC)). Patient blood samples were analyzed using the Guardant360 Liquid assay, reporting methylation-based prediction of MTT and MBS for samples predicted to be of BC origin. **Results:** A total of 120 patients (119 female, 1 male, median age 66 years) underwent biopsy a median 6.5 years after primary BC diagnosis. ctDNA was detected in 88% (105/120) subjects. Of these, 92% (97/105) yielded an evaluable MTT result with a high confidence score, with results as follows: Agreement between tissue pathology and ctDNA MTT was observed in 95 of 96 cases with diagnostic tissue pathology, including 99% agreement for breast cancer (88/89), and 100% agreement in lung adenocarcinoma (4/4), gynecological/ovarian (1/1), liver (1/1) and biliary (1/1). The non-diagnostic tissue biopsy was treated as BC by the oncologist. Among the 89 cases predicted BC by ctDNA, 88% (78/89) were evaluable for MBS while 2 did not have pathologic subtype available. In these 76 patients, positive predictive value for MBS predictions of HR+/HER2–, HER2+ and TNBC were 47/55 (85%), 6/11 (55%) and 8/10 (80%), respectively. Pathological tissue subtype of discordant HR+/HER2– cases were HER2+ (n = 7), TNBC (n = 1); of HER2+ cases were HR+/HER2– (n = 2), TNBC (n = 3) and of TNBC were HR+/HER2– (n = 2). **Conclusions:** Liquid biopsy demonstrated high agreement with tissue pathology for MTT classification, including identification of non-breast primary tumors. Differences in MBS classification between the two modalities warrant further investigation to assess potential contributing factors, including tumor heterogeneity. Research Sponsor: London Health Sciences Foundation; Academic Medical Organization of Southwestern Ontario (AMOSO); Medical Oncology Research Fund – London Health Sciences Centre; London Health Sciences Centre; Lawson Health Research Institute – Internal Research fund; Breast Cancer Canada; Epic Sciences (In kind); Guardant Health (In kind).

***TP53* status and licensing complex/IFN γ transcriptional profiles to stratify endocrine-related outcomes with CDK4/6i exposure in 10,833 real-world ER+/HER2- breast cancers and a treatment-naïve subset.**

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Background: Endocrine therapy (ET) durability for ER+/HER2- breast cancer (BC) with CDK4/6 inhibitor (CDK4/6i) exposure is vastly heterogeneous. Aberrant activation of CDK4/6-Rb axis is mechanistically linked to DNA replication origin licensing programs, and IFN γ -mediated signaling has been observed at onset of CDK4/6i resistance (PMID 33536276). We previously reported licensing complex (LC) mRNA to be predictive of ET benefit in primary ER+/HER2- BC (SABCS24-P1-03-20). Here we assessed these findings in a large, real-world cohort of primary and metastatic ET $\pm$ CDK4/6i-treated tumors. **Methods:** ER+/HER2- BC biopsies (N=10833 all-comers and a treatment-naïve subset of N=1960) with DNA- and RNA-seq profiling from Caris Life Sciences were reviewed. LC score was calculated as a mean z-score across 14 LC genes; IFN γ score of PMID 28650338 was used. Groupings of Q1 (low) and Q4 (high) LC and IFN γ score quartiles were compared (i.e., Q1/Q1, Q4/Q4, Q1/Q4, Q4/Q1). Endpoints inferred from claims data were time on 1st ET (To1) and cumulative time on ET (start of 1st ET to end of last ET; ToT). Logrank p-values and HRs were derived from Cox proportional hazard models. Immune microenvironment (TME) proportions were estimated via quanTIseq deconvolution. Corrected q-values were calculated for quanTIseq and genomic analyses. **Results:** For all-comers, LC score Q4 vs Q1 predicted shorter ToT for ET with or without CDK4/6i exposure (HR 1.27 [p<0.0001]; 1.13 [p=0.0019]). LC-Q1~IFN γ -Q1 tumors demonstrated longer ToT (ET HR 1.76 [p=0.0015]; ET+CDK4/6i HR 1.32 [p=0.022]) relative to Q4/Q4 when *TP53* was not mutated (^{mut}). In the treatment-naïve subset, the distribution of LC and IFN γ scores, PAM50 luminal subtype, and *TP53*^{mut} appeared similar to all-comers. IFN γ -Q4 vs Q1 predicted shorter To1 with CDK4/6i exposure (14.4 vs 19.9 months, HR 1.28 [p=0.0074]). LC/IFN γ profiles significantly stratified both To1 and ToT only with CDK4/6i exposure. Relative to Q1/Q1, all other quartile groups had shorter To1 (HR 1.53 [p=0.071], 1.88*, and 2.15* [*p<0.01]) and shorter ToT (HR 1.89, 2.33, and 1.98; all p<0.05). Relative to Q1/Q1, the Q4/Q4 cohort was enriched for *TP53*^{mut} (44.2% vs 12.5% [q=0.002]). In *TP53*^{WT} tumors, Q4~Q4 trended toward shorter ToT than Q1~Q1 (42.7 vs 26.5 months, HR 1.67 [p=0.075]). Finally, LC-Q4/IFN γ -Q4 vs Q1/Q1 tumors exhibited a more inflamed TME with higher M2 macrophages, myeloid DCs, and Tregs (all q $\leq$ 0.01). **Conclusions:** Real-world validation confirms the LC and IFN γ -stimulated transcriptional state jointly stratify outcomes in the CDK4/6i-treated setting, predicting shorter time on ET. Though enriched for *TP53*^{mut}, convergence of LC/IFN γ may hold potential predictive value in *TP53*^{WT} disease. The LC-Q1/IFN γ -Q1 CDK4/6i response predictor in the *TP53*^{WT} setting remains to be validated prospectively. Research Sponsor: None.

Rapid digital patient-derived organoid testing for guiding therapy in patients with metastatic breast cancer receiving antibody drug conjugates (ADCs).

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Background: MBC remains incurable despite recent incorporation of ADCs. The optimal sequencing of FDA-approved ADCs such as trastuzumab deruxtecan (T-DXd) or sacituzumab govitecan (SG) are lacking and real-world data have shown cross resistance between the ADCs. The current study aims to develop a clinical diagnostic assay to guide optimal treatment for patients with MBC using digital patient organoid (DPO) in patients with MBC receiving or progressed on ADCs for a precision tool to guide therapy in post-ADC resistance setting.

Methods: An institutional IRB was established for prospective collection of fresh tumor biopsies in patients with MBC undergoing ADC therapy. DPO drug sensitivity tests were conducted and analyzed for association with clinical outcome using progression free survival (PFS). DPO tests include ADCs (T-DXd, SG, Dato-DXd) or single agent chemo dosing experiments to determine drug sensitivities (AUC values calculated from CTG readouts) for downstream correlation analyses. **Results:** Between 09/2024–01/2026, 41 fresh tumor tissues were collected and processed. 22 samples had sufficient viable cells to pass QC for DPO establishment and were successfully assayed and 12 failed QC, giving a DPO establishment success rate of 64.71%. DPO success rates varies by breast cancer subtypes: 100% in HER2+, 73% in TNBC and 56% in HR+HER2- BC. and sites of metastasis. Sites of metastasis (met) also impacted DPO success rates: lymph node 0%, liver met 33%, skin met 60%, breast/ascites 100%. Organoids typically established and expanded within 7–14 days post-biopsy. The DPO drug assays were conducted for ADCs, payloads, and chemotherapy agents testing. Analysis revealed that prior clinical exposure and progression on an ADC correlated with reduced DPO sensitivity to the same agent, consistent with acquired resistance. The platform was capable of delineating between target-versus payload-based resistance. Notably, DPOs from heavily pretreated patients were often resistant to both ADCs but remained responsive to alternative agents, highlighting potential therapeutic opportunities. **Conclusions:** The DPO platform shows promise in predicting treatment responses and differentiating resistance mechanisms to ADCs in MBC. This approach provides a foundation for rational treatment selection in patients with MBC with prior ADC resistance. Research Sponsor: None.

Real-world outcomes and tumor gene expression analysis of sacituzumab govitecan (SG)- and trastuzumab deruxtecan (T-DXd)-treated metastatic breast cancer (MBC).

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Background: While the antibody-drug conjugates (ADCs) SG and T-DXd have transformed MBC care, predictive biomarkers of ADC response are lacking. This retrospective study evaluates real-world outcomes of MBC patients treated with SG or T-DXd and explores potential genomic and transcriptomic correlates of response. **Methods:** MBC patients treated with SG or T-DXd at BC Cancer who underwent tumor whole genome and transcriptome sequencing (WGTS) between January 2020 - May 2025 were included. Biopsy for WGTS was obtained either before (ADC-naïve) or after ADC exposure (ADC-exposed). Progression free survival (PFS) was clinically evaluated and assessed using Kaplan-Meier analysis. Treatment response was classified into 2 groups using PFS benchmarks from ASCENT (Bardia et al 2021, SG: expected ≤ 6 months (mo), favorable > 6 mo) and DESTINY-Breast04 (Modi et al 2022, T-DXd: expected ≤ 12 mo, favorable > 12 mo). RNA-seq data were assessed with DESeq2 differential expression and gene pathway enrichment analyses. Immune cell deconvolution was performed using CIBERSORT, with group comparisons by Wilcoxon rank-sum tests. **Results:** Forty-three patients met eligibility for inclusion (17 SG, 24 T-DXd, 2 treated with both agents). Median PFS was 4.0 mo (95% CI 2.0–6.0) for those treated with SG and 7.4 mo (95% CI 4.6–10.7) for those treated with T-DXd. Among T-DXd-naïve patients, *ESR1* expression was higher in those with poor ADC response (69.8 vs 7.8 transcripts per million, $p = 0.049$). Oxidative phosphorylation gene cluster expression was reduced in T-DXd-exposed vs T-DXd-naïve patients (normalized enrichment score -1.9 , $p = 0.005$). ADC target expression did not differ by response in either treatment cohort (*TACSTD2* $p = 0.86$, *ERBB2* $p = 0.67$). Whole genome sequencing identified 12 tumors with *FGFR1* amplifications, all with poor ADC response, and demonstrated homologous recombination deficiency in half of those with favorable SG response. While not statistically significant, the post-ADC tumor microenvironment of favorable responders trended toward enrichment with naïve B-cells and T-cell infiltrate in T-DXd-treated patients ($p = 0.28, 0.33$) and both monocytes and NK cells in SG-treated patients ($p = 0.1, 0.27$). **Conclusions:** This study highlights the heterogeneity of outcomes among SG- and T-DXd-treated MBC patients and identifies potential predictive and prognostic biomarkers warranting exploration in prospective trials of first-line ADC (NCT07299409) and ADC sequencing (NCT06665178). Research Sponsor: BC Cancer Foundation; Marathon of Hope Cancer Centres Network.

	SG-treated patients (n=19)	T-DXd-treated patients (n=26)
HR status:		
Positive	1	22
Negative	18	4
HER2 status:		
Negative/Ultralow	8	11
Low	10	11
Positive	1	4
Timing of biopsy for WGTS:		
Pre-ADC	12	15
Post-ADC	7	11
Favorable ADC response	4	3
Median lines of therapy for MBC pre-ADC (range)	2 (0-6)	4 (0-8)
Median lines of endocrine therapy for HR + MBC pre-ADC (range)	0 (N/A)	1 (0-5)

Dominant chromosomal abnormalities in breast cancer metastasis to CNS as compared with systemic metastasis demonstrated by liquid biopsy.

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Background: Breast cancer (BrC) central nervous system (CNS) metastases are believed to be biologically and therapeutically distinct from systemic metastases. Detecting BrC metastasis to CNS using liquid biopsy (LBx) of the CSF is emerging as a reliable approach not only for confirming metastasis, but also for defining the molecular and biological characteristics of this metastasis. We compared the findings of LBx performed on CSF with those obtained by peripheral blood (PB) LBx. **Methods:** LBx was performed by next generation sequencing (NGS) of cell-free DNA and RNA (cfDNA/cfRNA) in PB plasma or CSF as well as RNA sequencing of CSF cell pellet. RNA sequencing was performed using a panel of almost 1600 genes and DNA sequencing using 302 genes. **Results:** Of the 339 tested CSF samples, 29 (8.5%) were negative for any mutation and 57 (16.8%) showed low level mutations characteristic of CHIP (clonal hematopoiesis of indeterminate potential). However, two samples showed only chromosomal gain or loss without mutations and 2 showed chromosomal abnormalities with CHIP but no cancer-related mutations. In contrast, 19 of 279 PB samples (6.8%) were negative for any abnormality and 33 (11.8%) had CHIP. One sample of the PB cases showed chromosomal abnormalities without cancer-related somatic mutations. Of the 253 positive CSF samples 207 (82.1%) showed chromosomal structural abnormalities while only 71 of the 227 positive PB samples (31.2%) showed chromosomal structural gain or loss ($P < 0.0001$). The most common chromosomal abnormality was 1q gain, detected in 42.8% of CSF and in 18.5% of PB samples. 17p (TP53) deletion was detected in 25.4% of CSF and in 6.6% of PB samples. 10q (PTEN) deletion was detected in 9.4% of CSF and 3.1% of PB samples. ERBB2 gene amplification was detected in 6.3% of CSF cases and in 1.3% of PB cases. In CSF positive samples, the most mutated genes were TP53, KMT2C, PIK3CA, DNMT3A, CDH1, NF1, PTEN and ESR1, detected in 37.3%, 29%, 27.8%, 10.3%, 8.7%, 8.3%, 7.9%, and 7.5%, respectively. These genes were detected in positive PB samples at 51%, 35.2%, 42.7%, 81.1%, 11.8%, 8.8%, 9.6%, and 20.2%, respectively. Variant allele frequency in all mutations was significantly higher in CSF ($P = 0.0001$) than PB. Germline mutations in BRCA1/2 were detected in 5.1% of CSF and in 4.8% of PB. Ten patients had their PB and CSF tested concurrently. Two were positive by CSF and negative by PB and one was positive by PB but negative by CSF. The rest had concordant results. **Conclusions:** BrC with CNS involvement represents a distinct subgroup whose biological characteristics may best be defined using LBx to evaluate chromosomal abnormalities and gene gain/loss. As such, optimal characterization and qualification minimal residual disease in patients with BrC with CNS involvement warrants integration of CSF LBx-defined genetic abnormalities as it may permit earlier and targeted interventions. Research Sponsor: None.

Prognostic impact of *PIK3CA* amplifications and co-occurring mutations detected through circulating tumor DNA (ctDNA) in metastatic breast cancer (MBC).

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Background: Activating *PIK3CA* mutations are established oncogenic drivers and predictive biomarkers in MBC. In contrast, *PIK3CA* amplifications are rare, poorly characterized, and of unclear clinical significance. Tissue-based studies report a prevalence of 1–7%, but their detection and relevance in ctDNA are largely unexplored. Moreover, whether amplifications interact with co-occurring mutations to define a distinct high-risk subset is unknown. We therefore aimed to characterize the impact of *PIK3CA* amplifications detected in ctDNA through a multi-institutional cohort of patients (pts) with MBC. **Methods:** This retrospective study analyzed a multi-institutional cohort of 1579 pts with MBC and baseline ctDNA testing with the Guardant360 NGS panel within a large academic consortium (PMAC). Hormone Receptor positivity (HR+) and HER2 status were defined based on the most recent biopsy. Associations between SNVs, CNVs, and clinical characteristics were assessed using multivariable logistic regression. The impact of prognosis, adjusted for the number of prior treatment lines, was evaluated through Cox regression for overall survival (OS), defined from time of baseline ctDNA collection. **Results:** Among 1,579 pts, 1,121 (71%) were HR+/HER2–, 214 (13.5%) HER2+, and 244 (15.5%) had triple-negative breast cancer (TNBC). *PIK3CA* CNVs were detected in 7.7% of pts, and 44.7% harbored a concomitant *PIK3CA* SNVs. *PIK3CA* CNVs were significantly enriched in TNBC compared with other subtypes (Odds Ratio [OR] 2.02, $p=0.011$). In the overall population, *PIK3CA* CNVs were associated with significantly worse OS (HR 2.46, $p<0.001$), an effect observed across all subtypes, including HR+/HER2– (HR 2.21, $p<0.001$), HER2+ (HR 5.23, $p<0.001$), and TNBC (HR 1.81, $p=0.018$). In multivariable analysis, *PIK3CA* CNVs remained independently associated with inferior OS in the overall cohort (HR 1.61, $p=0.015$) and in HR+/HER2– disease (HR 1.38, $p=0.048$). Notably, the coexistence of a *PIK3CA* CNV and mutation identified a subset with particularly poor prognosis. Compared with patients harboring *PIK3CA* SNVs alone, those with concurrent SNVs and CNVs had significantly worse OS in the overall population (HR 1.80, $p=0.002$), in HR+/HER2– disease (HR 1.51, $p=0.037$), and in TNBC (HR 5.72, $p<0.001$). **Conclusions:** *PIK3CA* amplifications detected in ctDNA are relatively frequent in MBC and are associated with significantly worse survival across molecular subtypes. The coexistence of *PIK3CA* amplification and mutation identifies a distinct high-risk subset with particularly poor prognosis, beyond the effect of mutations alone. Further mechanistic understanding and real-world outcome analyses are needed to determine whether *PIK3CA* amplifications, alone or in combination with mutations, have predictive relevance for response or resistance to PI3K-pathway inhibitors. Research Sponsor: None.

HRD-positive breast cancer genomics: Cross-application of ovarian cancer HRD scores.

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Background: Homologous recombination deficiency (HRD) is a well-established biomarker for PARP inhibitor (PARPi) therapy in ovarian cancer and is increasingly being explored in breast cancer. However, current definitions of HRD positivity in breast cancer rely heavily on ovarian cancer-derived thresholds, raising questions about their biological relevance. Here, we characterize the genomic landscape of HRD-positive breast cancer and assess the applicability of ovarian cancer-based HRD scoring criteria. **Methods:** We performed next-generation sequencing on 1,159 breast cancer samples to evaluate HRD status, somatic alterations, and germline variants. HRD scores were calculated as the sum of loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST), using established ovarian cancer cutoffs. These results were compared with HRD scores from 617 ovarian cancer cases analyzed using the same methodology. **Results:** Pathogenic or likely pathogenic BRCA mutations were detected in 105 breast cancer patients (9.1%), including 33 somatic and 80 germline events, all of which occurred in HRD-positive tumors. Overall, 26.2% (304/1,159) of breast cancer cases were classified as HRD-positive, with a median HRD score of 21. HRD scores were significantly higher in triple-negative breast cancer (TNBC) than in non-TNBC subtypes ($P < 0.001$). HRD-positive tumors exhibited elevated genomic instability, marked by significantly higher copy number variation burden ($P < 0.001$) and tumor mutational burden (TMB) ($P < 0.001$), along with enriched TP53 alterations. Comparative analysis revealed that ovarian cancers had significantly higher HRD scores than breast cancers (median: 43 vs. 21, $P < 0.001$), suggesting that applying ovarian cancer-derived thresholds may underestimate HRD positivity in breast cancer. **Conclusions:** HRD-positive breast cancer displays distinct genomic features, including increased genomic instability and TP53 alterations. However, HRD scores in breast cancer are markedly lower than those in ovarian cancer, indicating that ovarian cancer-based cutoffs may not be optimal for breast cancer. Future studies should refine breast cancer-specific HRD thresholds to improve patient selection for PARPi therapy. Research Sponsor: YunnanInternational Joint Laboratory on Cancer MolecularImaging; 202503AP14,0032; Key Research and Development Program of Yunnan Provincefor Building a Science and Technology Innovation Center Facing South and Southeast Asia - The International Joint InnovationPlatform of Yunnan Province; Yunnan Science and Technology Talent and Platform Program (Academician Expert Workstation); 202505AF350067; Scientific Research Project of Yunnan Clinical Medicine Center; Startup Funds for Scientific Research of Yunnan Cancer Hospital; ZC0024.

Characterization of genomic alterations between local breast cancers and cutaneous metastases.

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Background: Cutaneous metastases (CM) are a distinct manifestation of advanced breast cancer (BC), yet their genomic alterations (GA) relative to primary tumors are incompletely defined. In this study, we aimed to identify similarities and differences between GA in local BC and CM. **Methods:** Local BC and CM were profiled by comprehensive next-generation sequencing (FoundationOne CDx). Genomic biomarkers included tumor mutational burden (TMB), microsatellite instability (MSI), homologous recombination deficiency signature (HRDsig), reported as a laboratory professional service, and GA prevalence. Odds ratios (ORs) for enrichment in local BC versus CM were calculated using Fisher's Exact Test with false discovery rate (FDR) correction. **Results:** Across 14,769 BC and 1,731 CM cases, most had TMB-low (<10 mutations/Megabase; 94% vs 90%), were not MSI-high (99%), and were HRDsig-negative (83% vs 87%), respectively. Among BC cases, the most prevalent GA included *TP53* (54.1%), *PIK3CA* (34.5%), *MYC* (20.9%), *RAD21* (19.0%), *CCND1* (16.7%), and recurrent 11q13/8p12 amplicon-associated genes (*FGF19*, *FGF3*, *FGF4*, *NSD3*, *ZNF703*, and *FGFR1*; each 13–15%). Among CM cases, the most prevalent GA included *TP53* (48.4%), *PIK3CA* (37.6%), *MYC* (22.7%), and *RAD21* (20.0%), and also *CDH1* (18.8%) and *ESR1* (12.5%). Multiple genes differed significantly in prevalence between BC and CM, including enrichment of *ESR1*, *CDH1*, *NOTCH1*, *MAP3K1*, *CTNNA1*, *CBFB*, *NFE2L2*, *AKT1*, *BRAF*, and *GATA4* in CM, and higher frequencies of *TP53*, *MCL1* and *KDM5A* in BC biopsies (Table 1). In addition, several therapeutically relevant GA were observed at lower but clinically meaningful frequencies between BC and CM, such as alterations in the *PI3K/AKT* pathway beyond *PIK3CA*, including *AKT2* (1.8% vs 2.4%), *AKT3* (3.2% vs 3.6%), and *PTEN* (13.1% vs 13.0%); DNA damage repair genes, including *BRCA1* (3.9% vs 2.7%), *BRCA2* (4.1% vs 3.9%), *PALB2* (1.1% vs 0.8%), *RAD51* (*RAD51B/C/D* combined 1.3% vs 1.1%), *ATM* (2.6% vs 1.9%), *ATR* (0.9% vs 0.7%), *CHEK1* (0.1% vs 0%), and *CHEK2* (1.5% vs 2.2%); and additional potentially actionable GA, such as the *MTAP* (4.0% vs 3.8%), *SMARCA4* (1.0% vs 0.8%), *CCNE1* (4.2% vs 5.3%), and *ERBB2* (11.1% vs 11.3%) genes in local BC and CM biopsies, respectively. **Conclusions:** CM largely retain the GA profile of local BC, but may exhibit distinct enrichment of alterations in estrogen signaling, likely from selective pressure, cell adhesion, possibly due to more frequent lobular *CDH1*-mutated BC involving skin, and oncogenic pathways. A substantial proportion of both BC and CM samples harbor targetable GA, underscoring opportunities for precision therapy not only in advanced disease, but also in early stages. Research Sponsor: None.

Clinically significant genes with significant differences between local BC and CM.

Gene	BC (%)	CM (%)	Odds Ratio (CM vs BC)	p-value (FDR adjusted)
<i>TP53</i>	54.1	48.4	0.79	<0.001
<i>CDH1</i>	11.4	18.8	1.80	<0.001
<i>ESR1</i>	4.7	12.5	2.89	<0.001
<i>AKT1</i>	4.7	6.3	1.38	0.046

Serum HER2 level as a predictor of treatment efficacy and prognosis in advanced breast cancer patients treated with trastuzumab deruxtecan (T-DXd).

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Background: No validated liquid biopsy biomarker currently exists to predict the efficacy of trastuzumab deruxtecan (T-DXd) in advanced breast cancer (aBC). Consequently, the role of serum HER2 (sHER2) in this setting remains unclear. This study aimed to determine whether baseline levels and early on-treatment dynamics of sHER2 are associated with progression-free survival (PFS) and objective response rate (ORR) in aBC patients receiving T-DXd. **Methods:** We analyzed 43 aBC patients treated with T-DXd who had baseline sHER2 data available. As the established 15 ng/mL cut-off was not associated with PFS in our preliminary analysis, the optimal baseline sHER2 cut-off for predicting PFS was determined using the maximally selected log-rank statistics method. Patients were stratified by this cut-off, and a multivariable Cox model adjusted for clinicopathological factors was used to evaluate the independent prognostic value of baseline serum HER2. In a subgroup of 20 patients, serum HER2 changes after two treatment cycles were assessed for association with efficacy outcomes. **Results:** Using the maximally selected log-rank statistics method, 10.94 ng/mL was identified as the optimal predictive cut-off, with PFS differing significantly between groups defined by this threshold ($P=0.015$). Multivariable Cox analysis confirmed that a baseline sHER2 level ≥ 10.94 ng/mL was an independent protective factor for longer PFS (Hazard Ratio [HR] = 0.129, 95% Confidence Interval [CI]: 0.019–0.875, $P=0.038$), corresponding to an approximately 87.1% reduction in disease progression risk. This predictive value was independent of primary tumor HER2 status, metastatic burden, and liver metastasis. Primary tumor HER2 status itself was not a significant prognostic factor in the model ($P=0.530$). Regarding ORR, no statistically significant difference was found between high and low sHER2 groups using the 10.94 ng/mL cut-off ($P=0.392$). In the 20-patient subgroup, early on-treatment sHER2 dynamics showed no significant association with PFS ($P=0.455$) or ORR ($P=0.256$). **Conclusions:** In aBC patients treated with T-DXd, a baseline serum HER2 level ≥ 10.94 ng/mL is a strong and independent predictive biomarker for PFS, with prognostic value potentially surpassing primary tumor HER2 status. This newly identified cut-off may help to better select patients who are most likely to benefit from T-DXd therapy using a convenient liquid biopsy approach. Clinical trial information: NCT06492447. Research Sponsor: None.

PD-L1 upregulation as a reflection of distinct immune contexts in luminal and basal breast cancer.

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Background: PD-L1 immunohistochemistry (IHC) is an approved biomarker to select patients with metastatic triple-negative breast cancer for immune checkpoint blockade (ICB). However, PD-L1 performs poorly in Luminal breast cancer, suggesting that PD-L1 upregulation may reflect distinct immune contexts across intrinsic subtypes. We hypothesized that PD-L1 expression can arise in either a canonical T-cell-inflamed state or a discordant PD-L1-high, T-cell-non-inflamed state. Discordance between PD-L1 expression and T-cell inflammation highlights the complexity of tumor-immune interactions, and accumulating evidence supports that malignancies can induce immune alterations systemically. To explore these broader immune features with a noninvasive approach, we examined plasma extracellular vesicles (EVs). **Methods:** We analyzed 1,084 primary invasive breast cancers from TCGA, focusing on Luminal (LumA/LumB) and Basal subtypes (n=867). PD-L1 status was defined using CD274 mRNA tertiles as a transcriptomic proxy for IHC, and a T-cell-inflamed signature (Ayers 18-gene TIS) classified tumors as inflamed (top 20th percentile), consistent with prior transcriptomic studies. Biomarker concordance was defined as the proportion of PD-L1-high tumors that were also TIS-high. Because CD274 is included in the TIS, analyses were interpreted conservatively with planned sensitivity analyses excluding CD274. For translational feasibility, EV profiling workflows were developed using plasma from the PyMT-N mouse model (immune-cold, myeloid-dominant TIME; method-development model, n=1). Plasma EVs from two patients with advanced breast cancer and one healthy control were profiled using proteomic and targeted EV RNA assays. **Results:** In Basal tumors, PD-L1 expression aligned with T-cell inflammation: 75.6% (65/86) of PD-L1-high tumors were TIS-high. In contrast, Luminal tumors showed reduced concordance, with only 39.4% (80/203) of PD-L1-high tumors classified as TIS-high. Basal PD-L1-high tumors were significantly more likely to be TIS-high than Luminal tumors (OR 4.76; 95% CI 2.70–8.39; $p=1.90 \times 10^{-8}$). These findings indicate frequent uncoupling of PD-L1 expression from T-cell inflammation in Luminal breast cancer. In PyMT-N plasma EVs, proteomic profiling detected myeloid-suppressive proteins with minimal T-cell-inflamed signals. In exploratory human plasma EVs, both proteomic and RNA assays captured immune-related signals, supporting EV profiling feasibility. **Conclusions:** PD-L1 upregulation occurs in distinct immune contexts that differ by intrinsic subtype, with reduced T-cell-inflamed concordance in Luminal breast cancer. This discordance may explain the limited utility of PD-L1 as a stand-alone biomarker in this subtype. Plasma EV profiling may capture systemic immune biology and provide orthogonal information to tumor-based assays, supporting further prospective evaluation. Research Sponsor: U.S. National Institutes of Health.

A phase II study of trastuzumab emtansine (T-DM1) combined with ribociclib in patients with HER2-positive metastatic breast cancer (RibHER).

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Background: HER2-targeted therapy has significantly improved outcomes for patients with HER2-positive metastatic breast cancer (MBC). Cyclin D and cyclin-dependent kinases 4/6 (CDK4/6) act as downstream effectors of HER2 signaling, providing a rationale for combining CDK4/6 inhibitors with anti-HER2 therapies. However, combining CDK4/6 inhibitors with anti-HER2 antibody-drug conjugates (ADCs) raises the concerns of hematologic toxicities. This prospective, single-center, single-arm, phase II study evaluated the antitumor activity and safety of trastuzumab emtansine (T-DM1) plus ribociclib in patients with HER2-positive MBC previously treated with trastuzumab and a taxane, and with no prior ADC exposure. **Methods:** Patients received T-DM1 (3.6 mg/kg IV, day 1 of each 21-day cycle) and ribociclib (400 mg orally, days 8–21). Those with ER-positive disease could receive concomitant endocrine therapy (aromatase inhibitor or fulvestrant) per prior treatment; premenopausal patients also received ovarian function suppression. The primary endpoint was overall response rate (ORR). Secondary endpoints included clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** From August 2020 to October 2024, 12 patients were enrolled. With the subsequent availability of trastuzumab deruxtecan (T-DXd), the study was terminated prematurely due to difficulties in patient enrollment. As of December 1, 2025, the median follow-up was 22.5 months (range: 8.7–25.2). The overall ORR was 41.7% and the CBR was 58.3%. Median PFS was 5.25 months (95%CI: 3.3–NA). In subgroup analyses, ORR (28.6% vs. 60.0%), CBR (57.1% vs. 60.0%), and median PFS (6.0 months, 95% CI: 3.5–NA vs. 4.5 months, 95% CI: 3.0–NA) differed between ER-positive and ER-negative subgroups, respectively. Median OS was not reached. All patients experienced treatment-related adverse events (TRAEs), most commonly thrombocytopenia (75.0%), neutropenia (66.7%), leukopenia (66.7%), anemia (50.0%), fatigue (50.0%), and elevated aspartate aminotransferase (50.0%). Grade ≥ 3 TRAEs included neutropenia (33.3%), leukopenia (25.0%), and thrombocytopenia (16.7%). Thrombocytopenia led to dose reduction in 5 patients and discontinuation in 2; one patient required platelet transfusion and another experienced grade 3 intracranial hemorrhage attributed to thrombocytopenia. No treatment-related deaths occurred. **Conclusions:** In this small preliminary study, T-DM1 plus ribociclib achieved an ORR of 41.7% in HER2-positive MBC. No clear PFS benefit was observed regardless of ER status. Overlapping hematologic toxicities, especially thrombocytopenia, were notable and warrant consideration in future combination strategies. Clinical trial information: NCT06481956. Research Sponsor: None.

Tucatinib (TUC) combined with trastuzumab and pertuzumab (HP) as first-line (1L) maintenance therapy for HER2+ metastatic breast cancer (MBC): An in-depth safety analysis of HER2CLIMB-05.

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Background: The primary analysis of the phase 3 HER2CLIMB-05 study (NCT05132582) showed the addition of TUC to 1L maintenance HP yielded a statistically significant improvement in progression-free survival (per investigator) versus control treatment (hazard ratio: 0.641, $P < 0.0001$) in patients with HER2+ MBC. Here we report our findings from an in-depth safety analysis of HER2CLIMB-05. **Methods:** Patients with centrally confirmed HER2+ MBC without evidence of progression following chemotherapy-based induction treatment (taxane + HP) were randomly assigned 1:1 to TUC (300 mg) or placebo (PBO) BID, both in combination with HP. The safety analysis set included all randomly assigned patients who received ≥ 1 dose of any study treatment. Treatment-emergent adverse events (TEAEs), laboratory values, and TUC/PBO dose modifications and discontinuations were examined. **Results:** Among patients in the safety analysis set (TUC arm = 326; PBO arm = 324), median treatment durations of TUC and PBO were 17.1 months (range: 0.4–36.5) and 15.5 months (range: 0.5–41.3), respectively. Grade (G) ≥ 3 TEAEs occurred in 42.3% of patients in the TUC arm and 24.4% in the PBO arm; the most frequent G ≥ 3 TEAEs in the TUC arm were elevated alanine aminotransferase (ALT; 13.5%) and aspartate aminotransferase (AST; 7.1%). TUC was discontinued in 13.5% of patients due to a TEAE. Cardiac TEAEs were similar between TUC and PBO arms (4.3% vs 6.2%). TEAEs of hepatic events (43.6% vs 15.7%) and diarrhea (72.7% vs 51.2%) occurred at higher incidence in the TUC arm versus the PBO arm (Table). In the TUC arm, increased ALT (28.2%) and AST (25.8%) accounted for the majority of hepatic TEAEs. Most hepatic and diarrhea TEAEs were managed with TUC dose modifications and/or discontinuation; 7.7% of patients discontinued TUC due to hepatic TEAEs and 1.5% discontinued due to diarrhea (Table). Among the patients with a TEAE of diarrhea, 57.7% and 29.9%, respectively, in the TUC and PBO arms used antidiarrheals; the most used medication was loperamide. Further details of the in-depth safety analysis will be presented. **Conclusions:** TUC addition to 1L HP maintenance therapy may be an effective option for HER2+ MBC with a clinically manageable safety profile. Clinical trial information: NCT05132582. Research Sponsor: Pfizer Inc.

TEAEs* Arm	Any		Any hepatic		Increased ALT/AST		Diarrhea	
	TUC	PBO	TUC	PBO	TUC	PBO	TUC	PBO
Any G, %	99.1	96.6	43.6	15.7	28.2/25.8	7.1/9.0	72.7	51.2
G ≥ 3	42.3	24.4	18.1	1.2	13.5/7.1	0.6/0.6	6.1	4.0
Any G: Median time to onset (days)			34.5	85.0			11.0	32.0
Median time to resolution (days)			25.0	22.0			2.0	5.0
Any G: TUC/PBO dose hold, %	49.4	25.3	19.3	2.5	12.6/4.0	0.6/0.6	8.6	3.4
TUC/PBO dose reduction, %	29.1	11.1	16.3	0.9	11.7/2.8	0.3/0.6	6.4	3.1
TUC/PBO discontinuation, %	13.5	2.2	7.7	0	4.0/0.3	0/0	1.5	0.9

*As of data cutoff, Sep 5, 2025.

Risk factors and long-term prognostic impact of trastuzumab deruxtecan-related interstitial lung disease in metastatic breast cancer.

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Background: Trastuzumab deruxtecan (T-DXd) has demonstrated substantial efficacy in HER2-positive and HER2-low metastatic breast cancer (MBC). Interstitial lung disease (ILD), however, remains a clinically significant safety concern. While ILD incidence has been reported, its long-term prognostic impact and associated risk factors are not well established. **Methods:** This retrospective, single-center study evaluated patients with MBC treated with T-DXd. ILD was defined as clinically and radiologically confirmed ILD, which led to T-DXd discontinuation per institutional protocol. Time to treatment failure (TTF) and overall survival (OS) were analyzed according to ILD occurrence. Potential clinical and treatment-related risk factors for ILD were assessed using univariable and penalized multivariable Cox regression models. **Results:** At a median follow-up of 12.7 months, 15 of 132 patients (11.4%) developed ILD leading to treatment discontinuation. Among these 15 patients, 9 (60%) had grade 1 disease, 3 (20%) had grade 2, and 3 (20%) had grade 3 disease; no grade 4 or fatal events were observed. There were no significant differences in TTF ($P = 0.59$) or OS ($P = 0.21$) between patients with and without ILD. Among patients who developed ILD, onset occurred significantly earlier in those with HER2-low disease compared with HER2-positive disease (median 6.0 vs. 14.6 months, $P = 0.029$). In univariable analyses, age ≥ 65 years (HR 3.39, 95% CI 1.18–9.68; $P = 0.023$), prior immune checkpoint inhibitor (ICI) therapy (HR 4.74, 95% CI 1.01–22.34; $P = 0.049$), and prior abemaciclib exposure (HR 4.11, 95% CI 1.19–14.14; $P = 0.025$) were significantly associated with ILD. In the penalized multivariable model, prior abemaciclib exposure remained the only independent risk factor (HR 10.38, 95% CI 1.07–NA; $P = 0.042$). **Conclusions:** Although ILD onset tended to occur earlier in HER2-low MBC, its development did not significantly affect long-term TTF or OS. Prior exposure to abemaciclib is a significant independent risk factor for T-DXd-related ILD, warranting careful monitoring in this population. Research Sponsor: None.

Zongertinib combination therapy in HER2-positive metastatic breast cancer (mBC): First results from a phase Ib/II trial.

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Background: Zongertinib, an irreversible TKI, selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities. Beamion BCGC-1 (NCT06324357) is an ongoing Ph Ib/II multicohort trial investigating zongertinib as monotherapy or in combination with other agents in HER2-positive mBC, metastatic colorectal cancer, and metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma. Here, we report the first data from 4 Ph Ib cohorts evaluating zongertinib plus antibody-drug conjugates (ADCs) or trastuzumab-based therapy in patients (pts) with HER2-positive mBC, focusing on ADC combinations, as well as supporting preclinical data. **Methods:** Preclinical activity of zongertinib combinations was assessed in xenograft mouse models. Beamion BCGC-1 includes pts with confirmed, unresectable HER2-positive mBC who progressed following HER2-directed therapy. Pts received escalating doses of zongertinib plus fixed doses of T-DM1 (Cohort A; 3.6 mg/kg), T-DXd (Cohort B; 5.4 mg/kg), trastuzumab (Cohort K; 8 mg/kg loading dose followed by 6 mg/kg) or capecitabine (1000 mg/m²) plus trastuzumab (Cohort G; 8 mg/kg loading dose followed by 6 mg/kg). The primary endpoint is the occurrence of DLTs during the MTD evaluation period. Secondary endpoints included further safety assessments and objective response (investigator-assessed; RECIST v1.1). **Results:** In xenograft mouse models, the addition of zongertinib to T-DM1 or T-DXd led to increased antitumor activity. As of November 4, 2025, 12 pts had been enrolled to Cohort A (median age: 58 years), 16 to Cohort B (median age: 58 years), 4 to Cohort G (median age: 48 years) and 7 to Cohort K (median age: 58 years). Most pts were heavily pretreated, with prior exposure to T-DXd, T-DM1 and/or TKIs. In Cohort A, treatment emergent adverse events (TEAEs) and zongertinib-related AEs (any grade [G]/G3) were reported in 12/5 (100%/42%) and 11/5 (92%/42%) pts, respectively. Three (25%) pts had AEs leading to zongertinib dose reduction. No pts had an AE leading to zongertinib discontinuation. The most common TEAEs (any G/G3) were increased AST (7/1 [58%/8%] pts), decreased platelet count (5/2 [42%/17%] pts) and increased ALT (5/1 [42%/8%] pts). In Cohort B, TEAEs and zongertinib-related AEs (any G/G3) were reported in 14/7 (88%/44%) and 14/5 (88%/31%) pts, respectively. Three (19%) pts had AEs leading to zongertinib dose reduction and 3 (19%) had AEs leading to zongertinib discontinuation. The most common TEAEs (any G/G3) were anemia (8/2 [50%/13%] pts), diarrhea (8/2 [50%/13%] pts) and nausea (8/1 [50%/6%] pts). No grade 4 or 5 TEAEs occurred in Cohorts A and B. Efficacy analyses are ongoing and will be presented. **Conclusions:** No new safety signals were observed with zongertinib plus T-DXd or T-DM1. Dose escalation was ongoing in Cohorts A and B at data cutoff. Clinical trial information: NCT06324357. Research Sponsor: Boehringer Ingelheim.

Overall survival by genomic profile in HER2-positive (HER2+) metastatic breast cancer (mBC): A large US clinico-genomic database study.

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Background: Over the past few years, the landscape of treatment for HER2+ breast cancer has evolved significantly. Multiple active 1L treatment options have emerged, including T-DXd plus pertuzumab, maintenance palbociclib or tucatinib, providing an opportunity to tailor treatment according to the disease profile. This study aims to describe real-world treatment patterns and evaluate overall survival (OS) in a modern cohort of patients with HER2+ mBC, with sub-analysis by genetic profile of the disease. **Methods:** This retrospective study used the Flatiron Clinico-Genomic database (CGDB), where each patient received at least one Foundation Medicine next generation sequencing (NGS) test along the course of disease. Adults (≥ 18 years) diagnosed with HER2+ mBC between 1 January 2018 and 31 March 2024 (one year prior to the data cutoff) were included. OS was examined using the Kaplan-Meier method, with descriptive analyses by genetic alteration. **Results:** Among 7,933 mBC patients who underwent NGS profiling, 732 (9.2%) patients with HER2+ mBC were included. The median age at diagnosis was 59 years (range: 23–85); 68.3% had hormone receptor positive disease, and 37% had de novo mBC. Patients received a median of 3 lines of therapy (range: 1–14). The use of anti-HER2 antibodies ranged from 59.4% to 33.6% across 1L through 5L. Trastuzumab deruxtecan was prescribed more often in later lines (23.9% for 3L, 19.6% for 4L, and 23.0% for 5L) compared to 2L and 1L (11.3% and 4.2%). Similarly, the use of anti-HER2 tyrosine kinase inhibitors increased in later lines. The median (95% CI) OS for the entire population was 48 (41.6–53.1) months, with notable differences based on the detection of key genetic alterations. Patients with mutations in DNMT3A (14.2%), ARID1A (11.9%), MLL2 (10.9%), and CHEK2 (9%) had numerically longer mOS (64 [49.5–NE], 51.4 [35.8–69.4], 51.4 [36.1–68.9], 51.4 [40.1–NE] months, respectively) while patients with mutations in BRCA1 (6.6%), CDH1 (10.9%), BRCA2 (10.9%), PIK3CA (37.4%), TP53 (59.6%), ERBB2 (11.5%), and ATM (12.7%) experienced numerically shorter mOS (36 [25.0–56.3], 40.1 [28.0–70.1], 40.1 [34.1–62.5], 40.1 [35.2–46.9], 40.6 [35.9–48.7], 43.3 [36.2–58.9], 44.3 [36.5–62.8] months, respectively). **Conclusions:** The present study provides key insights into clinico-genomic characteristics, modern treatment patterns and OS for HER2+ mBC patients in the US. Although survival was 4 years in the overall cohort, patients with mutations in key DNA repair genes (BRCA1, BRCA2, ATM, TP53), in CDH1, PIK3CA or ERBB2 experienced a numerically worse prognosis, representing key unmet needs for drug development. Research Sponsor: Boehringer Ingelheim.

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: Results from the 1L HER2-positive breast cancer cohort.

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Background: BAT8010 is an ADC targeting HER2, while BAT1006 is a humanized monoclonal antibody targeting another epitope of HER2, with ADCC enhancement activity via completely devoid of fucose. Expansion cohort of 1st-line HER2-positive breast cancer (BC) patients enrolled, treated with BAT8010 + BAT1006. **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 9, 2026, 46 HER2-positive BC patients were enrolled, and received BAT8010 2.4 mg/kg in combination with BAT1006 15 mg/kg. Favorable efficacy was observed with a manageable and predictable safety profile; dose optimization is ongoing in the BAT8010 2.1 mg/kg in combination with BAT1006 15 mg/kg dose cohort. **Safety:** Among the 46 patients who received at least one dose of BAT8010 in combination with BAT1006, at least one treatment-emergent adverse event (TEAE) was reported in 41/46 (89.1%) patients. The most common TEAEs ($\geq 30\%$) were neutropenia, leukopenia, anemia, infusion-related reaction (IRR), thrombocytopenia, elevated alanine aminotransferase and diarrhea. Most TEAEs were Grade 1/2; however, Grade 3 or higher AEs were reported in 67.4% of patients, including neutropenia (27/46, 58.3%), leukopenia (16/46, 34.8%), and anemia (7/46, 15.2%). No cases of interstitial lung disease (ILD)/pneumonitis were reported. **Efficacy:** Among 46 patients with at least one tumor assessment, 1 patient achieved CR, 34 PR, and 11 SD, yielding an ORR of 76% (35/46) and a DCR of 100% (46/46); mPFS: not yet mature. **Conclusions:** BAT8010 in combination with BAT1006 is well-tolerated with manageable toxicity, and demonstrates promising preliminary antitumor activity in HER2-positive BC. Dose expansion studies in this patient population are ongoing, and further confirmatory clinical trials are planned to initiate for the additional validation of its safety and efficacy. Clinical trial information: NCT06376136. Research Sponsor: None.

Efficacy, safety, and immunogenicity of pertuzumab biosimilar versus reference pertuzumab in combination with trastuzumab and docetaxel in HER2-positive metastatic breast cancer: A randomized, double-blind, multicenter, parallel group, phase III clinical trial.

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Background: Pertuzumab plus trastuzumab and docetaxel is a standard first-line treatment regimen for HER2-positive metastatic breast cancer (MBC). This phase III trial evaluated the therapeutic equivalence of pertuzumab biosimilar (manufactured by Intas Pharmaceuticals Ltd., Ahmedabad, India) versus Perjeta when combined with trastuzumab and docetaxel.

Methods: This was a randomized (1:1), double-blind, multicenter, parallel-group, phase III equivalence study. Adults with HER2-positive MBC were enrolled and received pertuzumab I.V. (biosimilar or reference product) 840 mg loading dose in cycle 1, then 420 mg every 3 weeks for 24 weeks, in combination with trastuzumab and docetaxel as first-line therapy. Primary endpoint was independently assessed objective response rate (ORR) at week 24 per RECIST v1.1. Secondary endpoints included PFS, OS, duration of response, time-to-event outcomes, pharmacokinetics (T_{max} , C_{max} , AUC_{0-t}), safety, and immunogenicity (anti-drug antibodies, ADA). **Results:** A total of 213 patients were randomized (pertuzumab biosimilar n=106; reference product n=107). ORR at week 24 was comparable between the biosimilar and reference pertuzumab arms: in the mITT set, ORR was 71.3% (72/101) versus 65.0% (67/103), respectively. 6-months PFS rate was 90.1% vs 89.3% in biosimilar and reference pertuzumab arms respectively. Pharmacokinetic parameters (T_{max} , C_{max} , AUC_{0-t}) and immunogenicity were comparable between both the arms. Treatment-emergent adverse events (AEs) occurred in 65.1% (pertuzumab biosimilar) and 72.9% (reference product) of patients; most common AEs observed in $\geq 5\%$ patients in pertuzumab biosimilar vs reference product arm were the following: diarrhea (32.1% vs 30.8%), alopecia (17.0% vs 12.1%), anaemia (8.5% vs 18.7%), vomiting (10.4% vs 11.2%), pyrexia (8.5% vs 10.3%), fatigue (8.5% vs 7.5%), neutropenia (6.6% vs 8.4%), leukopenia (6.6% vs 8.4%), nausea (4.7% vs 7.5%), cough (4.7% vs 5.6%) and headache (3.8% vs 5.6%). **Conclusions:** Pertuzumab biosimilar demonstrated therapeutic equivalence to reference product in combination with trastuzumab and docetaxel for first-line HER2-positive MBC. Efficacy, safety, pharmacokinetic similarity, and comparable immunogenicity support biosimilarity and its potential as an effective treatment option. Clinical trial information: CTRI/2022/12/048133. Research Sponsor: Intas Pharmaceuticals Limited, Ahmedabad, India.

Summary statistics for objective response rate (ORR) at week 24 (mITT set, N=204).

Parameter	Pertuzumab biosimilar (N=101), n (%)	Reference product (N=103), n (%)
Complete response	4 (4%)	1 (1%)
Partial response	68 (67.3%)	66 (64.1%)
Overall response rate	72 (71.3%)	67 (65.0%)
Difference in ORR (95% CIs)	-7.50, 19.97	

Phase Ia study of VRN101099, a brain-penetrant, highly selective covalent HER2 inhibitor, in HER2-positive or HER2-mutant advanced solid tumors.

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Background: Despite advances in HER2-targeted therapies, including trastuzumab deruxtecan (T-DXd), unmet needs remain in patients with HER2-driven solid tumors who develop treatment resistance, particularly those with central nervous system (CNS) metastases. VRN101099 is an orally bioavailable, brain-penetrant covalent HER2 inhibitor that irreversibly inhibits HER2 and induces receptor internalization and degradation. Preclinical studies demonstrated antitumor activity in subcutaneous and intracranial xenograft models of HER2-positive breast and gastric cancers. **Methods:** This open-label phase Ia study assesses the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of VRN101099 in patients with HER2 IHC 1+/2+/3+ or HER2-activating mutant advanced solid tumors. A standard 3+3 dose-escalation design determines the maximum tolerated dose and recommended phase 2 dose (RP2D), with dose-limiting toxicities assessed during the first 21-day cycle. VRN101099 is given orally once daily in continuous 21-day cycles. Optional backfill cohorts may enroll up to 12 patients at tolerated dose levels to characterize safety, PK, and PD further. Data are descriptive as of the 18 January 2026 cutoff and inform ongoing dose escalation, backfill enrollment, and RP2D selection; early reporting reflects emerging safety and activity. Safety is overseen by a Safety Review Committee defined by protocol. **Results:** As of January 2026, 17 patients received VRN101099 (80–320 mg). Median age was 63 years; 65% were female, and 35% had breast cancer. HER2 IHC 3+ expression was seen in 29% of patients; 35% were ISH-positive, and 24% had HER2-activating mutations. Patients had received a median of 3 prior systemic therapies (range 0–10); 58% had prior anti-HER2 therapy, including T-DXd (47%). No Grade ≥ 3 treatment-related adverse events occurred. The most common treatment-related adverse event was Grade 1–2 diarrhea. Among eleven patients with at least one post-baseline tumor assessment at data cutoff, five with HER2 IHC 3+ expression or HER2-activating mutations experienced tumor size reduction after two cycles. Confirmed partial responses were observed in two patients previously treated with T-DXd: one with HER2 IHC 3+ breast cancer and one with HER2 S310Y-mutant NSCLC. PK analyses showed dose-dependent exposure, with trough concentrations at 240 mg exceeding preclinically defined HER2 inhibitory thresholds. **Conclusions:** VRN101099 was well tolerated across evaluated dose levels and demonstrated encouraging antitumor activity in heavily pretreated HER2-driven solid tumors, including patients previously treated with T-DXd. These findings support continued dose escalation and expansion to define the RP2D and further characterize the therapeutic potential of VRN101099. Clinical trial information: NCT06806982. Research Sponsor: Voronoi Inc.

Phase II study of T-Bren (BL-M07D1) monotherapy or in combination with pertuzumab in patients with treatment-naïve HER2-positive unresectable locally advanced or metastatic (LA/M) breast cancer.

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Background: T-Bren is a HER2-directed antibody-drug conjugate (ADC) consisting of an anti-HER2 monoclonal antibody linked to a potent topoisomerase I inhibitor (Ed-04). In phase I study, T-Bren demonstrated encouraging antitumor activity with a manageable safety profile in patients (pts) with HER2-positive unresectable LA/M breast cancer (BC) who had failed standard treatments. Results of safety and efficacy from a phase II study assessing T-Bren monotherapy or in combination with pertuzumab in treatment-naïve HER2-positive unresectable LA/M BC are presented. **Methods:** Treatment-naïve pts with HER2-positive (IHC3+, or IHC2+/ISH+) unresectable LA/M BC were treated with T-Bren monotherapy at 4.4mg/kg Q3W (cohort A) or T-Bren 4.4mg/kg Q3W in combination with pertuzumab (cohort B). Primary endpoints were ORR and RP2D for combination treatment. **Results:** As of Nov 30, 2025, a total of 83 pts were enrolled and treated in cohort A (n = 43) and cohort B (n = 40). All pts were included in the analysis (see table below). The median follow-up was 10.6 months. In cohort A, ORR was 93.0%, confirmed ORR (cORR) was 86.0%. In cohort B, ORR and cORR were 87.5%. Median PFS have not reached in either cohort. The landmark PFS rate at 12-months was 79.1% in cohort A and 90.8% in cohort B. The most common grade 3 and above hematologic TRAEs in both cohorts were neutropenia (51.8%), anemia (37.3%), leukopenia (36.1%), and thrombocytopenia (26.5%); the most frequent grade 3 and above non-hematologic TRAEs were weight decreased (7.2%), hypokalemia (6.0%), and nausea (6.0%). Grade 3 and above TRAEs were able to be effectively managed with standard supportive measure including dose reductions, as demonstrated by the TRAE leading to discontinuation rate of 4.8%. No treatment related death or ILD was reported. **Conclusions:** T-Bren as monotherapy or in combination with pertuzumab has demonstrated a promising antitumor activity and a manageable safety profile in pts with treatment-naïve HER2-positive unresectable LA/M BC. Phase III study assessing T-Bren in treatment-naïve HER2-positive unresectable LA/M BC is in preparation. Clinical trial information: NCT06445400. Research Sponsor: Baili-Bio (Chengdu) Pharmaceutical Co., Ltd.

	Cohort A: T-Bren 4.4 mg/kg D1Q3W (N=43)	Cohort B: T-Bren 4.4 mg/kg D1Q3W+ pertuzumab D1Q3W (N=40)	Total (N=83)
ORR, % (95% CI)	93.0 (80.9, 98.5)	87.5 (73.2, 95.8)	90.4 (81.9, 95.7)
cORR, % (95% CI)	86.0 (72.1, 94.7)	87.5 (73.2, 95.8)	86.7 (77.5, 93.2)
DCR, % (95% CI)	100 (91.8, 100)	97.5 (86.8, 99.9)	98.8 (93.5, 100)
12-mo PFS rate, % (95% CI)	79.1 (32.9, 95.2)	90.8 (74.1, 97.0)	89.9 (77.8, 95.6)
12-mo OS rate, % (95% CI)	100 (100, 100)	95.0 (81.5, 98.7)	97.4 (89.9, 99.3)

Efficacy and safety results of a prospective phase II study (IPUtrial) of inetetamab and pyrotinib in combination with utidelone for first- or second-line treatment of HER2-positive metastatic breast cancer.

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Background: Despite standard anti-HER2 regimens with chemotherapy, therapeutic challenges persist in HER2-positive metastatic breast cancer (MBC). Inetetamab (anti-HER2 monoclonal antibody) and pyrotinib (tyrosine kinase inhibitor) demonstrate established efficacy in advanced disease. Utidelone, a novel epothilone analog, exhibits antitumor activity with a differentiated safety profile. This phase II study assessed the triplet combination in first- or second-line HER2-positive MBC. **Methods:** This multicenter single-arm phase II trial enrolled HER2-positive MBC patients for first- or second-line therapy. Patients who have previously used trastuzumab must meet the followings: for first-line treatment, neoadjuvant therapy was effective, and relapse occurred over 1 year after the end of adjuvant therapy; for second-line treatment, progressed in previous adjuvant/neoadjuvant therapy or progressed within 1 year of completion of trastuzumab therapy; disease progression occurred after 6 months of treatment with trastuzumab in advanced setting. Patients with stable brain metastases were enrolled with or without prior local treatment. ECOG PS 0-1, and measurable disease (RECIST v1.1). Eligible patients received inetetamab (8 mg/kg cycle 1, then 6 mg/kg, IV, day 1), pyrotinib (400 mg, PO, daily), and utidelone (30 mg/m², IV, days 1-5) every 21 days until progression or intolerance. Primary endpoint was investigator-assessed ORR. Secondary endpoints included PFS, OS, and safety. **Results:** By data cutoff (December 31, 2025), the recruitment has been completed. 94 patients were enrolled. Median treatment cycles were 11 (range 4-57). 56 (65.9%) and 29 (34.1%) patients were in first- and second-line settings, respectively. 85 patients were evaluable for response with 6 CR, 64 PR and 7 SD. The ORR was 82.4% (95% CI, 72.6%-89.8%). Median PFS was 13.1 months (95% CI, 10.420-15.780). Median OS was not reached. The OS rate of 12-month, 26-month and 35-month was 94.6% (95% CI, 89.5%-99.7%), 85.2% (95% CI, 76.6%-93.8%) and 78.5% (95% CI, 67.7%-89.3%), respectively. Predominant Grade $\geq$ 3 TRAEs were diarrhea (28.2%) and peripheral neuropathy (4.7%). Other Grade $\geq$ 3 TRAEs included nausea (3.5%), transaminitis (2.4%) and neutropenia (1.2%). Treatment discontinuations due to TRAEs occurred in 6 patients (6.6%). No treatment-related deaths occurred. **Conclusions:** The regimen demonstrated clinically meaningful activity of this triplet regimen for the first/second-line treatment of HER2-positive MBC, evidenced by high ORR (82.4%), durable median PFS (13.1 months), with encouraging 35-month OS rate (78.5%). Predominant toxicities (diarrhea, neuropathy) were controllable through supportive measures and dose adjustments. These data support phase III evaluation of this combination strategy. Research Sponsor: Beijing Biostar Pharmaceuticals Co., Ltd.

Real-world brain metastasis outcomes with T-DXd versus tucatinib-based therapy in second-line HER2-positive metastatic breast cancer.

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Background: Brain metastases (BM) remain a major cause of morbidity and mortality in HER2+ metastatic breast cancer (MBC). HER2CLIMB established tucatinib/trastuzumab/capecitabine (TTC) as a standard regimen with CNS activity, including improved outcomes in patients (pts) with active BM. DESTINY-Breast12 further demonstrated clinically meaningful intracranial outcomes with trastuzumab deruxtecan (T-DXd) in pts with stable and active BM. However, real-world (RW) comparative estimates of incident BM risk and timing between these two regimens among pts without baseline BM are limited, particularly in the second-line (2L) setting. **Methods:** We conducted a retrospective cohort study using TriNetX, a federated electronic health record network. Eligible pts had HER2+ MBC previously treated with first-line THP (taxane + trastuzumab + pertuzumab) and were BM-free at index. To approximate a 2L comparison, index was the first dose of T-DXd or TTC; cohorts were mutually exclusive and prior T-DM1 exposure was excluded. Pts with documented BM prior to index were excluded. To reduce misclassification from occult baseline BM, a landmark sensitivity analysis excluded BM events within 60 days post-index. Cohorts were balanced using 1:1 propensity score matching (PSM) for age, comorbidity burden, and lines of treatment. Incident BM was compared using risk-based measures (risk difference, risk ratio [RR]) and time-to-event analyses (Kaplan-Meier [KM]; Cox [HR]; log-rank). OS was assessed from index to death using KM and Cox regression. **Results:** In the PSM cohorts (n=540 per arm; mean age 57.8±12.4 vs 59.2±12.3 years), median follow-up was 13.4 months. Incident BM occurred in 12.6% (68/540) with T-DXd vs 20.9% (113/540) with TTC, corresponding to an absolute risk difference of -8.3% (95% CI -13.34% to -2.90%; p=0.0015) and RR 0.62 (95% CI 0.46-0.83). 1-year BM-free survival probability was 72.65% with T-DXd vs 67.89% with TTC (log-rank p=0.03), with an HR of 0.72 (95% CI 0.54-0.97). Among pts who developed BM, TTC was associated with higher BM-associated healthcare encounter burden compared with T-DXd (mean 9.64 vs 5.20; p=0.03). CNS morbidity events were less frequent with T-DXd vs TTC, including seizures (4.77% vs 13.06%; OR 0.33, 95% CI 0.23-0.49; p<0.0001) and cerebral edema (5.47% vs 14.22%; OR 0.35, 95% CI 0.24-0.51; p<0.0001). OS did not differ significantly between T-DXd and TTC (HR 0.89, 95% CI 0.76-1.04; p=0.16). **Conclusions:** In HER2+ MBC pts without baseline BM following first-line THP, T-DXd was associated with significantly lower incident BM, delayed onset, and reduced CNS morbidity compared with TTC. These findings warrant validation using standardized CNS surveillance and may help inform treatment selection in pts at high risk for BM. Research Sponsor: None.

BM outcomes in HER2+ MBC.

	T-DXd	TTC	
Incident BM	12.6%	20.9%	RR 0.62 (0.46-0.83)
1-year BM-free	72.65%	67.89%	HR 0.72 (0.54-0.97)

Molecular imaging as a tool to predict patient outcomes in advanced HER2-low breast cancer on trastuzumab deruxtecan (T-DXd): The FHERAD trial.

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Background: The DESTINY-Breast04 trial demonstrated for the first time that trastuzumab deruxtecan (T-DXd), a HER2-targeting antibody-drug conjugate (ADC), benefits patients with HER2-low metastatic breast cancer (mBC). This efficacy in HER2-low disease (45–65% of cases) has spurred research into optimal methods for identifying eligible patients. We propose molecular imaging to explore intra-/interpatient heterogeneity in HER2 mapping of metastatic disease and to identify patients unlikely to benefit from T-DXd. **Methods:** HER2-low mBC patients with IHC1+ or IHC 2+/FISH ≤ 2.2 scheduled for T-DXd underwent paired HER2-targeted [^{18}F]AlF-HER2-BCH PET/CT (HER2-PET) and [^{18}F]FDG-PET/CT (FDG-PET) at baseline and 2 cycle follow-up. High-uptake was defined as having $>50\%$ of tumors with a baseline SUVmax >6.0 on HER2-PET; otherwise, it was low uptake. HER2-PET was defined as non-responding showed no significant reduction of HER2 uptake (10%) at 2 cycle follow-up. Negative (NPV) and positive predictive values (PPV) of HER2-PET, FDG-PET, early HER2/FDG response, and their combination were assessed to predict morphological response (RECIST 1.1) after two T-DXd cycles and time-to-treatment failure (TTF). **Results:** In the 32 HER2-low mBC patients analyzed, 24 (75%) had high baseline HER2-PET uptake (SUVmax >6.0), while 8 (25%) had low uptake. Of 24 high-uptake patients, 14 (58.3%) achieved a complete response (CR), 7 (29.2%) initially reached a partial response (PR) after two T-DXd cycles but later developed progressive disease (PD) between cycles 5–10, and 3 (12.5%) experienced PD as early as cycle 2. In the low-uptake group (n=8), one patient (12.5%) with isolated pulmonary metastases maintained stable disease (SD) through 14 cycles, whereas 7 (87.5%) patients with multiple metastases developed rapid PD. Compared with RECIST1.1, respective NPV/PPV for baseline HER2-PET were 87.5%/87.5% for predicting treatment response at 2 cycles. When combining baseline HER2-PET uptake with early 2 cycles, patients with high baseline uptake and a $\Delta\text{SUVmax} >40\%$ had a median TTF of 15.3 months [n = 14, 95% confidence interval (CI) 7.7–not calculable], those with high baseline uptake and a $10\% < \Delta\text{SUVmax} <40\%$ a median TTF of 4.8 months [n = 7, 95% CI: 3.8–9.8]; and patients with a $\Delta\text{SUVmax} <10\%$ a median TTF of only 1.3 months [n = 10, 95%CI: 1.3, 3.9]. Baseline FDG uptake was not associated with lesion response status, and while trends in ΔSUVmax aligned with those observed in HER2-PET, no clear cutoff value was established in this study. **Conclusions:** Baseline HER2-PET uptake, especially when combined with early on-treatment ΔSUVmax , not only improves the understanding of tumor heterogeneity but also offers an imaging-guided strategy to personalize management and select patients most likely to benefit from T-DXd in HER2-low mBC. Clinical trial information: NCT06909604; NCT04547309. Research Sponsor: None.

Intracranial efficacy and safety of trastuzumab deruxtecan in HER2-positive and HER2-low metastatic breast cancer with central nervous system involvement: A systematic review and proportional meta-analysis.

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Background: Central nervous system (CNS) metastases and leptomeningeal disease (LMD) are major drivers of morbidity and mortality in metastatic breast cancer (MBC). Trastuzumab deruxtecan (T-DXd) has demonstrated intracranial activity across multiple studies; however, evidence remains fragmented across heterogeneous CNS subgroups. We conducted a systematic review and meta-analysis to assess intracranial efficacy and survival outcomes, along with interstitial lung disease (ILD) risk with T-DXd monotherapy in CNS-involved HER2-positive and HER2-low MBC. **Methods:** Following PRISMA guidelines, prospective trials and retrospective cohorts reporting CNS outcomes with T-DXd monotherapy were included. Fifteen unique cohorts met eligibility criteria. The primary endpoint was intracranial objective response rate (iORR). Secondary endpoints included progression-free survival (PFS) and overall survival (OS). Safety analysis included ILD incidence. Random-effects proportional meta-analyses and prespecified subgroup and sensitivity analyses were performed (RevMan 5.4.1). **Results:** In patients with active brain metastases (11 cohorts), pooled iORR was 0.61 (95% CI 0.55–0.66; $I^2=0\%$). Similarly, in stable brain metastases (6 cohorts), pooled iORR was 0.61 (95% CI 0.50–0.71; $I^2=75\%$); exclusion of an influential cohort increased pooled iORR to 0.65 (95% CI 0.55–0.75) and reduced heterogeneity. In LMD (3 cohorts), pooled CNS response was 0.53 (95% CI 0.35–0.70; $I^2=0\%$). HER2-low cohorts demonstrated a pooled iORR of 0.51 (95% CI 0.33–0.69), which did not differ significantly from HER2-positive CNS subgroups ($p=0.75$). Where comparative data were available, treatment with T-DXd was associated with improved PFS (HR 0.33, 95% CI 0.19–0.58) and overall survival (log HR -0.32 , 95% CI -0.55 to -0.09 ; $\approx$ HR 0.73). Safety analyses showed a pooled incidence of ILD (any grade) of 0.12 (95% CI 0.09–0.15), with higher rates observed in high-risk (0.16) and intermediate-risk (0.13) cohorts compared with low-risk cohorts (0.04). **Conclusions:** Across 15 cohorts, T-DXd demonstrates consistent and clinically meaningful intracranial activity in active and stable brain metastases, substantial activity in LMD, and a survival signal where comparative data exist, with quantifiable ILD risk. These findings support T-DXd as a key systemic therapy for CNS-involved HER2-positive and HER2-low MBC and underscore the need for standardized CNS endpoints and ILD mitigation strategies in future studies. Research Sponsor: None.

Neoadjuvant dalpiciclib combined with letrozole and dual HER2 blockade in HR+/HER2+ breast cancer: First-stage results of the HELEN HER2 017 trial.

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Background: Triple-positive breast cancer (TPBC; HR+/HER2+) represents a distinct subtype with suboptimal responses to conventional neoadjuvant chemotherapy combined with anti-HER2 therapy, with reported pCR rates of only 26%–43.8%, and is associated with significant treatment-related toxicities^{1–3}. This highlights an urgent need for more effective and less toxic therapeutic strategies. We hypothesize that simultaneously targeting ER, HER2, and CDK4/6 pathways may enhance antitumor efficacy while enabling chemotherapy de-escalation. This phase II study investigates a response-guided, chemotherapy-free neoadjuvant regimen using dalpiciclib (a CDK4/6 inhibitor), aromatase inhibitor (AI), and dual HER2 blockade. **Methods:** This prospective, single-arm, two-stage Simon optimal design study planned to enroll 71 patients. In stage one, 20 patients were enrolled; proceeding to stage two required ≥ 6 pCRs. The final success threshold is ≥ 24 pCRs in 71 patients ($\alpha=0.05$, power=80%, H_0 : pCR $\leq 25\%$ vs. H_1 : pCR $\geq 40\%$). Eligible patients had stage II–IIIa HR+/HER2+ invasive breast cancer. Treatment included oral dalpiciclib (150 mg/day, 3 weeks on/1 week off), oral letrozole (2.5 mg/day; with ovarian suppression if premenopausal), and IV trastuzumab (loading 8 mg/kg, then 6 mg/kg) plus pertuzumab (loading 840 mg, then 420 mg) every 3 weeks. This was a response-adaptive design: after 2 cycles, MRI assessed tumor response. Patients achieving PR ($\geq 30\%$ reduction per RECIST 1.1) continued the same regimen for 6 cycles; non-responders switched to TCHP chemotherapy (docetaxel, carboplatin, trastuzumab, pertuzumab). The primary endpoint was pCR (ypTo/is ypNo) in the all-treated population. Secondary endpoints included ORR, RCB 0–1, EFS, and safety. **Results:** In the first stage, 20 patients were enrolled. Median age was 48 years (range 34–59). All were ER+ and HER2+ by central review. After 2 cycles, 15 of 20 patients (75%) achieved PR and continued on the dalpiciclib, letrozole, and dual HER2 blockade regimen. Of the 20 patients, 8 achieved pCR, with a rate of 40%. Among the MRI responders who continued the experimental arm, the pCR rate was 40% (6/15). Treatment was generally well-tolerated; the most common adverse events were neutropenia, leukopenia, anemia, and thrombocytopenia. No treatment-related discontinuations or cardiac toxicity of grade 3 or higher were observed. **Conclusions:** The first stage of this response-guided study met its predefined efficacy threshold (≥ 6 pCR in 20 patients). The neoadjuvant regimen combining dalpiciclib, an AI, and dual HER2 blockade shows promising pCR rates and a favorable safety profile in TPBC, supporting continued evaluation in the second stage of the trial. Clinical trial information: NCT06276868. Research Sponsor: None.

Safety and efficacy of ZN-A-1041, a highly blood-brain barrier (BBB)–permeable HER2 tyrosine kinase inhibitor (TKI), + trastuzumab deruxtecan (T-DXd) or pertuzumab-trastuzumab (PH) in HER2-positive metastatic breast cancer (HER2+ mBC): Phase Ic expansion results from the ZN-A-1041-101-US trial.

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Background: Brain metastases (BMs) are a common site of progression in HER2+ mBC due to limited BBB penetration of systemic therapies. ZN-A-1041 is an oral, selective HER2 TKI designed for high intact BBB permeability. We report ZN-A-1041-101-US (NCT05593094) Phase Ic expansion results of ZN-A-1041 + T-DXd in patients (pts) with HER2+ mBC refractory to prior treatments (txs), or + PH as maintenance therapy after first-line taxane + H ± P induction. Phase Ia and Ib (dose-escalation as single agent or in combination therapies) results have been reported (Anders ASCO 2023). **Methods:** The study enrolled pts with HER2+ mBC, with or without BMs (including leptomeningeal disease). Pts in Phase Ic received ZN-A-1041 800 mg twice daily (BID) + PH (Arm C), or were randomized to ZN-A-1041 800 mg or 600 mg BID, + T-DXd 5.4 mg/kg every 3 weeks (Arms A and B, respectively). Primary objectives: safety and tolerability. Secondary objectives included systemic objective response rate (ORR) and disease control rate (DCR) per Response Evaluation Criteria in Solid Tumours version 1.1. **Results:** As of July 31, 2025 (last pt in), enrollment in Arms A, B, and C was 24, 23, and 20 pts, respectively; median age was 57, 54, and 46 years; 50, 36, and 70% had *de novo* stage IV disease. Baseline central nervous system (CNS) metastases were present in 58, 59, and 16% of pts. Median prior lines of therapy for metastatic disease was 1, 1, and 0. Median ZN-A-1041 tx duration was 23.0, 24.6, and 42.9 weeks. The most frequent all-grade tx-emergent adverse events (TEAEs) across Arms A, B, and C, respectively, were nausea (83, 96, and 47%), diarrhea (62, 77, and 68%), and vomiting (46, 64, and 47%); diarrhea (17, 9, and 5%) was the most frequent Grade ≥3 TEAE. Preliminary systemic efficacy is summarized in the Table. Intracranial lesion shrinkage was observed in pts with BMs across all tx arms. **Conclusions:** ZN-A-1041 showed manageable safety profiles and promising clinical activity when combined with standard anti-HER2 therapies in pts with HER2+ mBC, both with or without CNS metastases. High disease control in pts pretreated with T-DXd and notable continued responses in the PH maintenance setting support further clinical evaluation of these combinations. Clinical trial information: NCT05593094. Research Sponsor: F. Hoffmann-La Roche Ltd.

Arm	n	ORR, % (95% CI)	Complete response, % of pts	DCR, % (95% CI)
A: ZN-A-1041 800mg + T-DXd	20	65.0 (40.8, 84.6)	10.0	95.0 (75.1, 99.9)
B: ZN-A-1041 600mg + T-DXd	21	76.2 (52.8, 91.8)	9.5	90.5 (69.6, 98.8)
C: ZN-A-1041 800mg + PH	13*	30.8 (9.1, 61.4)	5.6	100 (75.3, 100.0)

*Efficacy reported for 13 pts with measurable disease receiving maintenance therapy with ZN-A-1041 + PH after taxane + H ± P induction.
CI, confidence interval.

TBCRC 050: A phase 1b/2 trial of niraparib and trastuzumab in HER2-positive metastatic breast cancer (MBC): Efficacy and correlative analyses.

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Background: Resistance to HER2-directed therapies remains a major challenge in HER2-positive MBC. In preclinical models, HER2+ tumors overexpress poly (ADP-ribose) polymerase (PARP), and PARP inhibition induces apoptosis through NF- κ B suppression even in the absence of pathogenic mutations in *BRCA 1/2*. We evaluated the safety, efficacy, and translational correlates of niraparib combined with trastuzumab in patients (pts) with refractory HER2+ MBC. **Methods:** This open-label Phase 1b/2 trial (NCT03368729) enrolled pts with HER2+ MBC (IHC 3+ and/or FISH amplified), measurable disease, LVEF $\geq 50\%$, and progression on ≥ 1 prior HER2-targeted therapy; stable CNS disease was allowed. Pts with germline *BRCA1/2* mutations or prior PARP inhibitor exposure were excluded. Niraparib 300 mg orally was administered on Days 1–21 of a 21-day cycle with trastuzumab 6 mg/kg IV every 3 weeks (loading dose 8 mg/kg on cycle 1). The Phase 2 portion used a Gehan/Simon two-stage design with early stopping for futility ($P_0=24\%$); ≥ 1 response among the first 20 patients triggered expansion to 40 patients. ORR was assessed by RECIST v1.1, meeting the primary endpoint and allowing response rate estimation with $<7\%$ standard error and a two-sided 95% exact CI width of 0.28. Gene expression profiling of paired tumor tissue and peripheral blood mononuclear cells (PBMCs) was performed using the NanoString nCounter Tumor Signaling 360 panel at pretreatment compared to cycle 2. **Results:** Forty-six pts were enrolled (9/2019–2/2025); 41 were evaluable for response. Pts were heavily pretreated (median 3 prior regimens), including trastuzumab deruxtecan in 22 pts; 33% had brain metastases. Treatment-related adverse events were predominantly grade 1–2 and manageable. Clinical benefit rate (CBR) was 44% (18/41) including 1 complete response, 2 partial responses, and 15 stable disease. Eleven patients achieved disease control ≥ 6 months; 1 patient remained on treatment at data cutoff. Tumor profiling revealed enrichment of a B-cell-driven tertiary lymphoid structure signature with reduced hypoxia signaling in responders. Matched PBMC analyses demonstrated coordinated down-regulation of interferon signaling, DNA damage response, metabolic activation, angiogenesis, and resistance pathways in clinical responders, whereas non-responders retained signatures of chronic stress and immune exhaustion. **Conclusions:** Niraparib plus trastuzumab demonstrated a favorable safety profile and durable clinical benefit in heavily pretreated HER2+ MBC. Integrated tumor and blood-based analyses identify immune-organized tumor microenvironments and systemic immune normalization as key correlates of prolonged response, supporting further investigation of PARP inhibition strategies. Clinical trial information: NCT03368729. Research Sponsor: GlaxoSmithKlin (GSK); V Foundation for Cancer Research; T20180005; Susan G. Komen; CCR17483582; National Cancer Institute; U54 CA118623; TBCRC by its foundation partners.; TESARO.

Real-world cardiotoxicity with HER2 antibody–drug conjugates and survival after treatment continuation.

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Background: HER2 antibody–drug conjugates (ADCs) are central to HER2-positive breast cancer (BC) treatment, yet cardiotoxicity remains a clinically relevant complication that may prompt treatment interruption. While HER2-related cardiac dysfunction is frequently reversible, uncertainty persists regarding the safety and survival impact of treatment continuation, particularly with newer ADCs. We assessed real-world cardiotoxicity and the association between treatment continuation and overall survival (OS), focusing on trastuzumab deruxtecan (T-DXd) and trastuzumab emtansine (T-DM1). **Methods:** Using the TriNetX Research Network (2010–2025), adults with BC treated with HER2-targeted therapy and no prior diagnosis of heart failure or cardiomyopathy were identified. Incident cardiotoxicity (heart failure or cardiomyopathy) within one year of therapy initiation was captured. OS from cardiotoxicity diagnosis was compared between patients (Pts) who resumed versus discontinued HER2-targeted therapy. Kaplan–Meier methods were used to estimate survival, and Cox proportional hazards models generated hazard ratios (HRs) with 95% confidence intervals (CIs). **Results:** Among 31,656 HER2-treated Pts, 4,593 (14.5%) developed cardiotoxicity within one year; 629 (11.1%) occurred with HER2 ADCs. Incidence was lower with ADCs than non-ADC therapy (T-DM1 11.6%, T-DXd 9.9%). After cardiotoxicity, 3,374 Pts (73.5%) resumed HER2 therapy, including 48.5% with T-DM1 and 47.7% with T-DXd. 5-year OS was significantly higher with HER2-targeted treatment resumption versus discontinuation (79.5% vs 66.9%; absolute difference 12.6%; $p<0.0001$), with a 55% mortality risk reduction (HR 0.45, 95% CI 0.39–0.51). ADC-specific analyses showed benefit, greatest for T-DXd (HR 0.25, 95% CI 0.14–0.43; absolute 5-year OS difference 19.3%) and T-DM1 (HR 0.34, 95% CI 0.23–0.50; absolute difference 21.0%). Pts who resumed therapy were younger than those who discontinued (58.0 ± 13.1 vs 61.8 ± 13.5 years). After multivariable adjustment, treatment resumption remained independently associated with improved OS (adjusted HR 0.45, 95% CI 0.39–0.51), though residual confounding cannot be excluded. **Conclusions:** In this large real-world cohort, continuation of HER2 ADCs after cardiotoxicity was associated with substantially improved OS. These findings support a multidisciplinary cardio-oncology approach and suggest that, when feasible, resuming HER2 ADCs—particularly T-DXd and T-DM1—may confer meaningful survival benefit. Research Sponsor: None.

Cardiotoxicity and survival outcomes with HER2/ADCs.						
Agent	Total Treat- ed (N)	Cardiotoxicity (%)	Therapy Re- sumed (%)	5-year OS % (Re- sumed vs Not)	Absolute OS Difference	HR (95% CI)
All	HER2 0.44 (0.39-0.51)	31,656	14.5	73.5	79.5 vs 66.9	+12.6%
T-DM1	DM1 0.34 (0.23-0.50)	4,085	11.6	48.5	74.9 vs 53.9	+21.0%
T-DXd	1,558	9.9	47.7	48.0 vs 28.7	+19.3%	0.25 (0.14–0.43)

HER2-targeted tyrosine kinase inhibitors in breast cancer: Real-world analysis of gastrointestinal and musculoskeletal toxicities using the FAERS database.

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Background: Human Epidermal Growth Factor Receptor 2 (HER2)-targeted tyrosine kinase inhibitors (TKIs) lapatinib, neratinib, and tucatinib are approved for HER2-positive breast cancer but have distinct adverse event (AE) profiles. We analyzed the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database to characterize gastrointestinal (GI) and musculoskeletal (MSK) toxicities associated with these agents. **Methods:** We conducted a retrospective FAERS data review to assess GI and MSK AEs associated with the three TKIs from 2020–2025. The chi-square test was used to compare categorical variables across drugs and age groups (<65 vs ≥ 65 years). **Results:** Among 9,045 total cases (lapatinib $n=1,897$; neratinib $n=1,113$; tucatinib $n=6,035$), neratinib demonstrated the highest GI toxicity rate at 64.2%, compared to 40.4% for tucatinib and 31.3% for lapatinib ($\chi^2=319.3$, $p<0.001$). Diarrhea was the predominant GI AE across all agents, affecting 82.1% of neratinib-treated patients, 64.8% of tucatinib-treated patients, and 55.6% of lapatinib-treated patients. Other common GI AEs included nausea (33.2 neratinib, 34.6 tucatinib, 23.1 lapatinib) and vomiting (21.1% neratinib, 19.5% tucatinib, 23.9 lapatinib). MSK AE rates were comparable across all three agents (lapatinib 10.5%, neratinib 11.3%, tucatinib 10.5%; $\chi^2=0.72$, $p=0.70$). The most frequent MSK AEs were pain in extremities (23% overall), arthralgia (18% overall), back pain (17.8% overall), and muscle spasms (17.6% overall). Age-stratified analysis revealed significant differences in GI toxicity. In patients <65 years, neratinib showed the highest GI AE rate at 63.1%, versus 34.8% for tucatinib and 28.1% for lapatinib ($\chi^2=74.0$, $p<0.001$). In patients ≥ 65 years, this pattern persisted with neratinib at 73.7%, tucatinib at 36.9%, and lapatinib at 40.1% ($\chi^2=49.4$, $p<0.001$). Moreover, older patients (≥ 65 years) experienced significantly higher rates of both GI and MSK AEs with lapatinib (GI: 40.1% vs 28.1%, $p<0.001$; MSK: 19.3% vs 9.6%, $p<0.001$) and neratinib (MSK: 25.3% vs 6.3%, $p<0.001$). Tucatinib showed no significant age-related differences in AE rates. **Conclusions:** The findings in this study highlight trends for selected AEs with various TKIs in order to help guide shared decision-making and tailored management strategies for patients with HER2-positive breast cancer. Research Sponsor: None.

Dual HER2 blockade with or without taxane induction in HR+/HER2+ metastatic breast cancer: A comparative analysis of clinical outcomes.

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Background: In the era of modern dual HER2 blockade, the necessity of taxane induction for ER+/HER2+ metastatic breast cancer (MBC) remains debated. While CLEOPATRA established pertuzumab/trastuzumab plus taxane as a standard backbone, emerging de-escalation strategies suggest that endocrine therapy (ET) combined with HER2 blockade may provide durable disease control in this favorable-prognosis subgroup (SYSUCC002, PERTAIN). Robust real-world comparative data addressing the survival-toxicity trade-off between chemotherapy-free versus taxane-induction approaches are limited. **Methods:** The TriNetX Global Collaborative Network (168 healthcare organizations; data updated Dec 2025) was queried for adults (≥ 18 years) with incident HR+/HER2+ MBC treated with dual HER2 blockade (trastuzumab + pertuzumab) plus ET. Patients receiving induction taxane (paclitaxel or docetaxel) comprised the induction cohort (IND); those treated with dual blockade + ET without induction comprised the chemotherapy-free cohort (Chemo-Free). 1:1 propensity-score matching (greedy nearest-neighbor; caliper 0.10) on demographics and comorbidities yielded 137 well-balanced pairs ($N=274$) with all post-match standardized mean differences < 0.10 . The primary endpoint was 3-year overall survival (OS; 1095-day window). Secondary outcomes included neutropenia, sepsis, heart failure, emergency department (ED) visits, and ICU admission. **Results:** Among 957 eligible patients, 153 received Chemo-Free and 804 received IND; 137 matched pairs were analyzed. Three-year OS was similar between cohorts with no statistically significant separation of survival curves (3-year OS 89.1% Chemo-Free vs 82.0% IND; HR 0.65 [0.32–1.31]; $p=0.219$). Deaths within 3 years were 13/137 (9.5%) in Chemo-Free versus 19/137 (13.9%) in IND, corresponding to an absolute death risk difference of -4.4% (95% CI -12.0% to $+3.2\%$). Omitting induction was associated with reduced neutropenia (12.4% vs 21.9%; absolute risk reduction 9.5%; OR 0.51 [0.26–0.97] and a lower time-to-neutropenia hazard (HR 0.50 [0.28–0.91]; $p=0.020$). Serious adverse events and acute care utilization were not increased with Chemo-Free: heart failure 16.1% vs 16.1%; sepsis 10.9% vs 13.1%; ICU admission 11.7% vs 13.9%; ED visits 40.9% vs 45.3%. **Conclusions:** In a propensity-matched real-world cohort receiving contemporary dual HER2 blockade plus ET, a chemotherapy-free strategy demonstrated similar 3-year OS compared with taxane induction, with a clinically meaningful reduction in neutropenia (number needed to treat ≈ 11 to prevent one event) and no signal for higher sepsis, heart failure, or acute care utilization. These data support the feasibility of chemotherapy de-escalation in selected HR+/HER2+ MBC patients and motivate prospective validation to refine patient selection and minimize treatment-related toxicity. Research Sponsor: None.

Nanochemo-immunotherapy of ER-positive metastatic breast cancer (MBC) with PEG-liposomal doxorubicin (PLD) and pembrolizumab (PEM).

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Background: PLD is a nanomedicine containing doxorubicin, a potent immunogenic cell death inducer. Based on the pharmacological profile of PLD, we hypothesized that PLD-based chemotherapy should allow for improved immune recognition of tumor cells and activation of T cells by PD1 blockade. We report here the results of a phase 1B study with a combination of PLD and PEM in ER+/Her2 negative MBC. **Methods:** Patients with MBC, whose disease progressed on hormonal, CDK 4/6 inhibitors and up to 3 lines of chemotherapy, were eligible for enrollment. Primary objectives were evaluation of safety and tumor response, and secondary objectives were overall survival and pharmacokinetic analysis of PLD and PEM. In a first cohort of 15 patients, PLD 30 mg/m² was infused along with PEM 200 mg on day 1 every 3 weeks. In a second cohort of 20 patients, PLD 40 mg/m² was infused on day 1 every 4 weeks without change of PEM dose-schedule. Responding and stable patients continued treatment until disease progression or treatment intolerance. All patients were followed up on for survival. **Results:** 35 patients were enrolled. A total of 201 PLD and 257 PEM treatments were administered until data lock. Treatment was well tolerated with no grade 3–4 neutropenia, no cardiac events, and no grade 2 hair loss. In one patient, a severe infusion reaction to PLD was observed forcing discontinuation of PLD in the 2nd cycle. There were 2 cases of grade 4 hepatitis, 1 case of grade 4 hemolytic anemia, and 5 cases of grades 1–2 hypothyroidism, possibly or probably related to PEM. PLD-related skin toxicity (palmar-plantar erythema, grades 1–2) was observed after 3 or more cycles, forcing treatment delays. Among evaluable patients receiving ≥ 3 cycles of PEM (n=30), we observed 8 partial and 2 complete responses with a long median duration of response (11 mo) and survival (28 mo). In 5 patients, near complete responses of large liver metastases were observed. Median survival was 25 mo for all patients and 26 mo for evaluable patients. Eight patients, including 1 patient still under treatment, remain alive at data lock with survival in the range of 10+ to 51+ mo. The plasma clearance of PLD was mono-exponential with high C_{max}, long T_{1/2} (~3 days), slow clearance, and small V_{cc}. There was a significant increase of ~20% in the average AUC of PLD between the 1st and 3rd cycle indicating delayed clearance upon PLD retreatment. Analysis of PEM plasma levels revealed a mean T_{1/2} of ~11 days with high trough concentration by end of the cycle implying saturation of all accessible PD1 receptors. **Conclusions:** The combination of both dose levels of PLD with PEM is well tolerated, active, and feasible for extended treatment with durable responses. The favorable response and survival data in this heavily pretreated patient group suggest that PEM has significant contribution to the anti-tumor effect. A randomized study in ER+ MBC patients based on this regimen is warranted. Clinical trial information: NCT03591276. Research Sponsor: Merck USA; MK-3475 733.

Effectiveness outcomes by treatment-free interval among patients receiving palbociclib plus endocrine therapy in HR+/HER2– advanced breast cancer in the real-world setting: Results from the PERFORM study.

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Background: Combination of CDK4/6 inhibitors (CDK4/6i) plus endocrine therapy (ET) is first-line (1L) standard of care for patients (pts) with HR+/HER2– advanced breast cancer (ABC). Treatment-free interval (TFI) is an established prognostic factor in ABC. Shorter TFI is associated with more aggressive disease biology, inferior treatment outcomes, and reduced overall survival (OS). Real-world (RW) evidence complements clinical trials by providing insights into pts underrepresented in clinical trials. We present interim analysis 5 (IA5) of the PERFORM study, evaluating outcomes by TFI in pts receiving 1L palbociclib + ET. **Methods:** The prospective, non-interventional study PERFORM (NCT04767594) enrolled pts across Germany and Austria receiving 1L palbociclib + ET. Primary endpoint is progression-free survival (PFS). Secondary endpoints include second line (2L) PFS, PFS2 (time from 1L start to progression on 2L or death) and OS. Tumor assessments followed local medical standards. Quality of life (QoL) was assessed using FACT-B questionnaires. Pts were stratified by TFI, defined as time from last (neo)adjuvant treatment to recurrence: >12 months, ≤12 months, and de novo advanced disease. Time-to-event endpoints were estimated using the Kaplan-Meier method. **Results:** At database cutoff (Sep 30th, 2025), 1268 pts were included in IA5 and 1010 pts had available TFI data for subgroup analysis (TFI >12 months: 373 pts; ≤12 months: 133 pts; de novo: 504 pts). Median age was 69.5, 64.4, and 68.8 years, respectively. Pts with TFI ≤12 months showed a more aggressive disease profile such as higher rates of G3 tumors, N2–3 nodal status and liver metastasis compared to other TFI subgroups. Overall median PFS was 25.5 months (95% CI: 23.0–28.6), while median PFS was 29.2 months (95% CI: 23.3–33.1) for TFI >12 months, 14.6 months (95% CI: 9.3–19.4) for TFI ≤12 months, and 31.5 months (95% CI: 26.5–36.7) for pts with de novo disease. Median PFS2 was 39.0 (95% CI: 33.7–51.4), 21.2 (95% CI: 17.4–37.0), and 40.9 months (95% CI: 37.0–46.9) for TFI >12, ≤12, and de novo, respectively. Median OS was not reached for TFI>12 months and was 37.4 and 52.8 months for TFI ≤12 and de novo, respectively. QoL with 1L therapy was maintained in all subgroups. **Conclusions:** The PERFORM IA5 supports TFI as a relevant prognostic factor for pts treated with palbociclib + ET in the 1L RW setting. QoL was maintained in TFI subgroups. Longest clinical benefit was observed in pts with TFI > 12 months and those with de novo disease. Treatment was associated with shorter clinical outcome in pts with TFI≤12 months compared to those in other TFI subgroups. These results complement those in the RCT setting. Research Sponsor: Pfizer Pharma GmbH, Germany.

Clinical efficacy of a novel oral SERD TFX06 in prior fulvestrant-treated ER+/HER2—advanced breast cancer patients in a dose expansion study.

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Background: Patients with ER+/HER2- advanced breast cancer who have progressed on prior endocrine therapies, including fulvestrant, represent an area of unmet medical need, particularly those harboring ESR1 mutations. As far as we know, there was limited reports on efficacy of oral SERD in prior fulvestrant treatment progressed patients. TFX06 is an investigational next-generation oral SERD. Here, we report results from a Phase I/II study of TFX06 in patients with ER+/HER2- advanced breast cancer who had progressed from prior fulvestrant treatment (NCT05927779). **Methods:** Eligible patients regardless of their menopausal status, who had received ≥ 1 lines of endocrine therapy (ET), prior fulvestrant (fulv) treated with or without CDK4/6i, and ≤ 2 line of chemotherapy in metastatic disease, were allowed to enroll. TFX06 tablets were orally administered at 150mg once daily (QD) in 28-day cycles until disease progression or intolerable toxicity. This analysis focuses on the subgroup with prior fulvestrant exposure. As of cut-off date December 22, 2025, 42 patients received TFX06 monotherapy at 150mg. Median age was 60.5 years (range, 34–73), 76.2% had an ECOG performance status of 1. 88.1% had visceral metastasis, and 16.7% had brain metastasis. The median number of prior endocrine therapies in the advanced or metastatic setting was 2 (range, 1–3), including fulvestrant (100%), CDK4/6i (85.7%) with combination (76.2%). Tumor assessments by investigators according to RECIST v1.1 were performed every eight weeks. **Results:** Of the 42 enrolled patients, 40 were evaluable for efficacy. In the full analysis set (n=40), median progression-free survival (PFS) was 5.5 months (95% CI, 3.2–7.8). The objective response rate (ORR) was 7.5% (3/40), disease control rate (DCR) was 60.0% (24/40), and clinical benefit rate (CBR) was 44.1% (15/34). In the ESR1-mutant subgroup (n=23), median PFS was 5.7 months (95% CI, 2.5–8.8), ORR was 8.7% (2/23), DCR was 65.2% (15/23), and CBR was 47.1% (8/17). Treatment emergent adverse events (TEAEs) occurred in 95.2% of patients (40/42), with grade ≥ 3 events in 26.2% (11/42). Most common TEAEs ($\geq 20\%$) are laboratory abnormalities; they included hypertriglyceridemia (47.6%), increased AST (31.0%), anemia (31.0%), decreased lymphocyte count (23.8%), and decreased white blood cell count (21.4%). No TEAEs led to treatment termination. **Conclusions:** TFX06 showed promising clinical activity and a manageable safety profile in patients who progressed from prior fulvestrant-treatments including combination with CDK4/6i in ER+/HER2- advanced breast cancer, including those with ESR1 mutations. These findings support further development of TFX06 as a potential therapeutic option in this population. Clinical trial information: NCT05927779. Research Sponsor: None.

Impact of adherence to interstitial lung disease (ILD)/pneumonitis toxicity management guidelines (TMGs) on ILD/pneumonitis outcomes: A retrospective analysis of patients (pts) treated with trastuzumab deruxtecan (T-DXd) in DESTINY-Breast06 (DB-06).

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Background: DB-06 (NCT04494425) showed a progression-free survival benefit with T-DXd vs physician's choice of chemotherapy for pts with hormone receptor-positive, HER2-low/-ultralow metastatic breast cancer, with no new safety signals. We report adherence rates to ILD/pneumonitis TMGs and their impact on ILD/pneumonitis outcomes. **Methods:** We retrospectively analyzed pts who received ≥ 1 dose of 5.4 mg/kg T-DXd and had adjudicated drug-related ILD/pneumonitis by the Mar 18, 2024 data cutoff. Adherence criteria were defined by ILD/pneumonitis severity at diagnosis (per investigator assessment) and associated TMGs (Table); adherence was classified as complete (CA), partial (PA), or non-adherence (NA) by TMG criteria met (all, ≥ 1 but not all, or none, respectively). Investigator-reported ILD/pneumonitis outcomes were 'recovered' ($\pm$ sequelae), 'recovering', 'not recovered', and 'fatal'. **Results:** Of 49 pts with adjudicated drug-related ILD/pneumonitis, respective rates of CA, PA, and NA were 73.5% (n=36), 14.3% (n=7), and 12.2% (n=6). By Mar 24, 2025, 66.7% (n=24) of pts with CA and 71.4% (n=5) with PA had an outcome of recovered $\pm$ sequelae, with no fatalities. Of pts with NA, 50% (n=3) did not recover, including one fatality. At diagnosis, 31 (63.3%), 15 (30.6%), and 3 (6.1%) pts had Grade (Gr) 1, 2, and 3 ILD/pneumonitis, respectively. Across all cases, 38.8% (n=19) progressed to a worse grade after diagnosis; progression from Gr 1 to Gr 2 represented 84.2% of progressions. Of 25 pts with Gr 1 ILD/pneumonitis and CA (optional steroid use), 16 received steroids and 9 did not; recovery rates were comparable (68.8% with steroids vs 66.7% without). For pts with Gr ≥ 2 ILD/pneumonitis and CA or PA (n=18), steroid use as recommended was associated with improved recovery rates (66.7% with steroids vs 33.3% without). Two pts with Gr 1 ILD/pneumonitis at diagnosis were rechallenged with 4.4 mg/kg T-DXd; both had recurrent Gr 1 ILD/pneumonitis but recovered. **Conclusions:** Adherence to ILD/pneumonitis TMGs was associated with improved ILD/pneumonitis outcomes in this small subset of pts. Steroid use as recommended for Gr ≥ 2 cases was associated with improved recovery. While further investigation of patient-level determinants of recovery is needed, these data demonstrate that adhering to ILD/pneumonitis TMGs may optimize ILD/pneumonitis outcomes. Clinical trial information: NCT04494425. Research Sponsor: AstraZeneca in collaboration with Daiichi Sankyo.

Adherence criteria by ILD/pneumonitis grade at diagnosis.

	Gr 1	Gr 2	Gr ≥ 3
T-DXd interrupted after AE onset	Yes	—	—
T-DXd discontinued after AE onset	—	Yes	Yes
500–1000 mg/day methylprednisolone for 3 days	—	—	Yes
≥ 1 mg/kg/day prednisone*	—	Yes	Yes
Steroid duration ≥ 14 days	—	Yes	Yes
≥ 4 -week taper	—	Yes	Yes
If no improvement 5 days from AE onset, switched to 2 mg/kg/day IV prednisone*	—	Yes	Yes

*Or equivalent; AE, adverse event.

CAPTURE: A phase II trial evaluating alpelisib + fulvestrant vs capecitabine in advanced breast cancer patients with *PIK3CA*-mutant circulating DNA following CDK4/6 inhibition.

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Background: *PIK3CA* mutations are a key therapeutic target in ER+ advanced breast cancer (ABC) readily detectable through circulating tumor DNA (ctDNA). The PI3K α inhibitor alpelisib is approved in ER+ HER2- ABC but it remains unclear when to incorporate it into the current treatment algorithm. To address this, we conducted a phase II study assessing superiority of alpelisib + fulvestrant vs capecitabine in ABC pts with detectable *PIK3CA* mutant ctDNA following CDK4/6i plus aromatase inhibition (AI). **Methods:** Eligible pts had ER+ HER2- ABC, prior progression on CDK4/6i+AI and *PIK3CA* mutations detected via ctDNA ddPCR. Pts were randomized 1:1 to receive alpelisib (300mg daily) + fulvestrant (Arm A), or capecitabine (1000-1250mg/m² BD D1-14 q21d) (Arm B); strata were prior chemo for ABC and visceral disease. Primary endpoint was progression free survival (PFS) defined from randomization until progressive disease per RECIST 1.1 or death. Secondary endpoints included objective response rate (ORR), clinical benefit rate (CBR) and adverse events (AE). Imaging was q8 weeks. Exploratory objectives included efficacy according to baseline ctDNA levels. Sample size was reduced from 140 to 66 pts randomized for 53 PFS events to detect median PFS of 9 vs 5 mo (HR=0.56; 1-sided $\alpha=0.1$, 80% power). Interim inefficacy analysis (60% events) estimated HR>1.0 and IDMC recommended early termination. Follow-up continued until all pts completed alpelisib. Reported are stratified Cox model HR (2-sided 80% CI) and 2-sided log rank test. **Results:** From July 2020-Oct 2024, 396 pts were screened, 113 (29%) had *PIK3CA* mutant ctDNA, 58 were randomized and 55 initiated treatment (Arm A: 29/30; Arm B: 26/28). Median age was 56 (32-82 yrs), 75% had visceral disease; 87% had no prior chemo for ABC. At final analysis, 43 PFS events occurred. Median PFS was 7.4 mo for alpelisib + fulvestrant vs 9.4 mo for capecitabine (HR 1.28, 80% CI: 0.84-1.96, p=0.45). For pts with visceral disease, median PFS was 5.4 mo (80% CI: 3.7-5.1) for alpelisib + fulvestrant and 12.1 mo (80% CI: 5.4-15) for capecitabine. ORR was 24.1% vs 50.0% and CBR 55.2% vs 61.5% for alpelisib + fulvestrant vs capecitabine. Overall, 79.3% pts on alpelisib + fulvestrant had grade 3/4 AEs with 24% grade 3 hyperglycemia vs 46.2% on capecitabine with 12% grade 3 palmar-plantar erythrodysesthesia. Six of 30 pts discontinued alpelisib due to AEs; 5 of the 6 continued fulvestrant. There was no evidence of association between baseline ctDNA levels (*PIK3CA* mutant copies/ml; median 90; range 2-13678) and PFS (HR 1.03; 90%CI: 0.90-1.19). **Conclusions:** In our trial of pts with *PIK3CA* mutant ABC after progression on CDK4/6i plus AI, targeted therapy with alpelisib + fulvestrant was not superior to standard chemotherapy with capecitabine. Compared with the targeted therapy, capecitabine was better tolerated and resulted in longer PFS. Clinical trial information: ACTRN12619001117101. Research Sponsor: National Health and Medical Research Council (NHMRC); #1143025.

Subgroup analysis of participants (pts) with HER2 IHC0 in the ASCENT-07 study of sacituzumab govitecan (SG) vs chemotherapy in HR+/ HER2– metastatic breast cancer (mBC).

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Background: SG was evaluated in the phase 3 ASCENT-07 study (NCT05840211) of pts with HR+/HER2–, locally advanced unresectable or mBC who had received prior endocrine therapy (ET) and were eligible for first chemotherapy; the primary end point (PFS by blinded independent central review [BICR] vs chemotherapy treatment of physician's choice [TPC]) was not met (HR 0.85; 95% CI, 0.69–1.05; $P = .130$). We report exploratory outcomes in pts with HER2 IHC0 expression status. **Methods:** Pts were randomized 2:1 to receive SG 10 mg/kg IV or TPC (capecitabine, nab-paclitaxel, or paclitaxel). Descriptive analyses of pts with HER2 IHC0 were performed for the primary end point of PFS by BICR, secondary end points of PFS by investigator (INV), overall survival (OS), objective response rate (ORR) and duration of response (DOR) by BICR, and safety. HER2 status was tested locally. **Results:** Of 690 pts enrolled, 292 (42%) had HER2 IHC0 (SG: 192; TPC: 100). Baseline demographics and pt characteristics were similar to the overall population. Median age was 58 yrs; 176 (92%) and 91 (91%) pts in SG and TPC groups, respectively, received prior ET + CDK4/6i in the metastatic setting; 88% and 86% had visceral disease. At 15.4-mo median f/u, SG showed numerical improvement in PFS vs TPC by BICR (HR 0.75; 95% CI 0.55–1.02; nominal $P = .0601$) and by INV (HR 0.66; 95% CI 0.50–0.86; nominal $P = .0024$). Although OS data were not mature (maturity rate for IHC0 subgroup, 28%), an early improvement trend favoring SG was observed. ORR by BICR was similar for SG and TPC, and median DOR by BICR was longer for SG vs TPC. Despite a higher proportion of pts experiencing grade ≥ 3 treatment-emergent adverse events (TEAEs) with SG vs TPC, the rate of treatment discontinuation was lower with SG (Table). The most common grade ≥ 3 TEAEs were neutropenia (SG: 54%; TPC: 21%), leukopenia (12%; 7%), and anemia (11%; 5%). Safety profile was consistent with overall population and prior reports. **Conclusions:** In this exploratory analysis from ASCENT-07, numerical trends of improved efficacy vs TPC and the overall population as well as a manageable safety profile support further investigation into the potential benefit of SG in patients with HR+/HER2– mBC and HER2 IHC0 status who are candidates for first chemotherapy. Clinical trial information: NCT05840211. Research Sponsor: Gilead Sciences, Inc.

	SG (n = 192)	TPC (n = 100)
Median PFS by BICR (95% CI), mo	9.2 (8.2–10.4)	8.1 (6.3–10.4)
HR (95% CI)	0.75 (0.55–1.02); $P = .0601^a$	
Median PFS by INV (95% CI), mo	8.5 (8.2–10.4)	6.1 (4.5–8.1)
HR (95% CI)	0.66 (0.50–0.86); $P = .0024^a$	
Median OS (95% CI), mo	Not reached (NR-NR)	20.2 (19.5–NR)
HR (95% CI)	0.68 (0.44–1.05); $P = .0820^a$	
ORR by BICR (95% CI), %	41 (34–48)	40 (30–50)
Median DOR by BICR (95% CI), mo	n = 78 10.8 (6.4–12.6)	n = 40 8.3 (5.5–11.2)
TEAEs, n (%)	n = 190	n = 100
Any grade	189 (99)	97 (97)
Grade ≥ 3	139 (73)	46 (46)
Led to dose reduction	83 (44)	35 (35)
Led to treatment discontinuation	4 (2)	7 (7)

^aNominal P value; unstratified log rank.

First disclosure of frontline treatment (1L tx) with the selective CDK4 inhibitor BGB-43395 in combination with letrozole for metastatic HR+/HER2– breast cancer (BC): A phase 1 safety expansion.

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Background: BGB-43395, a highly selective CDK4i, showed preclinical antitumor activity characterized by improved CDK4 target coverage and selectivity over CDK6. This enhanced selectivity may reduce off-target toxicity and the need for tx modifications. BGB-43395 is being evaluated as monotherapy or with endocrine therapy in patients (pts) with HR+/HER2– BC and other advanced solid tumors in an ongoing phase 1a/1b open-label, international study (NCT06120283). We report on the safety, preliminary anti-tumor activity, and pharmacodynamics (PD) of BGB-43395 + letrozole as 1L tx for BC. **Methods:** In safety expansion cohort 2, CDK4/6i-naïve pts with advanced/metastatic HR+/HER2– BC were randomized to receive BGB-43395 240, 400, or 600 mg PO BID + letrozole to determine the recommended dose for further development. The objectives were to assess safety, preliminary anti-tumor activity, and PD. **Results:** As of Nov 11, 2025, 58 pts received study tx (240 mg n = 19; 400 mg n = 19; 600 mg n = 20). Treatment emergent adverse events (TEAEs) occurred in 98% of pts; grade (G) ≥ 3 TEAEs in 32%, 37%, and 65% of pts on 240 mg, 400 mg, and 600 mg, respectively. The most common TEAEs (mostly G1/2) were (240 mg / 400 mg / 600 mg): diarrhea (79% / 95% / 90% [G3 5% / 11% / 30%]), nausea (53% / 68% / 85% [G3 0% / 5% / 0%]), and vomiting (26% / 47% / 60% [G3 0% / 0% / 0%]). Rates of TEAE hematologic toxicities (mostly G1/2) were low; neutrophil count decreased/neutropenia (240 mg 26% [G3 0%]; 400 mg 21% [G3 0%]; 600 mg 20% [G3 10%]); anemia (240 mg 5% [G3 0%]; 400 mg 21% [G3 0%]; 600 mg 20% [G3 5%]); platelet count decreased/thrombocytopenia ([all G1 or 2] 240 mg 5%; 400 mg 0%; 600 mg 5%). TEAEs led to dose modification in 53% of pts (median relative dose intensity: 240 mg 100%; 400 mg 97%; 600 mg 69%), tx discontinuation in 3% (240 mg, 1 pt; 600 mg, 1 pt), and 0 deaths. BGB-43395 + letrozole demonstrated early efficacy (Table) and strong PD effects, indicated by TK1 reduction and ctDNA decrease. Median study follow-up was 6.8 (range 3.2–9.7) mo, median time-to-response was 3.6 (range 1.6–8.4) mo, and median PFS was not reached. **Conclusions:** The CDK4-selective inhibitor BGB-43395, in combination with letrozole, demonstrated a favorable safety profile, with low hematologic and manageable gastrointestinal toxicity. Antitumor activity in 1L tx of pts with advanced HR+/HER2– BC was promising. Doses of 400 mg and 240 mg BID demonstrated efficacy and safety that support further development in combination with letrozole. Clinical trial information: NCT06120283. Research Sponsor: BeOne Medicines, Ltd.

BGB-43395 BID dose + letrozole	240 mg (n=19)	400 mg (n=19)	600 mg (n=20)
Median tx follow-up, mo	7.0	7.1	5.2
Best overall response, %			
PR ^a	58	68	40
SD	37	32	55
PD	5	0	0
NE	0	0	5
Objective response rate (CR + PR), %(95% CI)	58(33-80)	68(43-87)	40(19-64)
Disease control rate (CR + PR + SD), %(95% CI)	95(74-100)	100(82-100)	95(75-100)

RECIST v1.1 (investigator).

^aUnconfirmed.

Vepdegestrant, a proteolysis targeting chimera (PROTAC) estrogen receptor (ER) degrader, plus abemaciclib (ABE) in ER+/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC): TACTIVE-U phase 1b/2 results.

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Background: Substudy A of the open-label, phase 1b/2 TACTIVE-U umbrella study is evaluating vepdegestrant, an oral PROTAC ER degrader, in combination with ABE for treatment of ER+/HER2- ABC (NCT05548127). Here, we report results for all patients (pts) in phases 1b and 2 treated with vepdegestrant (200 mg orally once daily) plus ABE (150 mg orally twice daily). **Methods:** Eligible pts were adults (age ≥ 18 years) with ER+/HER2- ABC who had received 1–2 prior lines of therapy in the ABC setting; 1 prior cyclin-dependent kinase 4/6 inhibitor (CDK4/6i)-based regimen (in any setting) was required. The primary endpoint of phase 1b was dose-limiting toxicities during the first cycle. The primary endpoint of phase 2 was objective response rate (ORR); secondary endpoints included clinical benefit rate (CBR), progression-free survival (PFS), safety, and pharmacokinetics (PK). **Results:** As of October 10, 2025, 37 female pts (median age, 59 years [range, 38–84]; 20 pts [54.1%] had ESR1-mutated [ESR1m] tumors) received vepdegestrant plus ABE in phases 1b and 2, with 26 pts treated for ≥ 5 28-day cycles; 10 remain on treatment. All pts received prior CDK4/6i (ribociclib, 48.6%; palbociclib, 43.2%; ABE, 8.1%) in any setting; prior treatments in the metastatic setting included aromatase inhibitors (64.9%), fulvestrant (35.1%), and chemotherapy (21.6%). Among pts with measurable disease at baseline, the ORR was 30.6% (95% CI, 18.0–46.9) in all pts and 45.0% (95% CI, 25.8–65.8) in pts with ESR1m tumors. The CBR was 59.5% (95% CI, 43.5–73.7) in all pts and 65.0% (95% CI, 43.3–81.9) in pts with ESR1m tumors. Median PFS was 7.2 months (95% CI, 5.5–16.5) in all pts and 10.9 months (95% CI, 5.5–not estimable) in pts with ESR1m tumors. Five pts (13.5%) discontinued treatment due to treatment-emergent adverse events (TEAEs). TEAEs led to dose reduction of vepdegestrant in 6 pts (16.2%) and dose reduction of ABE in 19 pts (51.4%). Treatment-related adverse events of any grade that occurred in $\geq 20\%$ of pts were diarrhea (73.0% [grade 1/2, 70.3%; grade 3/4, 2.7%]), fatigue (54.1% [grade 1/2, 40.5%; grade 3/4, 13.5%]), neutropenia (54.1% [grade 1/2, 21.6%; grade 3/4, 32.4%]), nausea (35.1% [grade 1/2, 32.4%; grade 3/4, 2.7%]), anemia (32.4% [grade 1/2, 29.7%; grade 3/4, 2.7%]), vomiting (24.3% [grade 1/2, 21.6%; grade 3/4, 2.7%]), and decreased appetite (21.6% [grade 1/2, 18.9%; grade 3/4, 2.7%]). There were no grade 5 TEAEs. PK data showed that vepdegestrant was associated with a modest 22% increase in exposure of ABE and its active metabolites, indicating no significant drug-drug interaction. **Conclusions:** In this phase 1b/2 study of pts with ER+/HER2- ABC, vepdegestrant plus ABE demonstrated antitumor activity and a safety profile that was generally consistent with the known profiles of each agent. Clinical trial information: NCT05548127. Research Sponsor: Pfizer Inc.

Long-term safety results and adverse event (AE) management recommendations in patients with ER+/HER2– metastatic breast cancer (mBC) receiving prifetrastat, a first-in-class KAT6 inhibitor, at the recommended phase 3 dose (RP3D) of 5 mg once-daily (QD).

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Background: Prifetrastat (PF-07248144) is a first-in-class, potent, and selective inhibitor of the epigenetic modifiers KAT6A and KAT6B. In an ongoing phase 1/2a study (NCT04606446), prifetrastat has demonstrated encouraging antitumor activity and manageable safety when combined with fulvestrant (FUL) in patients with heavily pretreated ER+/HER2– mBC (Mukohara T, et al. *Nat Med.* 2024;30:2242–50). Here, we report comprehensive and long-term safety results and AE management recommendations after extended follow-up of patients receiving prifetrastat ($\pm$ FUL) in this phase 1/2a study. **Methods:** This dose escalation (part 1)/expansion (part 2) study included patients with ER+/HER2– mBC whose disease progressed after prior treatment with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) and endocrine therapy. In part 1, patients received prifetrastat at varying doses as monotherapy or in combination with 500 mg FUL. In part 2, patients received prifetrastat ($\pm$ FUL) at the recommended dose for expansion (RDE; 5 mg QD) identified in part 1. Primary objectives were safety/tolerability assessment and RDE selection. **Results:** 5 mg QD prifetrastat was previously identified as the RDE and RP3D in combination with FUL based on safety, PK/PD, and antitumor activity. As of Oct 13, 2025, a total of 92 patients were treated at the 5 mg QD dose (43 as monotherapy and 49 in combination with FUL). The most common treatment-related AEs (TRAEs) were dysgeusia (84.8%; all grade [G] 1 [66.3%] or 2 [18.5%]), neutropenia (68.5%), and anemia (50.0%). Weight loss was reported infrequently as a TRAE (5.4%). The most common G3/4 TRAEs were neutropenia (G3, 34.8%; G4, 6.5%), anemia (G3, 15.2%; no G4), and leukopenia (G3, 12.0%; no G4); no G5 TRAEs were reported. TRAEs led to dose reductions in 45 (48.9%) patients, 75.6% (n = 34/45) of whom reduced their dose due to reversible neutropenia. TRAEs led to discontinuation in 2 patients (G2 neutropenia [n = 1]; G3 myocardial injury/troponin increased [n = 1]). G3/4 neutropenia was reversible and well-managed with dose modifications and supportive care. No febrile neutropenia was reported. Dysgeusia was managed with supportive care, including patient education, weight monitoring, and nutrition consultation, as clinically indicated. Dysgeusia did not lead to any treatment discontinuations or dose reductions. **Conclusions:** After extended follow-up of the phase 1/2a study, the RP3D of prifetrastat (5 mg QD) maintained a manageable safety profile when dose modifications and supportive care measures were implemented for AEs such as neutropenia and dysgeusia. These AE management strategies have been incorporated into the ongoing phase 3 study (KATSIS-1; NCT07062965) in patients with HR+/HER2– mBC after progression on CDK4/6i-based therapy. Clinical trial information: NCT04606446. Research Sponsor: Pfizer Inc.

HRS-8080, an oral selective estrogen receptor degrader (SERD), in ER+/HER2– advanced breast cancer (aBC) with *ESR1* mutations (*ESR1m*): Results from a first-in-human phase 1 trial.

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Background: HRS-8080 is a novel, potent oral SERD that binds ER with high affinity. We conducted a multi-part, first-in-human phase 1 trial of HRS-8080 in ER+/HER2– aBC, and here report findings in the *ESR1m* subset from the dose-escalation/expansion parts for HRS-8080 monotherapy. **Methods:** This multicenter, open-label, single-arm phase 1 study enrolled patients (pts) with locally advanced/metastatic ER+/HER2– BC previously treated with ≥ 1 line of endocrine therapy (ET) and ≤ 2 lines of chemotherapy for aBC; *ESR1m* status was centrally assessed by ctDNA. In Part A (i3+3 design), pts received HRS-8080 QD (50, 150, 300, 600, or 900 mg) or BID (300 mg); in Part B, 300 mg BID/600 mg QD were selected for expansion. Safety was a primary objective. **Results:** 40 pts with *ESR1m* were treated (≥ 2 prior lines of therapy, 70.0%; ≥ 2 prior lines of ET for aBC, 42.5%; chemotherapy for aBC, 57.5%), including 32 at expansion doses. Overall, grade ≥ 3 treatment-related adverse events (TRAEs) occurred in 8 (20.0%) of 40 pts; the most common were decreased lymphocyte count and decreased neutrophil count (2 [5.0%] pts each). TRAEs led to dose reduction in 1 (2.5%) pt. There were no treatment-related deaths. Efficacy in the *ESR1m* subset is shown in Table 1. At expansion doses of 300 mg BID/600 mg QD, the confirmed objective response rate was 34.4% (11/32; 95% CI 18.6–53.2) and the disease control rate was 75.0% (24/32; 95% CI 56.6–88.5). Median duration of response was 11.1 mo (95% CI 6.5–not reached), with over half of responses remained ongoing. As of data cutoff, 21 (65.6%) pts had disease progression or died; median progression-free survival was 7.2 mo (95% CI 3.6–11.1). **Conclusions:** HRS-8080 demonstrated a favorable safety and tolerability profile and encouraging antitumor activity in *ESR1m* ER+/HER2– aBC, supporting ongoing clinical development both as monotherapy and in combination regimens. Clinical trial information: NCT05189717. Research Sponsor: None.

Key baseline characteristics and efficacy in *ESR1m* subset.*

	50mg QD~300mg QD (n=6)	300mg BID+600mg QD (n=32)	900mg QD (n=2)	All patients (n=40)
≥ 2 prior lines of therapy, n (%)	5 (83.3)	21 (65.6)	2 (100.0)	28 (70.0)
≥ 2 prior lines of ET for aBC, n (%)	3 (50.0)	13 (40.6)	1 (50.0)	17 (42.5)
Chemotherapy for aBC, n (%)	5 (83.3)	16 (50.0)	2 (100.0)	23 (57.5)
Confirmed ORR, % (n/N; 95% CI)	0	34.4 (11/32; 18.6–53.2)	0	27.5 (11/40; 14.6–43.9)
Median DoR, mo (95% CI)	–	11.1 (6.5–NR)	–	11.1 (6.5–NR)
Median PFS, mo (95% CI)	2.2 (1.7–5.5)	7.2 (3.6–11.1)	NR (9.2–NR)	7.2 (3.6–10.9)
Median follow-up, mo (range)	3.0 (0.3–24.6)	6.7 (1.5–34.3)	21.3 (10.4–32.2)	6.6 (0.3–34.3)

Data cutoff, Dec. 18, 2025.

*Patients relapsed after 24 months if receiving adjuvant ET, and had disease progression ≥ 6 months of the first-line ET in the advanced setting. aBC, advanced breast cancer; DoR, duration of response; ET, endocrine therapy; NR, not reached; ORR, objective response rate; PFS, progression-free survival.

Real-world survival benefit of glucagon-like peptide-1 receptor agonists (GLP-1 Ras) concomitant with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) and endocrine therapy in hormone receptor-positive (HR+)/HER2– metastatic breast cancer: A large propensity-matched analysis.

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Background: Obesity increases hormone receptor-positive (HR+) breast cancer risk through adipose-derived estrogens and inflammation. In metastatic HR+/HER2– disease, endocrine therapy (ET) combined with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) is standard first-line therapy, improving survival. The widespread use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for diabetes and obesity management induces meaningful weight loss and may enhance ET efficacy by reducing body fat mass, which modulates estrogen levels and cancer-related inflammation, albeit their impact on mBC survival in patients receiving ET plus CDK4/6i remains unclear. **Methods:** Using the TriNetX Global Collaborative Network, we retrospectively identified two cohorts of patients with mBC receiving endocrine therapy (ET) plus a CDK4/6i: 26,689 patients treated with ET+CDK4/6i alone and 604 patients who also received a GLP-1 RA initiated within 3 months of CDK4/6i start. Propensity score matching (PSM) was applied to balance cohorts for age, race, body mass index, heart failure, hypertension, diabetes mellitus, fulvestrant use, and type of CDK4/6i. Overall survival (OS) was estimated using the Kaplan–Meier method, and hazard ratios (HRs) were calculated to compare OS between cohorts. **Results:** After PSM, 604 matched pairs of patients were identified in the ET plus CDK4/6i and GLP-1 RA groups, respectively (mean age $\pm$ standard deviation: 61.4 ± 11.3 and 61.8 ± 11.8 years), with well-balanced baseline characteristics. After a median follow-up of 18.8 months (interquartile range, IQR 27.9) in the non-exposed cohort and 15.8 months (IQR 24.5) in the non-exposure and in the exposure cohorts, median OS was 67.9 months among patients receiving GLP-1 RA compared with 49 months in those not receiving GLP-1 RA (HR 0.70; 95% CI, 0.56–0.89; $P=0.003$), corresponding to a 30% reduction in the risk of death mortality risk. **Conclusions:** This is the largest real-world, propensity-matched analysis demonstrating a significant OS benefit with GLP-1 RAs added to ET+CDK4/6i in HR+/HER2– mBC. These provocative findings warrant prospective validation to elucidate underlying mechanisms—such as metabolic reprogramming or immune modulation—and explore GLP-1 RAs as a novel therapeutic strategy in this setting. Research Sponsor: None.

Beyond *ESR1*: Multi-pathway genomic drivers of endocrine resistance in HR⁺/HER2⁻ breast cancer.

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Background: Endocrine resistance in HR⁺/HER2⁻ breast cancer is often associated with acquisition of *ESR1* point mutations, but many patients at progression remain *ESR1* wild type. Identifying *ESR1*-independent, multi-pathway acquired resistance mechanisms is critical for guiding subsequent therapy. **Methods:** We analyzed 1,429 HR⁺/HER2⁻ breast cancer samples (468 tissue, 1,171 cfDNA), including 210 paired cases, from patients with metastatic breast cancer undergoing molecular testing for treatment guidance or disease monitoring. Next-generation sequencing performed at Datar Cancer Genetics assessed SNVs, CNAs, and gene fusions. Alterations implicated in endocrine resistance were analysed for incidence, specimen type, and co-alteration patterns. **Results:** *ESR1*-wild-type tumors frequently harbored clinically relevant endocrine resistance mechanisms, most commonly involving the *PI3K/AKT*, *FGFR*, *ERBB2*, *MAPK*, and cell-cycle pathways. At least one resistance-associated alteration was identified in 40.4% (473/1172) of evaluable *ESR1*-wild-type cases, while 14.8% (173/1172) harbored alterations across multiple resistance pathways, highlighting substantial *ESR1*-independent resistance biology. Among *ESR1*-driven mechanisms, *ESR1* SNVs were detected slightly more frequently in cfDNA than tissue (13.7% vs 12.8%), despite inclusion of cfDNA samples obtained during clinical surveillance, supporting the sensitivity of liquid biopsy for detecting emergent resistance. *ESR1* fusions represented a distinct, non-overlapping resistance mechanism, identified in 7.4% (28/379) of tissue samples, most commonly *ESR1-CCDC170* (71%) and *ESR1-AKAP12* (14%); 21 fusion-positive cases lacked *ESR1* SNVs, underscoring the need for fusion assessment to fully capture *ESR1*-driven resistance. Dynamic pathway activation was further supported by acquired *PI3K* pathway mutations, detected in cfDNA in 3.3% (4/122) of cases initially *PIK3CA*-wild-type in paired tissue samples. **Conclusions:** Endocrine resistance in HR⁺/HER2⁻ breast cancer is mediated by multiple actionable genomic pathways beyond *ESR1*, including *PI3K/AKT*, *FGFR*, *ERBB2*, *MAPK*, and cell-cycle alterations. These findings expand opportunities to personalize therapy and guide clinical trial selection by targeting non-*ESR1* resistance mechanisms. Research Sponsor: None.

Incidence of endocrine resistance-associated genomic alterations beyond *ESR1* point mutations in tissue and liquid biopsy for HR⁺/HER2⁻ breast cancer.

Endocrine Resistance Biomarker	<i>ESR1</i> -Mutant Cases (%)	<i>ESR1</i> Wild-Type Cases (%)
<i>ESR1</i> fusions	11.1	6.7
<i>FGFR1</i> alterations	13.2	7.0
<i>CCND1</i> amplification	15.2	7.0
<i>FGFR2/3</i> alterations	3.7	2.0
<i>HER2</i> -mutant, non-amplified	2.5	2.6
<i>PIK3CA</i> mutation	43.7	25.1
<i>PTEN</i> mutation	2.0	1.6
<i>AKT1</i> mutation	5.6	3.6
<i>MAPK</i> Pathway (<i>RAS/RAF/MEK</i>)	4.6	4.0

A phase 1/2 trial of tertsolisib (LY4064809/STX-478), a pan-mutant-selective PI3K α inhibitor (PI3K α i), in *PIK3CA*-mutant advanced solid tumors: Updated results from PIKALO-1.

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Background: PI3K α i have demonstrated clinical benefit in ~40% of patients (pts) with HR+, HER2- advanced breast cancer (ABC) with *PIK3CA* mutations (*PIK3CA*m). However, broad use is often constrained by toxicities mediated through wild-type PI3K α inhibition, and exclusion of pts with diabetes (DM) or prediabetes (pDM). Here we report updated results from PIKALO-1 evaluating tertsolisib (terso), an oral, allosteric CNS-penetrant, pan-mutant-selective PI3K α i in pts with *PIK3CA*m HR+ HER2- ABC. **Methods:** PIKALO-1 enrolled pts to receive terso (≥ 1 prior treatment [tx]), terso + fulvestrant (fulv, 1-2 prior txs), or terso + fulv/implunestrant (imlu) and CDK4/6i (≤ 2 prior txs). Pts with pDM/DM (HbA1c $< 8\%$ /FBG $< 140\text{mg/dL}$) were eligible. **Results:** As of 6 Jan 2026, 193 pts with *PIK3CA*m HR+ HER2- ABC were treated: terso (n=52; 20-160 mg QD); terso (60 mg or 100 mg QD) + fulv (n=45) and terso (20-100 mg QD) + fulv + CDK4/6i (palbociclib, n=70; ribociclib, n=21; abemaciclib, n=5) (n=96). Median age was 62 yrs (Range: 27-84), 54% had pDM/DM. Median prior txs was 2 (0-7) including: CDK4/6i (81%) and SERD (47%). Hyperglycemia (HG) rates (any Grade [G]/G ≥ 3) were 16%/0% in pts without pDM+DM and 37%/1% in pts with pDM+DM. TEAEs (any G/G ≥ 3) $\geq 25\%$ of all pts; neutropenia (39%/27%), fatigue (35%/4%), diarrhea (34%/<1%), and nausea (31%/1%). Incidence of PI3Ki-class toxicities (rash; 4%/0% and stomatitis; 12%/<1%) were relatively low. TEAEs led to terso dose reduction/discontinuation in 11%/<1%. T. no significant drug-drug interactions. *PIK3CA*m ctDNA was reduced at all dose levels. Updated data, including dose escalation data with terso + imlu+ abemaciclib, will be presented. **Conclusions:** Terso, alone or combined with fulv $\pm$ CDK4/6i, continues to be well-tolerated, with lower incidence of PI3Ki-class toxicities and no 3 HG in pts with normal baseline glycemic control. Target engagement was robust and clinical benefit continues to mature favorably in heavily pretreated pts with *PIK3CA*m HR+ HER2- ABC, supporting further study in the Phase 3 PIKALO-2 trial (NCT07174336). Clinical trial information: NCT05768139. Research Sponsor: Eli Lilly and Company.

Efficacy summary.

	Terso	Terso + fulv	Terso + fulv + CDK4/6i ^c
Efficacy Evaluable Population^a, n	48	31	48
Prior Therapies^b, n (Range)	3 (1-7)	1 (0-5)	1 (0-6)
ORR, n (%)	9 ^d (19)	11 ^e (35)	13 ^f (27)
DCR, n (%)	32 ^d (67)	27 ^e (87)	38 ^f (79)

^aPts who had measurable disease and ≥ 1 post baseline response assessment or discontinued prior to first post baseline response assessment.

^bLocally Advanced/Metastatic Setting, summary based on safety population; all enrolled pts who received ≥ 1 tx dose.

ORR incl. PR, uPR; DCR incl. PR, uPR, SD.

^cIncl. palbociclib, ribociclib, abemaciclib.

Incl. ^d1, ^e4, ^f6 uPR (ongoing, pending confirmation).

(RW) post-progression outcomes following first-line (1L) ribociclib (RIB) + aromatase inhibitor (AI) versus AI alone in African American and low socio-economic status (SES) patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer (MBC) in US.

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Background: RIB + endocrine therapy (ET) demonstrated significant overall survival over ET alone in all three phase III MONALEESA trials for HR+/HER2- MBC. RW studies can provide insight into pt subgroups who may be under-represented in clinical trials. This is particularly important for African American pts and those with low SES, groups who often face disparities in access and outcomes. This study assessed RW post-progression outcomes among these under-represented populations in the US, to guide treatment (tx) for those affected by social determinants of health. **Methods:** This retrospective study used deidentified data from the Flatiron Health Research Database, including 5,649 US women with HR+/HER2- MBC who began 1L RIB + AI or AI monotherapy between Jan 1, 2020 and Jan 31, 2025, with follow-up through Jul 31, 2025. Analyses of RW progression-free survival 2 (rwPFS2; time from start of 1L to first disease progression during 2L, or death during 1L or 2L, whichever occurred first) and RW chemotherapy-free survival (rwCFS) used unadjusted and adjusted time-to-event methods (Kaplan-Meier and Cox regression), with baseline differences addressed using inverse probability tx weighting with stabilized weights (sIPTW). Key pt demographics and characteristics were used for adjustment; details to be provided in the full presentation. **Results:** A total of 520 African American pts were included in the analysis; 243 received RIB + AI and 277 received AI monotherapy. After sIPTW, median rwPFS2 was 19.4 months longer for the RIB + AI group vs AI monotherapy (median 36.8 vs 17.4 months; HR, 0.44; 95% CI, 0.29–0.67). Median rwCFS was also extended by 14.3 months with RIB + AI (median 39.5 vs 25.2 months; HR, 0.49; 95% CI, 0.33–0.72). Among 1805 pts with low SES index (pts area-level SES categorized in the lowest two quintiles to represent the lowest 40% of block groups in terms of SES), 810 received RIB + AI and 995 received AI monotherapy. The median rwPFS2 was 14.2 months longer for those receiving RIB + AI vs AI monotherapy (median 37.2 vs 23.0 months; HR, 0.54; 95% CI, 0.44–0.67) after sIPTW adjustment. Similarly, median rwCFS was prolonged by 22.0 months for the RIB + AI group vs AI monotherapy (median 51.4 vs 29.4 months; HR, 0.58; 95% CI, 0.47–0.71). **Conclusions:** This study demonstrates that treating African American pts and individuals with low SES using 1L RIB + AI, compared with AI alone, leads to longer rwPFS2 and rwCFS. These results support 1L RIB + AI as an effective tx choice for these pt groups and underscores the importance of ensuring access to optimal tx for better outcomes. Research Sponsor: Novartis Pharmaceuticals Corporation.

Vepdegestrant, a proteolysis-targeting chimera (PROTAC) estrogen receptor (ER) degrader, plus atirmociclib (ATI) in ER+/HER2– advanced breast cancer (ABC): TACTIVE-K phase 1b/2 results.

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Background: There is unmet need for therapies that improve clinical outcomes in patients (pts) with ER+/HER2– ABC and disease progression on existing endocrine therapies (ETs). Both vepdegestrant, and ATI, a selective cyclin-dependent kinase (CDK) 4 inhibitor (CDK4i), have shown antitumor activity in pts with ER+/HER2– ABC previously treated with CDK4/6i plus ET. This study evaluated the efficacy and safety of vepdegestrant plus ATI in pts with ER+/HER2– ABC. **Methods:** This open-label, multicenter, phase 1b/2 study (NCT06206837) enrolled pts with ER+/HER2– ABC who received >1 (phase 1) or 1–2 (phase 2) prior lines of therapy in the ABC setting; 1 prior CDK4/6i-based regimen in any setting was required in phase 2. The study included a dose escalation/de-escalation phase 1b to select recommended doses, and a randomized phase 2 to further assess efficacy, safety, and PK. Baseline ESR1 mutation status (via ctDNA) and its association with efficacy outcomes were also assessed in phase 2. **Results:** As of Sep 5, 2025, 70 pts (median age, 60 y) received vepdegestrant 200 mg daily plus ATI 100 mg BID (ATI100; n = 36), or 300 mg BID (ATI300; n = 34). Pts received a median of 1.0 prior regimens in the ABC setting. Most pts previously received an aromatase inhibitor (ATI100, n = 33, 91.7%; ATI300, n = 26, 76.5%) and/or a CDK4/6i (ATI100, n = 36, 100%; ATI300, n = 32, 94.1%). Confirmed objective response rate (ORR), clinical benefit rate (CBR; complete response, partial response, or stable disease for ≥ 24 wks), and median progression-free survival (mPFS) are shown in the Table. Efficacy outcomes for pts with baseline ESR1 mutations (n = 27) were consistent with the total population (Table). Two dose-limiting toxicities were reported in phase 1b: a grade (G) 3 platelet count decreased (ATI100) and a G3 neutrophil count decreased (ATI300). Most treatment-related adverse events (TRAEs) were G1/2; G3/4 TRAEs were mainly neutropenia (ATI100, 16.7%; ATI300, 35.3%). PK parameters including AUC_{tau} and C_{max} for vepdegestrant and ATI100/300 at steady state were consistent with previous reports, indicating no clinically impactful drug-drug interactions. **Conclusions:** In previously treated pts with ER+/HER2– ABC, vepdegestrant plus ATI showed clinical activity in the full pt population and in pts with ESR1 mutations. The safety profile of the combination was consistent with each agent. Clinical trial information: NCT06206837. Research Sponsor: Pfizer Inc.

	Vepdegestrant + ATI 100 mg	Vepdegestrant + ATI 300 mg
Pts with measurable disease at baseline	n = 31	n = 33
Confirmed ORR, % (95% CI)	16.1 (7.1–32.6)	24.2 (12.8–41.0)
All pts	n = 36	n = 34
CBR, % (95% CI)	44.4 (29.5–60.4)	52.9 (36.7–68.5)
mPFS, mo (95% CI)	9.3 (5.4–NE)	11.5 (7.2–NE)
Pts with ESR1 mutation	n = 13	n = 14
Confirmed ORR, % (95% CI)	15.4 (4.3–42.2)	21.4 (7.6–47.6)
CBR, % (95% CI)	46.2 (23.2–70.9)	64.3 (38.8–83.7)
mPFS, mo (95% CI)	NR (3.0–NE)	NR (3.7–NE)

NE, not estimable; NR, not reached.

Efficacy and safety of SPH4336 plus endocrine therapy in HR-positive/HER2-negative metastatic breast cancer with brain metastases: A multicenter, single-arm, phase II study.

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Background: Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors plus endocrine therapy are standard first-line treatment for HR-positive/HER2-negative (HR⁺/HER2⁻) metastatic breast cancer (MBC). However, patients with brain metastases have poor prognosis and limited treatment options due to inadequate blood-brain barrier penetration of most agents and limited evidence for intracranial efficacy. SPH4336, a novel oral CDK4/6 inhibitor, exhibits potent CDK4/6 inhibition in preclinical models with favorable blood-brain barrier penetration. It has shown acceptable safety profiles and preliminary antitumor activities in advanced solid tumors, including HR⁺/HER2⁻ MBC. This study assessed the efficacy and safety of SPH4336 plus endocrine therapy in HR⁺/HER2⁻ MBC with brain metastases. **Methods:** This open-label, single-arm, phase II study enrolled patients aged 18–75 years with histologically confirmed HR⁺/HER2⁻ and radiologically confirmed brain metastases at 25 centers in China. Prior CDK4/6 inhibitor exposure before brain metastases was limited to <2 agents. Patients received SPH4336 (400 mg orally once daily) plus physician's choice of endocrine therapy (letrozole, fulvestrant, or exemestane) in 28-day cycles until disease progression or unacceptable toxicity. Primary endpoint was intracranial objective response rate (ORR) per RANO-BM criteria. **Results:** Between September 19, 2023, and August 22, 2025, 30 patients were enrolled. Two patients (6.7%) had a history of palliative radiotherapy for brain metastases. As of December 10, 2025, the median follow-up was 11.7 months (range: 1.6–26.7). Per RANO-BM criteria in 29 evaluable subjects, the intracranial ORR, disease control rate (DCR), and clinical benefit rate were 37.9% (95% CI: 20.7–57.7), 72.4% (95% CI: 52.8–87.3), and 44.8% (95% CI: 26.4–64.3), respectively. Based on RECIST 1.1, the extracranial ORR and DCR were 33.3% (95% CI: 17.3–52.8) and 66.7% (95% CI: 47.2–82.7), respectively. The overall ORR was 33.3% (95% CI: 17.3–52.8), and the overall DCR was 60.0% (95% CI: 40.6–77.3). The median intracranial, extracranial, and overall progression-free survival were 8.4 months (95% CI: 1.9–not reached [NR]), 11.0 months (95% CI: 1.9–NR), and 8.1 months (95% CI: 1.9–11.0), respectively. Grade ≥3 treatment-related adverse events occurred in 70.0% of patients, most commonly γ-glutamyltransferase elevation (43.3%), aspartate aminotransferase elevation (20.0%), and neutrophil count decrease (20.0%). No treatment-related death occurred. **Conclusions:** SPH4336 plus endocrine therapy demonstrated clinically meaningful intracranial antitumor activity with a manageable safety profile in HR⁺/HER2⁻ MBC with brain metastases. These findings warrant further investigation in randomized studies for this patient population with high unmet medical need. Clinical trial information: NCT05872347. Research Sponsor: Shanghai Pharmaceuticals Holding Co., Ltd.

[¹⁸F] Fluoroestradiol PET/CT to guide second-line treatment decision-making in patients with estrogen receptor–positive, HER2-negative advanced breast cancer after progression on first-line aromatase inhibitor and CDK4/6 inhibitor: Primary results of ESTROTIMP.

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Background: Despite availability of novel endocrine treatment (ET) options for patients with ER+ HER2- ABC, many patients experience early disease progression under 2nd line ET-based regimen after AI+CDK4/6i, underscoring a significant rate of endocrine resistance. Timely identification of endocrine-refractory disease at progression under 1st line is critical to optimize treatment selection and consider non-ET strategies, such as antibody-drug conjugates or chemotherapy. FES PET/CT enables a non-invasive, whole-body assessment of ER expression; absent or heterogeneous FES uptake may indicate ER loss or downregulation, key mechanisms of resistance. Our objective was to evaluate the impact of FES PET/CT on 2nd line treatment decisions. **Methods:** In this non-randomized prospective multicenter trial (NCT05486182), patients with ER+ HER2- ABC progressing on 1st line AI+CDK4/6i underwent standard-of-care FDG PET/CT followed by FES PET/CT. Oncologists prospectively documented therapeutic management plans, before and after FES PET/CT. Patients rated pain and apprehension for FES PET/CT vs. biopsy on a Visual Analogue Scale. Primary endpoint was the proportion of patients with a therapeutic management change after FES PET/CT, and primary objective was to demonstrate that at least 10% of patients had their therapeutic management changed after FES PET/CT (Wald test). **Results:** Of 153 patients enrolled, 129 were evaluable for the primary endpoint. When compared with FDG PET/CT, FES uptake was classified as “all lesions ER+” in 65 (50%), “mixed ER+/- lesions” in 38 (30%), and “all lesions ER-” in 25 (19%) patients. Therapeutic management was changed based on incorporation of FES PET/CT results in 46/129 patients (35.7%; 95% CI [27.0–44.3], $p < 0.0001$), including treatment type ($n=38$), diagnostic modalities ($n=8$), and planned follow-up ($n=12$). Treatment changes mostly consisted of using chemotherapy instead of ET ($n=16$), ET instead of chemotherapy ($n=3$), adding targeted therapy to single agent ET ($n=2$), changing the targeted therapy paired with ET ($n=8$), adding radiation therapy to disease sites ($n=4$), and performing surgery ($n=2$). Oncologist confidence in FES PET/CT was on average 7.8/10 (Q1–Q3: 7–9). Patients reported significantly lower pain and apprehension for FES PET/CT vs. biopsy (Pain: Mean 0.8 vs 4.5; Apprehension: Mean 1.8 vs 5.2; both $p < 0.0001$). **Conclusions:** ESTROTIMP shows that, at progression under AI+CDK4/6i, ER expression is completely or partially lost in about half of patients with ER+ HER2- ABC. The trial reached its primary endpoint, demonstrating a clinically meaningful impact on therapeutic management, and supporting the use of FES PET/CT as a standard workup at time of progression under 1st line AI+CDK4/6i. Clinical trial information: NCT05486182. Research Sponsor: GE HealthCare.

BL0175, a novel nano-mediated polypeptide conjugate of protein degrader, in patients (pts) with locally advanced/metastatic HR+/HER2– breast cancer (HR+, HER2– LA/mBC): Initial results from a phase 1 study.

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Background: BL0175 is a novel nano-conjugate (~10 nm) composed of PEG-modified poly (amino acid), enzyme-responsive peptide linkers, and the protein-degrader payload fulvestrant. It accumulates in the tumor microenvironment (TME), where enzymatic cleavage releases fulvestrant continuously. The released fulvestrant penetrates tumor cells, effectively inducing cell death. Nonclinical studies demonstrated that BL0175 provides superior tumor distribution of fulvestrant, enhanced tumor growth inhibition, and greater progesterone receptor suppression compared with conventional fulvestrant injection at equivalent doses. This first-in-human Phase I study reports preliminary safety, efficacy, and pharmacokinetic (PK) data for BL0175. **Methods:** Postmenopausal pts with HR+, HER2– LA/mBC received intramuscular BL0175 (Cycle 1: Days 1, 15; thereafter every 4 weeks) at doses ranging from 50 mg to 500 mg. Data are summarized across all cohorts unless otherwise specified. **Results:** As of January 14, 2026, 22 pts were treated (50 mg: n=1; 100, 200, 300, 400, 500 mg: n=3 each; 250 mg: n=6). The median number of prior lines of therapy was 3 (range: 1–7). Safety: Adverse events (AEs) and treatment-related AEs (TRAEs) occurred in 64% of pts (14/22). All AEs were Grade 1–2, with no dose-dependent trends or unexpected safety signals. Efficacy: Eleven pts had post-baseline tumor assessments (50 mg & 300 mg: n=1 each; 100, 200, 400 mg: n=3 each). Disease control rate (DCR) was 100% in cohorts receiving ≥ 200 mg. Three partial responses (PR) were observed in cohorts ≥ 200 mg, yielding an objective response rate (ORR) of 42.9% (3/7). The pts who achieved PR comprised individuals with prior progression on standard CDK4/6 inhibitor (CDK4/6i) plus endocrine therapy (aromatase inhibitor or fulvestrant injection), as well as those presenting with brain metastases at baseline. These data suggest that 200 mg may be an effective therapeutic dose. Pharmacokinetics: PK exposure (C_{max} and AUC_{0-336h}) of both released and total fulvestrant increased dose-proportionally. BL0175 was stable in systemic circulation (release rate $\leq 0.03\%$ across doses). Notably, in two pts (50 mg and 100 mg cohorts), released fulvestrant concentrations in tumor tissue were 9-fold and 18-fold higher, respectively, than in plasma, confirming tumor-specific enrichment. **Conclusions:** BL0175 demonstrated promising efficacy in pts with HR+, HER2– LA/mBC, including those with prior progression on fulvestrant injection and CDK4/6i-based therapy and in brain metastases. The preliminary results validate BL0175's design rationale, supporting its tumor-targeted delivery and potential for enhanced efficacy at lower doses. These findings warrant further investigation of BL0175 in this patient population. Clinical trial information: NCT06738966. Research Sponsor: None.

Outcomes by lobular (lob) histology status at initial diagnosis in patients (pts) in the INAVO120 phase 3 trial with *PIK3CA*-mutated (mut), hormone receptor-positive (HR+), HER2-negative (HER2-), endocrine-resistant advanced breast cancer (aBC) treated with inavolisib (INAVO)/placebo (PBO) + palbociclib (PALBO) + fulvestrant (FULV).

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Background: INAVO (a highly potent and selective PI3K α inhibitor that also promotes mut p110 α degradation) + PALBO + FULV is approved for *PIK3CA*mut, HR+, HER2-, endocrine-resistant aBC based on statistically significant and clinically meaningful investigator-assessed progression-free survival (PFS) benefit over PBO + PALBO + FULV in INAVO120 (NCT04191499). We report exploratory analyses of treatment (tx) outcomes by lob histology status documented at initial diagnosis. **Methods:** Baseline characteristics, PFS, overall survival (OS), objective response rate (ORR), and duration of response (DoR) were evaluated for 53 pts with reported lob only and 64 with reported lob only or mixed lob (lob + ≥ 1 other selected subtype) histology at initial diagnosis. *PIK3CA*mut distribution, and association of histology and PFS with *CDH1* alteration (alt) status, were also assessed. **Results:** At the clinical data cut-off for the updated PFS and final OS analyses (Nov 15, 2024), 24 and 29 pts with lob only histology, and 29 and 35 pts with mixed lob histology, were randomized to the INAVO and PBO arms, respectively. Baseline characteristics were balanced across tx arms. Median follow-up was 34.2 and 32.3 months (m) in the INAVO and PBO arms, respectively. Pathogenic *CDH1*alts were more frequent in the lob only (65.2%) and mixed lob (58.9%) subgroups compared with no lob histology (6.3%). Efficacy by lob status is shown in the Table. *PIK3CA*mut distribution was similar across histologies. PFS benefit of INAVO over PBO was observed regardless of baseline *CDH1*alt status (hazard ratio 0.3 for *CDH1*alt and 0.5 for no alt detected). **Conclusions:** In this INAVO120 exploratory analysis, efficacy was improved with INAVO vs PBO, regardless of lob histology status at initial diagnosis and *CDH1*alt status. This further supports the benefit of INAVO + PALBO + FULV in *PIK3CA*mut, HR+, HER2-, endocrine-resistant aBC. Clinical trial information: NCT04191499. Research Sponsor: F. Hoffmann-La Roche Ltd.

	Lob only: INAVO n = 24	Non-lob: INAVO n = 137	Lob only: PBO n = 29	Non-lob: PBO n = 135	Mixed lob: INAVO n = 29	Non-mixed lob: INAVO n = 132	Mixed lob: PBO n = 35	Non-mixed lob: PBO n = 129
PFS, m (95% CI)	21.7 (9.3–25.8)	17.2 (11.6–24.3)	7.2 (3.7–9.4)	7.4 (5.8–9.7)	21.7 (11.3–27.9)	16.6 (11.2–24.2)	7.2 (3.8–9.4)	7.4 (5.8–9.7)
OS, m (95% CI)	NR (18.1–NR)	33.0 (27.1–44.8)	24.1 (11.1–NR)	27.0 (22.8–40.7)	NR (28.4–NR)	33.0 (27.0–38.0)	24.1 (11.1–NR)	28.0 (22.8–40.7)
ORR, n (%)	15 (62.5)	86 (62.8)	6 (20.7)	40 (29.6)	19 (65.5)	82 (62.1)	7 (20.0)	39 (30.2)
95% CI	40.6–81.2	54.1–70.9	8.0–39.7	22.1–38.1	45.7–82.1	53.3–70.4	8.4–36.9	22.5–38.9
DoR, m (95% CI)	21.2 (9.3–NR)	18.7 (12.2–28.3)	11.1 (8.5–NR)	10.7 (7.5–20.2)	20.3 (9.6–NR)	18.8 (11.1–28.7)	11.1 (3.1–NR)	11.1 (7.5–20.2)

CI, confidence interval; NR, not reached.

Impact of FES-PET imaging in the management of estrogen receptor–positive breast cancer: Real-world experience.

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Background: F18 labeled estradiol PET imaging (FES–PET) is endorsed by NCCN guidelines to identify advanced/recurrent estrogen receptor positive (ER+) breast cancer, especially invasive lobular disease. As an adjunct to conventional imaging, FES–PET may provide information about estrogen dependence in lesions that are not readily biopsied. We reviewed the use of FES–PET imaging at City of Hope, Southern California and how it impacted treatment. **Methods:** This is a retrospective chart review study of pts undergoing FES–PET imaging in the management of ER+ breast cancer. Demographic data, indications for FES–PET imaging, and impact on subsequent care were extracted from the electronic medical record. **Results:** Between 1/21/22 and 12/31/25, 191 patients with a median age of 52 (Range 32–89) underwent an initial FES–PET scan at City of Hope and its Southern California Network. All had a diagnosis of estrogen receptor + (ER+) breast cancer; 124 were Invasive Ductal Carcinoma (IDC), 59 Invasive Lobular Carcinoma (ILC), 7 mixed IDC with ILC features, and 1 adenocarcinoma. FES–PET was used to stage “high-risk” local disease in 85, 76 continued their initial treatment plan, 8 were found to have metastatic disease, and 1 underwent additional surgical resection for residual disease in the breast. Of 102 pts. with metastatic disease, 58 were FES positive; 44/50 responded to endocrine therapy, 7 received chemotherapy and 1 refused treatment; 44 were FES negative and 23 received chemotherapy, 10 had no response to endocrine therapy, and 11 received no further treatment. Four patients had synchronous primary tumors and FES was used to distinguish lesions that were attributable to breast cancer. Of the patients with metastatic FES+ disease, 33 underwent serial FES–PET imaging; 3 were part of a clinical trial assessing radiation therapy in oligometastatic disease, 3 had been on prolonged treatment with chemotherapy and FES–PET was obtained to assess potential for reintroduction of endocrine therapy, 27 had response evaluation to aromatase inhibitor therapy where conventional staging did not adequately assess the measurable/evaluable disease as well as FES–PET. **Conclusions:** Our data support the use of FES–PET which altered treatment in 11% of patients with high-risk localized and identified patients for whom chemotherapy was the appropriate choice of systemic therapy. In select pts, serial FES–PET imaging was more helpful in monitoring disease response to AI-based therapy than conventional imaging and should be considered in future guideline recommendations. Research Sponsor: National Cancer Institute; P30CA033572.

Oral selective estrogen receptor degraders in HR+/HER2- advanced breast cancer and impact of ESR1 mutation status: A systematic review and meta-analysis.

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Background: Oral selective estrogen receptor degraders (SERDs) are a promising therapeutic class for hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer. Several randomized controlled trials (RCTs) have evaluated oral SERDs, but results have varied across agents and populations. **Methods:** We searched MEDLINE, EMBASE, CENTRAL, and conference proceedings until December 31st 2025 and identified RCTs comparing oral SERDs with standard endocrine therapy in adults with HR+/HER2- advanced breast cancer. Two reviewers independently screened studies, extracted data, and assessed risk of bias using Cochrane RoB 2. Random effects meta-analysis was performed using generic inverse variance for hazard ratios for progression-free survival (PFS). Odds ratios for safety outcomes were pooled using Mantel-Haenszel (fixed effect). **Results:** A total of 9 trials comprising 4,258 participants were included. Overall, oral SERDs demonstrated a statistically significant improvement in PFS compared with standard endocrine therapy (HR 0.76, 95% CI 0.60 to 0.97; p=0.03). In the estrogen receptor 1 gene mutated (ESR1m) subgroup (7 trials, n=1,273), oral SERDs showed a more pronounced PFS benefit (HR 0.53, 95% CI 0.39 to 0.70; I²=53.4%; p=0.002). In contrast, patients with ESR1 wild-type tumors (6 trials, n=1,212) derived no significant benefit (HR 0.95, 95% CI 0.81 to 1.12; I²=0%). The interaction between ESR1m and treatment was statistically significant (p<0.001). Grade ≥3 adverse events were similar between groups (RR 1.09, 95% CI 0.87 to 1.38). Treatment discontinuation due to adverse events was significantly higher with oral SERDs (RR 1.65, 95% CI 1.02 to 2.65). **Conclusions:** Oral SERDs lead to a statistically significant improvement in PFS over standard endocrine treatments albeit with the effect seemingly limited to patients with ESR1m. These results support the use of biomarkers to determine which patients are most likely to receive clinical benefits from oral SERD therapy and underscore the importance of ESR1 testing in order to tailor treatment optimally. Research Sponsor: None.

ESR1 mutation status subgroup analysis.					
Subgroup	Trials	Participants	HR	95% CI	P-value
ESR1 Mutant	7	1,273	0.53	0.39 – 0.70	0.0015
ESR1 Wild-Type	6	1,212	0.95	0.81 – 1.12	0.4684

Culmerciclib (CDK2/4/6 inhibitor) plus fulvestrant in HR+/HER2– advanced breast cancer after progression on CDK4/6i: Preliminary results from a phase II trial.

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Background: CDK4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) have been the standard first line treatment for HR+/HER2– advanced breast cancer (ABC). However, there is currently no established standard treatment after progression on a CDK4/6i–based regimen. Culmerciclib (Culm), a novel potent CDK2/4/6 inhibitor, has shown significant PFS benefits when combined with Fulvestrant (Ful) in both first-line and later-line settings for HR+/HER2– ABC (ESMO 2025; CSCO 2024). Here we evaluated the combination in HR+/HER2– ABC following disease progression on prior CDK4/6i + ET. **Methods:** In this prospective, multicenter, single-arm phase II trial (TQB3616-II-04), eligible patients (pts) who had progressive disease on a CDK4/6i + ET as initial therapy for ABC or relapse on/after a CDK4/6i + ET as adjuvant therapy for early BC, previous up to 2 lines of ET and 1 line of chemotherapy for ABC, received Culm (180mg, qd) + Ful. The primary endpoint was ORR, and secondary endpoints included DCR, PFS, DOR, CBR and safety. Assuming a power of 0.9 to test the hypothesis that ORR would be 30.0% against the null hypothesis that it would be 8.0% or lower, with 0.025 as one-sided significance level; considering the dropout rate of 20%, a total of 33 pts was required. **Results:** 35 female pts were enrolled and treated, 31.4% were pre- or perimenopausal (received a concomitant GnRH agonist), 71.4% had visceral metastases (including 45.7% with liver metastases and 5.7% with brain metastases). All pts had received prior CDK4/6i + ET (AI and/or SERM) therapies, prior CDK4/6i was 68.6% palbociclib, 28.6% dalpiciclib, and 8.6% ribociclib (2 pts with dual CDK4/6i); 28.6% had received prior two lines endocrine therapy, also 37.1% had received prior chemotherapy for metastatic disease. As of data cutoff on Jan 17, 2026, median follow-up time was 7.3 months. Among 34 evaluable pts, the overall ORR was 29.4% (95% CI: 15.1, 47.5, $p < 0.0001$), meeting the predefined primary endpoint, which significantly rejected the null hypothesis of ORR. The overall DCR was 88.2% (95% CI: 72.6, 96.7), and the CBR was 82.4% (95% CI: 65.5, 93.2). Median TTR was 3.7 months, mPFS and mDOR were not yet reached, while 6-month PFS rate was 72.5% (95% CI: 52.7, 84.7). Grade ≥ 3 TRAEs and serious TRAEs were reported in 14 (40.0%), 3 (8.6%) pts, respectively. The most common TRAEs included diarrhea, neutropenia, vomiting etc. No new safety signals were observed, with findings consistent with the known safety profile of Culm. Dose reductions due to TRAEs occurred in 14.3% of pts, and no deaths or discontinuations related to TRAEs were reported. **Conclusions:** Culm combined with Ful demonstrated promising antitumor activity in HR+/HER2– ABC after progression on previous CDK4/6i + ET, offering a potential targeted therapeutic strategy for this population (NCT06702618). Clinical trial information: NCT06702618. Research Sponsor: None.

Genomic markers of resistance to first-line (1L) therapy with a CDK4/6 inhibitor (CDKi) and endocrine therapy (ET) in patients (pts) with hormone receptor–positive (HR+) metastatic breast cancer (MBC).

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Background: Pts with HR+ MBC exhibit variable responses to 1L ET + CDKi therapy. We analyzed clinicopathologic features and genomic landscapes of biopsies obtained at the time of the diagnosis of MBC to identify determinants of sensitivity/resistance to 1L CDKi, with a focus on distinguishing endocrine-sensitive from endocrine-resistant (ETR) disease. **Methods:** A single center cohort included pts with biopsies obtained within 3 months of diagnosis of HR+, HER2-negative MBC (distant recurrent and de-novo [DNIV]), diagnosed between 2013 – 2020. Tumors underwent targeted DNA sequencing (OncoPanel). Clinical data were obtained from the EM-BRACE database. **Results:** The entire cohort included 666 pts, of them 321 (48%) treated with 1L ET + CDKi. Among pts who received adjuvant ET (n = 347), 54 (15.6%) had primary ETR, 140 (40.3%) secondary ETR, and 153 (44.1%) were endocrine-sensitive. Of these pts, 56% (n = 191) received 1L CDKi therapy. The median time to next treatment (TTNT) in pts treated with 1L CDKi differed significantly by disease presentation, with a median of 1.3 years (95% CI, 0.9–1.5) for recurrent MBC and 2.3 years (95% CI, 1.7–3.6) for DNIV (log-rank p = 0.0005). TTNT also varied significantly according to endocrine sensitivity, with median TTNT of 0.6, 0.9, and 1.8 years for primary ETR, secondary ETR, and endocrine-sensitive disease, respectively (p = 0.0005). In the entire cohort, SNVs/indels were most frequent in *PIK3CA*, *TP53*, and *CDH1*. *CCND1*, *FGFR1*, and *MYC* amplifications were most frequent amplifications. *TP53* and *ESR1* mutations were enriched in ETR tumors, compared with ET sensitive cancers (q < 0.2). *ESR1* mutations were detected in 15% of ETR tumors, versus 8% in endocrine-sensitive cancers and 3% in DNIV. Prior adjuvant aromatase inhibitor exposure occurred in 39%, 61%, and 44% of patients with primary ETR, secondary ETR, and ET-sensitive tumors, respectively. When comparing poor and exceptional responders to 1L CDKi, TTNT <6 months versus >36 months, mutations in *TP53* and *NF1* were significantly enriched in the poor responders (q < 0.2). We also evaluated the association between specific genomic alterations and TTNT on 1L CDKi; mutations in *TP53*, *NF1*, and *ERBB2*, as well as amplifications of *RAD21*, *FGFR1* and deletions of *RB1*, *CDKN2A* were associated with shorter TTNT on 1L ET plus CDKi (q < 0.2). **Conclusions:** In our cohort, distinct genomic alterations were associated with ETR and shorter TTNT on 1L CDKi. These findings underscore the biology of ETR and support the clinical relevance of early genomic profiling to refine risk stratification and guide therapeutic decision-making. Notably, the high prevalence of *ESR1* alterations in ETR tumors carries important implications for adjuvant and 1L treatment strategies, particularly the potential role of oral selective estrogen receptor degraders in this setting. Research Sponsor: None.

Impact of oral SERDs, including giredestrant, on survival in HR+ HER2– metastatic breast cancer: A meta-analysis.

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Background: Oral selective estrogen receptor degraders (SERDs) are designed to overcome endocrine resistance in HR+ HER2– breast cancer due to ESR1 mutations. Several SERDs have been evaluated in recent trials. We performed a meta-analysis evaluating oral SERDs in previously treated patients with HR+ HER2– metastatic breast cancer (MBC). **Methods:** Randomized controlled trials comparing oral SERDs to standard endocrine therapy in previously treated HR+, HER2– MBC, reporting progression-free survival (PFS) or overall survival (OS) and adverse events (AEs), were identified via a systematic PubMed search. To incorporate the latest SERDs data, results from the recently presented giradestrant trial were included. Meta-analysis was performed for the overall intention-to-treat (ITT) population and the ESR1-mutant (ESR1m) subgroups. Leave-one-out analyses excluding giradestrant were conducted to highlight its specific impact. Rates of serious adverse events (grade ≥ 3) and treatment discontinuation were also analyzed. **Results:** A total of 2324 patients from six phase III trials were included in this analysis. Oral SERDs improved PFS compared with standard endocrine therapy in the ITT population (HR 0.734, CI 0.620–0.869, $p < 0.001$) with greater benefit observed in the ESR1m subgroup (HR 0.538, CI 0.430–0.673, $p < 0.001$). Excluding giradestrant data from the evERA trial led to modest reduction in PFS benefit in both the ITT (HR 0.755, CI 0.661–0.908, $p < 0.05$) and the ESR1m (HR 0.582, CI 0.471–0.718, $p < 0.05$) subsets, though overall PFS benefit remained. Additionally, SERDs were associated with an OS advantage in pooled analyses for the ITT population (HR 0.743, CI 0.621–0.889, $p < 0.05$) and ESR1m population (HR 0.584, CI 0.433–0.768, $p < 0.001$). Excluding giradestrant did not result in significant changes in OS estimates. Grade ≥ 3 AEs were more frequent with SERDs (OR 1.53, CI 1.20–1.95, $p < 0.001$) while discontinuation rates were similar between groups (OR 1.53, CI 0.99–2.37, $p = 0.06$). **Conclusions:** Oral SERDs significantly improve PFS in previously treated HR+ HER2– MBC with the greatest benefit in patients with ESR1 mutations. Pooled analysis suggests an OS advantage favoring SERDs. Giradestrant contributes to the observed PFS class effect without altering OS outcomes. SERDs are associated with increased toxicity. Although a trend towards higher discontinuation rates was noted, it did not reach statistical significance, and discontinuation rates remain comparable to standard endocrine therapy. These findings support the use of oral SERDs in the second- and third-line treatment of HR+ HER2– MBC, particularly in ESR1-mutant disease. Research Sponsor: None.

Ethnicity-based comparative analysis of treatment endpoints of 30,000 HR+/HER2– metastatic breast cancer patients on CDK4/6 inhibitors (palbociclib/ribociclib/abemaciclib).

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Background: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), in combination with endocrine therapy, are the mainstay for HR+/HER– metastatic breast cancer (MBC). However, ethnically diverse populations remain underrepresented in randomised clinical trials, limiting the ability to stratify by ethnicity. This meta-analysis utilises real-world evidence to compare treatment endpoints i.e., overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and adverse effects (AE) across ethnic groups. **Methods:** 116 studies from MEDLINE and Embase were included (Palbociclib: 67, Abemaciclib: 29, Ribociclib: 20). 31580 HR+/HER– MBC patients (Asian [AS]:22067; White [WH]: 8993; Black [BL]: 510) were included. Median survival and response rates were calculated using a random effects model to account for between-study variability. Parentheses represent 95% confidence intervals (CI). **Results:** Pooled analysis shows disparities in efficacy and significant variation in haematological toxicity. Maximum mOS benefit for AS was on palbociclib (61.8mo) whereas for WH was ribociclib (63.9mo), primarily driven by long-term follow-up in MONALEESA. mPFS benefit was longest in BL patients on abemaciclib (17mo), WH patients on palbociclib (27.7mo), AS patients on ribociclib (25.2mo). ORR was highest for ribociclib across all ethnic groups (Table). Meta-regression indicated ethnicity was not a significant independent moderator of AE risk ($p > 0.05$). AS cohorts demonstrated the highest incidence of Grade 3+ neutropenia across all agents: Palbociclib (72.0%; 49.5–87.1), Abemaciclib (52.8%; 46.1–59.4), and Ribociclib (45.8%; 39.1–52.5; $p < 0.0001$). In contrast, WH and BL patients exhibited significantly lower G3+ neutropenia rates, ranging from 12.0% to 33.8% ($p < 0.0001$). AS patients also showed the highest rates of leukopenia and anaemia across all CDK4/6i. **Conclusions:** Our large-scale meta-analysis findings establish a novel, evidence-based ethnicity-informed CDK4/6i selection framework to optimize treatment endpoints in HR+/HER2– MBC patients. This highlights the urgent need for prospective trials focused on underrepresented populations to close the survival gap. Research Sponsor: None.

Metric	Subgroup	Palbociclib	Abemaciclib	Ribociclib
ORR (%)	AS	34.0 (27-42)	28.7 (16.1-41.3)	52.4 (46.4-58.5)
	WH	34.0 (28-65)	41.9 (14.9-68.9)	44.9 (32.1-57.7)
	BL	25.0 (17-23)	N/A	34.6
mPFS (mo)	AS	21.0	13.0	25.2
	WH	27.7	21.8	24.1
	BL	14.1	17.0	10.8
mOS (mo)	AS	61.8	25.2	58.7
	WH	60.5	37.6	63.9

An early resistance genomic state (ERGS) as an identifier of primary CDK4/6 inhibitor failure in HR+/HER2– metastatic breast cancer.

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Background: CDK4/6 inhibitors combined with endocrine therapy are the standard first-line treatment for patients with hormone receptor-positive (HR+), HER2-negative metastatic breast cancer (mBC). However, a substantial subset of patients experience early disease progression, and there are currently no clinically practical tools available at treatment initiation to identify patients unlikely to derive lasting benefit. In this study, we attempt to define a clinically actionable genomic resistance phenotype using routine tumor sequencing. **Methods:** We conducted a retrospective real-world analysis using the MSK CHORD 2024 cohort, including 1,690 patients with HR+/HER2– mBC treated with first-line CDK4/6 inhibitors (palbociclib, ribociclib, or abemaciclib). An Early Resistance Genomic State (ERGS) was pre-specified based on alterations in five genes with established roles in endocrine and cell-cycle resistance: TP53, ESR1, RB1, PTEN, and NF1. The primary endpoint was time to first documented progression following CDK4/6 initiation, with early progression defined as progression within 6 months. Multivariable Cox proportional hazards models were adjusted for age, visceral disease, and central nervous system (CNS) involvement. Model performance was assessed using internal validation with resampling. **Results:** ERGS alterations were present in 41% of patients. ERGS demonstrated a graded, dose-dependent association with progression risk. Compared with ERGS-negative patients, those with one ERGS alteration had a 29% higher risk of progression (Hazard Ratio (HR) = 1.29, 95% CI: 1.15–1.45), those with two alterations had a 58% higher risk (HR = 1.58, 95% CI: 1.30–1.91), and those with three or more alterations had more than double the risk (HR = 2.19, 95% CI: 1.24–3.87; global log-rank $p < 0.0001$). Twelve-month progression rates were 48%, 62%, 71%, and 85% across ERGS 0, 1, 2, and ≥ 3 groups, respectively. The prognostic impact of ERGS remained consistent across endocrine partner (aromatase inhibitor vs fulvestrant) and metastatic pattern subgroups. Incorporation of ERGS significantly improved model discrimination beyond clinical covariates alone, increasing the concordance index from 0.61 to 0.85 in internal validation analysis. **Conclusions:** ERGS defines a systems-level intrinsic CDK4/6 resistance phenotype identifiable using routine tumor sequencing at treatment initiation. This parsimonious genomic state provides clinically meaningful risk stratification beyond standard clinicopathologic features and identifies patients unlikely to derive lasting benefit from CDK4/6-based therapy. Therefore, ERGS may serve as a practical biomarker to prioritize enrollment on escalated first-line trials or alternative therapeutic strategies in HR+/HER2– metastatic breast cancer. Research Sponsor: None.

Oral estrogen receptor (ER) degraders compared to standard endocrine therapy (ET) in ER-positive, human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer (MBC): A systematic review and meta-analysis.

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Background: Treatment with ER-positive HER2-negative (ER+HER2-) MBC has evolved during the past decade. Several novel oral ER degraders have shown to modestly improve progression free survival (PFS) compared to standard ET, with significant results specifically in patients carrying activating *ESR1* mutations. However, whether overall survival (OS) is also improved is unknown. **Methods:** This was a PRISMA guided meta-analysis. We identified all randomized controlled trials (RCTs) comparing ER degraders to standard ET in patients with ER+HER2- MBC. Efficacy outcomes included PFS and OS for the intention to treat (ITT) population, as well as for patients with *ESR1* mutation, and for patients with wildtype *ESR1*. Hazard ratios (HRs) and 95% confidence intervals (CI) for PFS and OS were extracted, and pooled into meta-analysis using RevMan Version 9.18.0. Statistical tests were two-sided, and statistical significance was defined as $p < 0.05$. Subgroup analyses comparing outcomes based on *ESR1* mutation were also performed. In trials with multiple investigational arms, the monotherapy ER degrader arm (EMBER-3) and the dose selected for further development (SERENA-2) were included. **Results:** Seven RCTs comprising 3926 patients were analyzed. Compared to standard ET, ER degraders were associated with statistically significant improvement in OS in the ITT population, HR 0.74, 95% CI 0.62–0.89, $p = 0.001$. Analysis by *ESR1* status demonstrated that ER degraders were associated with significant improvement in OS for patients with *ESR1* mutation (HR 0.60, 95% CI 0.47–0.77, $p < 0.001$), but not for patients with *ESR1* wild type (HR 0.87, 95% CI 0.66–1.15, $p = 0.33$), $p = 0.05$ for the subgroup difference. ER degraders were associated with significant improvement in PFS in the ITT population, HR 0.80, 95% CI 0.66–0.98, $p = 0.03$. Analysis based on *ESR1* status demonstrated significant improvement in PFS for patients with *ESR1* mutation (HR 0.54, 95% CI 0.43–0.68, $p < 0.0001$), but not for patients with *ESR1* wild type (HR 0.95, 95% CI 0.82–1.09, $p = 0.46$), $p = 0.001$ for the subgroup difference. **Conclusions:** Compared to standard ET, ER degraders were associated with statistically significant improvement of OS and PFS. While this impact was notable in the ITT population, subgroup analyses confirmed the statistically significant benefit is limited to patients with *ESR1* mutations. Research Sponsor: None.

Capivasertib plus fulvestrant in Chinese patients with HR+/HER2– advanced breast cancer: Interim analysis of CAPItrue.

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Background: After disease progression on cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) plus endocrine therapy (ET), patients (pts) with HR+/HER2– advanced breast cancer (ABC) face limited treatment options and poor prognosis, particularly those with PI3K/AKT pathway tumor alterations, which are major drivers of disease progression and treatment resistance mediated centrally by AKT. Targeting the PI3K/AKT pathway represents a mechanism-driven precision strategy to overcome CDK4/6i/ET resistance, with potential to maximize ET benefit and delay subsequent chemotherapy. In the phase III CAPItello-291 trial, capivasertib (CAPI) plus fulvestrant (FUL) improved progression free survival (7.3 vs 3.1 months, HR 0.50) versus placebo plus FUL in pts with *PIK3CA/AKT1/PTEN*-altered tumors. CAPItrue (NCT06635447) is an ongoing phase IIIb study of CAPI plus FUL in Chinese pts with HR+/HER2– ABC progressing on ET, with a focus on *PIK3CA/AKT1/PTEN*-altered disease, aiming to inform precision 2nd line treatment following CDK4/6i progression. **Methods:** CAPItrue enrolled Chinese pts with HR+/HER2– ABC progressing on ET±CDK4/6i. All pts received oral CAPI (400 mg BID, 4 days on, 3 days off) and intramuscular FUL. This pre-specified interim analysis was performed in the cohort (C1) without prior FUL (conducted after the last C1 pt received ≥1 dose of study treatment). Baseline characteristics, biomarker profiles, preliminary efficacy (interim objective response rate [ORR] was evaluated in pts with ≥4 months of follow-up) and safety were summarized. **Results:** By Aug 20, 2025, 195 pts were enrolled in C1 and received study treatment. *PIK3CA/AKT1/PTEN* alterations were detected in 115 (59.0%) pts (altered group). The median age was 55.0 yrs; 64.1% were post-menopausal. Prior therapy for ABC included: 75.4%/8.7% 1/2 prior lines of ET; 65.1% CDK4/6i, 17.9% chemotherapy. The altered group showed similar characteristics. In patients with ≥4 months of follow-up, ORR was 35.6% overall (37/104, 1 complete and 36 partial responses [PR]) and 43.1% in the altered group (25/58, 25 PR). Overall, at a median follow-up of 4.1 months, 92.8% had ≥1 adverse event (AE); 88.7% had AEs possibly related to CAPI; and 34.9%/11.8% had grade ≥3/serious AEs (SAE). A similar safety profile was seen in the altered group (any AE: 92.2%, grade ≥3 AE: 30.4%, SAE: 11.3%). No new safety signal was observed. **Conclusions:** In Chinese pts with *PIK3CA/AKT1/PTEN*-altered HR+/HER2– ABC previously treated with ET±CDK4/6i, CAPI plus FUL showed encouraging preliminary efficacy and safety. Follow-up is ongoing. Clinical trial information: NCT06635447. Research Sponsor: AstraZeneca AB.

CBFB mutations as a predictive biomarker of endocrine therapy benefit in hormone receptor–positive (HR+) breast cancer: Discovery and validation in 3,799 patients.

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Background: Endocrine therapy (ET) is the mainstay approach for treating HR+ breast cancer, yet resistance frequently limits efficacy. Identifying reliable genomic biomarkers to predict superior treatment response remains an unmet clinical need. **Methods:** We performed unbiased genomic analysis of HR+ patients from the MSK-CHORD cohort (n=2,058), stratified by disease stage (metastatic vs. non-metastatic). Outcomes included progression-free survival (PFS), recurrence-free survival (RFS), and overall survival (OS). FDR-corrected Cox models were used for gene-level discovery. A chemotherapy-treated subset of the MSK-CHORD cohort served as a control to assess treatment specificity. Findings were externally validated in the independent METABRIC cohort (n=1,741). **Results:** Beyond known resistance biomarkers (ESR1, TP53, RB1), loss-of-function mutations in CBFB emerged as a significant predictor of ET benefit. CBFB mutations were present in 6.7% of metastatic breast cancer (MBC; n=80) and 6.3% of non-MBC (n=54). In MBC patients, CBFB mutations were associated with significantly longer PFS (HR=0.44; p=0.0002); in the adjuvant setting, RFS was similarly improved (HR=0.48; p=0.009). OS was prolonged in both settings (HR=0.49 and 0.50; p<0.05 for both). CBFB mutations were enriched in lobular histology (OR=2.3; p<0.0001); however, multivariable Cox regression confirmed CBFB as an independent predictor after adjusting for histology (HR=0.46; p=0.0003). To provide biological validation, we analyzed RUNX1, the obligate functional partner of CBFB in the CBF transcription complex. Combined CBFB/RUNX1 mutations (n=122, 10.2% in MBC; n=82, 9.5% in non-MBC) demonstrated consistent predictive benefit (HR=0.48 and 0.56; p<0.0001 and p=0.007, respectively). Notably, the survival benefit associated with CBFB or CBF-complex mutations was absent in chemotherapy-treated controls, confirming treatment-specific predictive value rather than general prognostic effect. In the METABRIC validation cohort, CBFB mutations (5.9%; 103/1,741) independently predicted longer relapse-free survival (HR=0.59; p=0.005) and OS (HR=0.52; p<0.0001). Gene expression analysis revealed that CBFB mutations were associated with significantly lower APOBEC gene family expression (p<0.001), suggesting a mechanistic link between CBF-complex loss and reduced APOBEC-mediated mutagenesis, an established driver of endocrine resistance. **Conclusions:** We identify CBF-complex (CBFB/RUNX1) mutations as a novel genomic biomarker of ET benefit in HR+ breast cancer, independent of disease stage and histology, and validated across two large cohorts. These findings highlight a subset of patients with exceptional outcomes and provide a potential mechanistic link between CBF alterations and APOBEC-mediated resistance. Research Sponsor: None.

First-line fovinaciclib versus placebo combined with aromatase inhibitor for advanced breast cancer: A randomized, double-blind phase 3 study.

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Background: Endocrine therapy combined with a cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor is the standard first-line therapy for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer. Fovinaciclib is a novel CDK4/6 inhibitor that showed survival benefit when added to fulvestrant in the later-line setting. This randomized, double-blind, placebo-controlled phase 3 trial evaluated the efficacy and safety of fovinaciclib plus an aromatase inhibitor (AI) as initial therapy. **Methods:** Adult women with HR-positive, HER2-negative advanced breast cancer who had no prior systemic therapy in the advanced setting were enrolled across 63 centers. Eligible patients were randomized in a 1:1 ratio to receive oral fovinaciclib (200 mg, once daily, days 1–21) or placebo plus an AI (letrozole 2.5 mg or anastrozole 1 mg, orally, once daily, days 1–28) in 28-day cycles. Pre- or perimenopausal patients also received goserelin (3.6 mg, subcutaneous, day 1). The primary endpoint was progression-free survival (PFS) assessed by blinded independent central review (BICR). Secondary endpoints included other efficacy endpoints and safety. **Results:** A total of 417 patients were assigned to the fovinaciclib ($n = 208$) or placebo arm ($n = 209$) with balanced baseline characteristics. At the protocol-specified interim analysis (median follow-up 16.6 months, data cutoff date June 25, 2024), adding fovinaciclib significantly improved PFS (hazard ratio 0.55, 95% CI 0.38–0.77; $p = 0.0003$): median PFS was not reached in the fovinaciclib arm and 20.2 months (95% CI 16.4 months–not evaluable) in the placebo arm. The 2-year PFS rates were 65.5% (95% CI 55.3%–73.9%) and 38.9% (95% CI 27.5%–50.2%), respectively. Consistent PFS benefit was observed in investigator assessments (hazard ratio 0.49 [95% CI 0.36–0.68], $p < 0.0001$) and across most subgroups. Fovinaciclib also showed favorable results across secondary efficacy endpoints. OS data remain immature. Treatment-emergent adverse events (TEAEs) occurred in 207 (99.5%) and 199 (95.2%) patients in the fovinaciclib and placebo arms, respectively, with serious adverse events (SAEs) reported in 30 (14.4%) and 24 (11.5%). Discontinuation due to TEAEs was only 1.4% in both arms. The most common TEAEs were hematologic toxicities, which did not lead to SAEs or study drug discontinuation. Grade ≥ 3 gastrointestinal toxicities (2.4% versus 0) or renal toxicities (0 versus 0.5%) were rare. **Conclusions:** Adding fovinaciclib to first-line AI therapy provided a significant and clinically meaningful PFS benefit, along with consistent improvements in other survival outcomes and a manageable safety profile. These findings support fovinaciclib as a first-line treatment option for patients with HR-positive, HER2-negative advanced breast cancer. Clinical trial information: NCT05439499. Research Sponsor: Avanc Pharmaceutical Co., Ltd.

Effects of SGLT2 inhibitor dapagliflozin on anticancer resistance and alpelisib- and fulvestrant-induced cardiomyocyte injury under hyperglycemic conditions.

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Background: Activating PIK3CA mutations occur in approximately 40% of hormone receptor-positive (HR+)/HER2-negative breast cancers and drive resistance to endocrine therapy. The PI3K α -selective inhibitor alpelisib combined with fulvestrant significantly improves progression-free survival, as demonstrated in the SOLAR-1 trial, but its clinical benefit is limited by frequent treatment-induced hyperglycemia. Beyond metabolic toxicity, hyperglycemia promotes oxidative stress, inflammation, and mitochondrial dysfunction, thereby increasing cardiovascular vulnerability and potentially reactivating oncogenic PI3K/AKT signaling through compensatory hyperinsulinemia. Retrospective clinical evidence suggests that sodium-glucose cotransporter-2 (SGLT2) inhibitors may mitigate these effects. We investigated the direct redox-dependent cardiotoxic effects of alpelisib and fulvestrant under hyperglycemic conditions and evaluated whether dapagliflozin confers cardioprotection in human cardiomyocytes. **Methods:** Human iPSC-derived cardiomyocytes were exposed to alpelisib and fulvestrant under hyperglycemic conditions (25 mM glucose) in the absence or presence of dapagliflozin. Cell viability (MTS), mitochondrial membrane potential, reactive oxygen species generation, lipid peroxidation (MDA and 4-HNE), intracellular antioxidant defenses (GSH/GSSG, SOD, catalase/GPx), inflammatory and inflammasome-related mediators (IL-1 β , IL-18, IL-6, TNF- α , NLRP3, MyD88), and apoptotic signaling (caspase-3/7 activity) were quantified. Cardiac injury was assessed by high-sensitivity cardiac troponin I and T release. Transcriptomic profiling was performed to interrogate cardiometabolic and redox signaling pathways. **Results:** Alpelisib and fulvestrant synergistically induced a pro-oxidative and pro-inflammatory injury phenotype characterized by mitochondrial depolarization, increased ROS and lipid peroxidation, depletion of antioxidant defenses, activation of the NLRP3/IL-1 axis, and caspase-dependent apoptosis. Dapagliflozin markedly restored redox homeostasis, preserved mitochondrial integrity, suppressed inflammasome and cytokine signaling, and reduced troponin release, indicating robust cardioprotection. Transcriptomic analysis confirmed coordinated downregulation of oxidative stress, inflammatory, and insulin-stress pathways. **Conclusions:** Dapagliflozin directly protects human cardiomyocytes from hyperglycemia-driven, PI3K α inhibitor-associated oxidative injury by restoring redox and mitochondrial homeostasis. These findings provide a strong mechanistic rationale for repurposing SGLT2 inhibitors as dual cardio-metabolic protectants in precision oncology. Research Sponsor: Ministero della Salute, 5x1000 project 5XMILLE_2022_17.

Prognostic impact of tumor recurrence dynamics in patients with HR+/HER2-advanced breast cancer treated with ET+CDK4/6i: Results from the multicenter, Italian study PALMARES-2.

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Background: Endocrine sensitivity/resistance (ES/ER) is a key prognostic and predictive factor in patients (pts) with Hormone Receptor-positive, Human Epidermal growth factor Receptor 2-negative advanced Breast Cancer (HR+/HER2- aBC). Cyclin Dependent Kinase 4/6 inhibitors (CDK4/6i)+Endocrine Therapy (ET) are standard 1st line therapy for HR+/HER2- aBC pts regardless of tumor ES/ER status at diagnosis. However, the prognostic value of tumor recurrence dynamics within ES/ER groups has never been investigated. **Methods:** We conducted a pre-planned analysis of the multicenter, real-world, Italian study PALMARES-2 (NCT06805812) to evaluate the prognostic role of tumor recurrence dynamics, de novo aBC presentation and distant recurrence-free interval (DRFI) in pts with HR+/HER2- aBC treated with 1st line ET+CDK4/6i between January 2016 and September 2024. DRFI was defined as the time from surgery to the detection of aBC. The primary endpoint was real-world progression-free survival (rwPFS), defined as the time between ET+CDK4/6i initiation and disease progression (PD) or patient death. Results were adjusted through Multivariable Cox regression for 16 relevant covariates. **Results:** Of 4,234 pts enrolled, 2,858 (67.5%) had ES and 1,376 (32.5%) had ER disease at aBC diagnosis. Median follow-up was 38.6 and 42.7 months, respectively. After adjustment, ER was associated with poorer rwPFS compared to ES (adjusted hazard ratio [aHR] 1.78, 95% CI 1.60-1.96). In the ER cohort, secondary tumor resistance with recurrence during years (y) 3-5 of adjuvant (adj) ET or <1 y from its end, and recurrence during extended adj ET or <1 y from its end, were associated with increasingly better rwPFS when compared to primary resistance (Table). In the ES cohort, pts with tumor recurrence >10 y from adj ET end had significantly longer rwPFS when compared to pts recurring <10 y from adj ET end, or pts with no prior adj ET or de novo aBC (Table). Among pts with recurrent disease (N=2,792), any additional y of DRFI resulted in 3% reduction in the risk of disease progression (aHR:0.97, 95% CI: 0.96-0.99). **Conclusions:** The current ES/ER classification fails to capture the whole spectrum of prognostic heterogeneity in HR+/HER2- aBC pts treated with 1st line ET+CDK4/6i. Recurrence dynamics, including DRFI, improve prognostic classification and may inform treatment selection and personalised patient management in this clinical context. Clinical trial information: NCT06805812. Research Sponsor: Associazione Italiana per la Ricerca sul Cancro; Italian Health Ministry.

Recurrence dynamic	N	rwPFS (mo)	aHR (95% CI)
Primary resistant	334	13.4	Ref
Secondary resistant-during 5 y adj ET	668	15.7	0.85 (0.72-0.99)
Secondary resistant-during extended adj ET	375	19.4	0.73 (0.61-0.89)
No adjuvant ET	288	30.0	0.46 (0.36-0.59)
1-5 y from adj ET end	453	29.3	0.54 (0.45-0.65)
5-10 y from adj ET end	377	32.6	0.50 (0.40-0.61)
>10 y from adj ET end	275	45.2	0.30 (0.23-0.40)
De novo aBC	1422	31.3	0.50 (0.42-0.59)

Association of *ESR1* amplification with survival and benefit from CDK4/6 inhibition in breast cancer.

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Background: While *ESR1* mutations are established mediators of endocrine resistance in breast cancer (BC), the significance of *ESR1* amplification (amp) remains poorly understood with reported amp rates vary widely due to platform-specific differences. We leveraged a large clinico-genomic real-world database and applied a stringent NextGen sequencing (NGS) approach to test *ESR1* amp. We identify *ESR1* amp as a molecular entity distinct from canonical estrogen-driven resistance mechanisms. **Methods:** Breast tumors underwent NGS of DNA and RNA (WES/WTs; NextSeq and NovaSeq; Caris Life Sciences, Phoenix, AZ). Gene copy number was determined by CNVKit with ≥ 6.0 copies defined as amp to identify focal, high-level copy number events, minimizing misclassification of chromosome 6 copy gains. Real-world clinical data were obtained from insurance claims. Time on treatment (TOT) was defined treatment start to end; overall survival (OS) from tissue collection to last contact. Cox proportional hazards model and log-rank tests were used for survival analysis. Molecular comparisons used χ^2 or Mann-Whitney U with multiple-testing adjustment ($q < 0.05$). Gene set enrichment analysis was performed, with significance defined as $FDR < 0.05$. **Results:** Among 27,979 BC tumors, 165 were *ESR1* amp (0.6%), a prevalence much lower than prior reports. *ESR1* amp was significantly enriched in the Luminal B (LumB) subtype (1.4%, 81/5,915) versus other subtypes (0.1–0.4%, $p < 0.0001$). *ESR1* amp tumors exhibited features of genomic instability, including higher genomic loss of heterozygosity (61% vs 24%), TP53 mutations (59% vs 27%), and amplifications on chromosomes 6, 8, and 11 ($q < 0.05$). Transcriptomically, *ESR1* amp tumors had significant enrichment of G2M checkpoint and MYC target gene sets by GSEA in the overall cohort (G2M NES 2.61, MYC NES 2.41,) and in LumB (G2M NES 3.18; MYC NES 3.04, all $FDR < 0.001$), consistent with CDK4/6-independent cell-cycle progression. Unlike *ESR1* mutations, *ESR1* amplification was not associated with increased GREB1 expression (4.4 vs 4.2 TPM, $p > 0.05$), consistent with the absence of estrogen-response pathway enrichment. Clinically, *ESR1* amp was associated with reduced OS in the overall cohort (HR 1.296, $p = 0.016$) and LumB subset (HR 1.43, $p = 0.009$). Palbociclib TOT was significantly shorter in *ESR1* amp vs. non-amp tumors (all BC: 7.0 vs 11.0 months, HR 1.39 [95% CI 1.045–1.85], $p = 0.023$; LumB: 4.9 vs 11.4 m, HR 1.57 [1.1–2.2], $p = 0.01$). This effect was significant after adjusting for TP53, gLOH, and CDH1 alterations (adjusted HR 1.47 [1.04–2.06], $p = 0.027$). No TOT difference was observed with aromatase inhibitors. **Conclusions:** In this large real-world analysis, *ESR1* amplification defines a rare, genomically unstable breast cancer subset with proliferative signaling and reduced clinical benefit from CDK4/6 inhibition, supporting its potential role as a negative predictive biomarker. Research Sponsor: None.

A phase 1/2, first-in-human study of AVZO-021, a selective cyclin-dependent kinase 2 inhibitor (CDK2i), as monotherapy and in combination for patients with advanced solid tumors, including hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) breast cancer (BC) and cyclin E1 (CCNE1)–amplified solid tumors: Updated safety and efficacy results.

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Background: AVZO-021 is a potent, once-daily, oral CDK2i with high selectivity against CDK1, thus minimizing off-target toxicity. Initial Phase 1 data from the ongoing first-in-human Phase 1/2 study of AVZO-021 (NCT05867251) showed clinical responses and a favorable tolerability profile. **Methods:** The ongoing Phase 1 portion of the study is evaluating the safety, pharmacokinetics (PK), and preliminary efficacy of AVZO-021 alone and in combination with fulvestrant. As of January 20, 2026, the safety population included all patients treated with AVZO-021 monotherapy (n=50) or in combination with fulvestrant (n=13). Efficacy evaluable population included patients treated at ≥ 150 mg once daily (QD) with HR+/HER2– breast cancer or CCNE1–amplified solid tumors with at least 1 post-baseline scan (n=23 in monotherapy and n=12 in combination with fulvestrant). **Results:** The median age was 63 years for monotherapy patients and 60 years for combination with fulvestrant. Overall, 95% of patients were female, 78% had BC, 10% had ovarian/fallopian tube cancer, and 5% had endometrial/uterine cancer. AVZO-021 monotherapy patients had a median of 3 prior lines of systemic therapy and those in combination therapy had a median of 4 prior lines, in the metastatic setting. All patients with HR+/HER2– BC received prior CDK4/6i and hormonal therapy. Most common ($>25\%$) all-grade treatment-emergent adverse events (TEAEs) were nausea (51%), fatigue (43%), anemia (33%), and vomiting (32%); 13 patients required dose reductions due to TEAEs and 2 patients discontinued due to TEAEs (1 unrelated Grade 3 intestinal obstruction, 1 related Grade 4 neutropenia). Four patients with HR+/HER2– BC and CCNE1–amplified solid tumors had confirmed partial responses and remain ongoing, demonstrating prolonged clinical benefit. Additionally, 23 patients had stable disease for a disease control rate of 77%. Continuous CDK2 target coverage and significant decreases in ctDNA were observed at ≥ 90 mg QD monotherapy and in combination with fulvestrant. **Conclusions:** With longer follow-up, AVZO-021 as monotherapy and in combination with fulvestrant continues to show an encouraging tolerability profile and clinically meaningful efficacy. Gastrointestinal and hematologic adverse events continue to be of low incidence and severity allowing for prolonged treatment and potential safe combination with AVZO-023, a highly potent and selective CDK4i currently enrolling patients with HR+/HER2– BC in combination with fulvestrant. Clinical trial information: NCT05867251. Research Sponsor: Avenzo Therapeutics.

Liquid-based methylation profiling of molecular breast cancer subtypes (MBS) in hormone receptor positive (HR+) metastatic breast cancer (MBC) treated with CDK4/6 inhibitor (CDK4/6i).

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Background: MBC remains incurable due to the invariable development of resistance, with most deaths resulting from HR+ MBC that acquires resistance to endocrine therapy (ET) combinations. HR and HER2 remain the most important biomarkers in MBC but, while it is known that receptor status and expression based molecular subtypes (e.g. PAM50) can vary over an individual patient's (pts) disease course, serial evaluation is currently limited in routine clinical care by tissue requirements. **Methods:** The EMBRACE cohort study collects biospecimens with matched clinical annotations from pts with MBC at Dana-Farber Cancer Institute. A subset of 510 plasma samples collected around CDK4/6i treatment (tx; pre-tx: -90 to +30 days from start; on-tx; post-tx: -30 to +90 days from end) from 323 pts with HR+ MBC were assessed with Guardant360 Liquid. MBS calls were generated using a previously described cell-free DNA methylation-based deconvolution model that classifies HR and HER2 status in cases with tumor fraction (TF) $\geq 0.5\%$ with accuracy $>85\%$, and compared with tissue-based HR and HER2 status by immunohistochemistry (IHC). **Results:** Of 510 samples profiled, 308 (60.4%) were evaluable for MBS with TF $\geq 0.5\%$. The evaluable rate was lowest in on-tx samples at 48.7%, in line with lower median TF in this set. Of evaluable samples, 285 (92.5%) aligned with sufficient confidence to report a subtype: 273 (88.6%) of evaluable samples were classified as HR+, 23 (7.5%) undetermined, and only 12 (4.9%) HR-, all of which were either from on- or post-tx timepoints. MBS calls on pre-tx samples showed high concordance with clinical IHC, with higher concordance at metastatic diagnosis (91%) than primary diagnosis (86%). Notably, all discordances were cases abstracted as HR+/HER2- at metastatic diagnosis by IHC where MBS yielded HR+/HER2+. Overall, samples from 28 pts were assigned a HER2+ MBS and, in 9 (32%) of these, a concordant genomic alteration in *ERBB2* (copy number gain, gain-of-function mutation and/or fusion) was detected on Guardant360 Liquid. Out of 48 pts with multiple classifiable samples, 11 (22.9%) showed differences in MBS across serial samples including 9 with changes in HER2 (5 gaining and 4 losing HER2 MBS), and 2 with changes in HR (both with an on-tx sample classified as HR- but the subsequent post-tx sample HR+). **Conclusions:** A methylation-based liquid biopsy assay can classify MBS with high correlation to clinical pathology in pre-tx samples and facilitate identification of discordant, or perhaps heterogeneous, subtype while capturing the dynamics of MBS over disease course and treatment. Future studies are indicated to investigate the clinical utility of this assay as a biomarker for therapy selection. Research Sponsor: None.

Time on treatment for systemic therapies for patients with hormone receptor-positive breast cancer and *BRCA1*, *BRCA2*, or *PALB2* pathogenic variants.

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Background: For patients with hormone receptor-positive/HER2- (HR+) metastatic breast cancer and pathogenic variants (PVs) in *BRCA1*, *BRCA2* or *PALB2* (mBRCA), data suggests longer cancer-specific survival compared to patients without PVs (wtBRCA). One hypothesis is that their innate DNA repair deficiency improves response to cytotoxic therapy, as seen in poly (ADP-ribose) polymerase inhibitors (PARPi), which results in longer progression free survival (PFS). However, it remains unclear whether mBRCA is associated with a longer PFS with other therapies such as endocrine therapies (ET), including aromatase inhibitors (AI) and Selective Estrogen Receptor Degraders (SERDs). Some data suggests a shorter PFS with CDK 4/6-inhibitors (CDK4/6i) for mBRCA. Therefore, we compared time-on-treatment (TOT), a real-world surrogate for PFS, for mBRCA vs wtBRCA treated with ET, CDK4/6i, or PARPi. **Methods:** DNA and RNA somatic sequencing were performed on tumors submitted to Caris Life Sciences. HR+ was defined by IHC per ASCO/CAP. TOT was calculated from first to last of treatment time based on insurance claims. Univariable Cox-proportional hazard analyses were utilized to assess TOT between mBRCA vs wtBRCA for each therapy (ET, PARPi and CDK4/6i). Protocol was approved prior by Caris research committee. **Results:** From 8263 HR+ breast cancer patients, 628 were mBRCA+ (median age: 57 years; range 23–90; 96% Female, 4% Male), and 7635 were wtBRCA (median age: 63 years; range 22–89; 98% Female, 2% Male). PVs were *BRCA2*: 66%, *BRCA1*: 19% and *PALB2*: 15%. As shown in Table 1, there was a shorter TOT for AI, SERDs and CDK4/6i, but a longer TOT with PARPi among mBRCA. Patients with mBRCA and high tumor mutational burden (TMB-Hi ≥ 10 mutations/Mb) had shorter TOT across all analyzed treatments vs low TMB (27.9 vs 35.8 mos, HR=1.47 95%CI 1.14–1.89; $p = 0.003$), except AI where TMB-Hi had longer TOT (23.5 vs 16.9 mos; HR=0.79, 95%CI 0.62–1.021; $p = 0.07$). **Conclusions:** This real-world data analysis demonstrates distinct TOT patterns among ET, CDK4/6i and PARPi for mBRCA patients when compared to wtBRCA. This calls for further studies in this specific patient population to understand the various treatment responses, associated tumor biology and immunologic landscape of mBRCA. Research Sponsor: None.

TOT comparisons by therapy between mBRCA and wtBRCA patients.

	Therapy	TOT (months) mBRCA	TOT (months) wtBRCA	Hazard Ratio (HR), Confidence Interval (CI) at 95%
Samples collected at all sites (including breast)	AI	21.7	25.8	HR=1.16 (CI 1.04-1.29 $p=0.009$)
	SERDs	7.6	11.1	HR=1.40 (CI 1.21-1.62) $p<0.00001$
	CDK4/ 6i	10.3	13.6	HR=1.39 (CI 1.22-1.59) $p<0.001$
	PARPi	5.8	2.1	HR=0.51 (CI 0.36-0.73) $p<0.001$
Samples collected at metastatic sites	AI	25.2	28.3	HR=1.14 (CI 0.994-1.30; $p=0.06$)
	SERDs	6.4	11.5	HR=1.40 (CI 1.20-1.68; $p<0.0001$)
	CDK4/ 6i	10.3	13.6	HR=1.31 (CI 1.12-1.54; $p<0.001$)
	PARPi	5.8	1.8	HR=0.46 (CI 0.31-0.70; $p<0.001$)

Influence of *TONSL* on tumor suppressor function of *RAD51* and resistance to CDK4/6 inhibitors in ER+ breast cancer.

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Background: Homologous Recombination (HR) and Replication Stress (RS) resolution mechanisms help to maintain genomic stability. *TONSL*, *MMS22L*, *RAD51*, *BRCA1/2* are the few proteins that cooperatively coordinate HR and RS resolution. Therefore, genes in these pathways are expected to function as tumor suppressors. However, only *BRCA1/2* function as tumor suppressors as their germline mutations increase cancer susceptibility. *TONSL* and *RAD51* are frequently overexpressed in tumors. Here, we investigated the relationship between *TONSL*-*RAD51* axis in breast cancer (BC) outcome and response to CDK4/6 inhibitors (CDK4/6i) and endocrine therapy (ET). **Methods:** 10,980 ER+ BC samples tested by NGS (592, NextSeq; WES/WTS, NovaSeq, Caris Life Sciences). Dual expression group *TONSL*/*RAD51*-high (H), *TONSL*-H/*RAD51*-low (L), *TONSL*-L/*RAD51*-H, and *TONSL*/*RAD51*-L were classified by RNA expression above or below median. HRD score and *TONSL*/HRD-H/L survival was analyzed using METABRIC (ER+ BC, n = 1904) dataset. *TONSL*-*RAD51* role in sensitivity to CDK4/6i was determined using *TONSL*-amplified ER+ MCF-7 cells. Real-world median overall survival (mOS) of *TONSL*/*RAD51* groups was derived from insurance claims and calculated from biopsy, start of ET or CDK4/6i to last contact using Kaplan-Meier. Statistical significance was assessed using chi-square and Mann-Whitney U with multiple comparison adjustments ($q < 0.05$). **Results:** *TONSL*-H had higher HRD score (33.7 vs 21.1, $p < 0.01$) compared to *TONSL*-L (n=952 each). *TONSL*/HRD-H (n=573) had worse mOS (109 m vs 138 m, $p < 0.05$) compared to *TONSL*/HRD-L (n=630). *TONSL*-H had higher frequency of LOH (31.6% vs 19.8%), *BRCA2* (5.1% vs 2.9%) and *BRCA1* (1.5% vs 0.8%) mutation, all $q < 0.05$. *TONSL*/*RAD51*-H had worse mOS compared to *TONSL*-H/*RAD51*-L, *TONSL*-L/*RAD51*-H or *TONSL*/*RAD51*-L (Table). *TONSL*-H/*RAD51*-L had worse survival with ET compared to other groups. With ET+CDK4/6i, *TONSL*/*RAD51*-H and *TONSL*-H/*RAD51*-L had similar but worse mOS compared to *TONSL*-L/*RAD51*-H and *TONSL*/*RAD51*-L (Table). *TONSL* knockdown in CDK4/6i resistant MCF-7 cells created *TONSL*-L/*RAD51*-H phenotype and cells regained the sensitivity to CDK4/6i. **Conclusions:** These findings suggest that *TONSL*-H independent of *RAD51* expression is associated with poor response to ET or ET+CDK4/6i. Therapeutic targeting of *TONSL* to create *TONSL*-L/*RAD51*-H status may improve response to ET+CDK4/6i. Moreover, as the activity of *TONSL* is regulated by various protein complexes, destabilizers of *TONSL*-protein complexes could potentially help in sensitizing ER+ BC to ET or CDK4/6i. Research Sponsor: Susan G Komen for the Cure; SAC232147.

	<i>TONSL</i> / <i>RAD51</i> -H OS in months	<i>TONSL</i> -H/ <i>RAD51</i> -L OS in months	<i>TONSL</i> -L/ <i>RAD51</i> -H OS in months	<i>TONSL</i> / <i>RAD51</i> -L OS in months	p-value
Overall	35 m (n=4176)	41.4 m (n=1473)	37.9 m (n=1476)	44.3 m (n=4173)	<0.01
ET	63.4 m (n=1361)	58 m (n=461)	65.2 m (n=508)	76.1 m (n=1430)	<0.01
ET+CDK4/6i	73.8 m (n=2261)	73.8 m (n=866)	84.6 m (n=799)	80.7 m (n=2291)	<0.01

Elacestrant in combination with capivasertib in patients with ER+/HER2– advanced breast cancer: Update from ELEVATE, a phase 1b/2, open-label, umbrella study.

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Background: Disease progression in patients (pts) with ER+/HER2– ABC on 1L ET+CDK4/6i is associated with several mechanisms of resistance, including intrinsic alterations in the PI3K/AKT/mTOR or cell cycle pathways, and/or *ESR1* mutations, a type of acquired resistance that emerges in up to 50% of pts. Elacestrant is the only single-agent oral SERD to significantly improve PFS vs SOC ET in all pts (HR 0.70; 95% CI 0.55–0.88; $P=0.0018$) and in those with *ESR1* tumors (HR 0.55; 95% CI 0.39–0.77; $P=0.0005$) with manageable safety in EMERALD, a trial that required prior ET+CDK4/6i [Bidard 2022]. In CAPItello–291, capivasertib + fulvestrant showed a mPFS of 7.3 mo (AKT–pathway altered) and 5.5 mo (prior CDK4/6i exposure) [Turner 2023]. In ER+ BC MCF7 CDX and CTG–2308 PDX models (*ESR1*wt/*PIK3CA*m), elacestrant + capivasertib showed superior antitumor activity compared with single-agent treatment, including an improvement in activity vs fulvestrant + capivasertib, further supporting the rationale to combine elacestrant with an AKT inhibitor in ER+ BC [Data on file]. This analysis reports updated Ph 1b safety and preliminary efficacy for elacestrant + capivasertib. **Methods:** ELEVATE is evaluating elacestrant in combination with everolimus, alpelisib, capivasertib, abemaciclib, ribociclib, or palbociclib to address different resistance mechanisms. Pts with ER+/HER2– ABC and 1–2L of prior ET±CDK4/6i are eligible regardless of *ESR1*m status; no prior chemo allowed in the ABC setting. Objectives are to identify the RP2D (Ph 1b) and evaluate PFS (Ph 2). **Results:** As of Dec 2025, 31 pts have been enrolled in the Ph 1b elacestrant (258–345 mg) + capivasertib (320–400 mg) cohorts. Key baseline characteristics include pts with visceral mets (90%), primary endocrine resistance (23%), *ESR1*m (45%), prior CDK4/6i (94%), and prior fulvestrant (45%). The most common ($\geq 35\%$) TEAEs were diarrhea (81%; 6% Gr 3), nausea (74%; 0% Gr 3), rash (61%; 13% Gr 3), fatigue (58%; 3% Gr 3), vomiting (42%; 0% Gr 3); observed hyperglycemia was 29% (10% Gr 3). Elacestrant 345 mg QD + capivasertib 320 BID [4 days on/3 days off] was determined as the RP2D based on the safety profile and PK analysis; no DLTs were observed. In RP2D response–evaluable pts ($n=9$), preliminary efficacy showed an ORR of 22%, CBR₂₄ wk at 67% (1 CR, 1 PR, and 6 SD), and a mPFS of 11.3 mo. Median follow-up is 10.2 mo [1.8–12.0]. Updated results and additional data will be reported. **Conclusions:** Elacestrant + capivasertib shows a manageable safety profile, consistent with known capivasertib + fulvestrant Gr 3 AEs, and clinically important efficacy in pts with AKT–pathway altered ER+/HER2– ABC with progressive disease. Enrollment in Ph 2 is ongoing. Elacestrant + capivasertib combination therapy offers pts the benefit of receiving both drugs with manageable safety and potential extended clinical benefit as an all-oral treatment option. Clinical trial information: NCT05563220. Research Sponsor: Menarini Group.

Real-world comparative safety and outcomes of ribociclib versus palbociclib in hormone receptor-positive, HER2-negative metastatic breast cancer: A propensity score-matched sensitivity analysis.

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Background: Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors are widely used in hormone receptor-positive (HR+) / HER2-negative (HER2-) metastatic breast cancer, yet real-world differences in survival and clinically relevant toxicities across agents remain unclear. We performed a propensity score-matched (PSM) sensitivity analysis comparing ribociclib and palbociclib, focusing on mortality and selected safety endpoints. **Methods:** Using the TrinetX database, a federated real-world data network, adult patients with HR+/HER2- metastatic breast cancer treated with ribociclib (cohort 1) or palbociclib (cohort 2) were identified. 1:1 propensity score matching was performed on more than 20 baseline characteristics. Outcomes were evaluated using (1) risk analyses excluding patients with the outcome prior to the time window and (2) Kaplan-Meier time-to-event analyses with hazard ratios (HRs). Endpoints included all-cause mortality, prolonged QT, cardiac arrest, liver injury, hospital admission, and emergency department (ED) visits. **Results:** Patient counts were 2,819 vs 11,871 before matching and 2,696 vs 2,696 after matching. In the matched cohorts, ribociclib was associated with significantly lower all-cause mortality compared with palbociclib (HR 0.65, 95% CI 0.552–0.758, $p < 0.0001$). No statistically significant differences were observed in major cardiovascular safety outcomes. Specifically, rates of cardiac arrest were comparable between groups (HR 0.76, 95% CI 0.384–1.505, $p = 0.43$), as were rates of long QT syndrome (HR 0.837, 95% CI 0.425–1.648, $p = 0.61$). With respect to hepatic and healthcare utilization outcomes, liver injury occurred numerically more often in the ribociclib group, but this difference did not reach statistical significance (HR 1.209, 95% CI 0.896–1.632, $p = 0.21$). Ribociclib was associated with numerically lower rates of hospitalization (HR 0.845, 95% CI 0.700–1.021, $p = 0.08$) and ED visits (HR 0.82, 95% CI 0.659–1.02, $p = 0.07$), though neither outcome met conventional thresholds for statistical significance. **Conclusions:** In this PSM analysis of HR+/HER2- metastatic breast cancer, ribociclib was associated with significantly lower all-cause mortality compared with palbociclib. Rates of hospitalization, ED visits, prolonged QT, and cardiac arrest were not significantly different. These real-world findings support clinically meaningful heterogeneity across CDK4/6 inhibitors and highlight the importance of individualized agent selection, balancing survival, hepatic toxicity, and healthcare utilization. Research Sponsor: None.

Impact of GLP-1 receptor agonists in hormone receptor–positive breast cancer patients receiving CDK4/6 inhibitors.

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Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly prescribed for type 2 diabetes and obesity due to their efficacy in weight reduction and glycemic control. Beyond their metabolic benefits, GLP-1 RAs delay gastric emptying, which may affect the absorption of oral medications like cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i). Additionally, CDK4/6i and GLP-1 RAs share overlapping gastrointestinal (GI) toxicities such as diarrhea and nausea, which could impact medication tolerability and clinical outcomes. This investigation aimed to characterize the safety of concomitant GLP-1 RA and CDK4/6i use in patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer. **Methods:** We performed a single-center, retrospective chart review evaluating adult patients prescribed a CDK4/6i for HR+ breast cancer at Winship Cancer Institute between October 2022 and May 2025. Patients receiving concomitant GLP-1 RA and CDK4/6i (Group 1) were matched 1:1 to patients receiving a CDK4/6i without GLP-1 RA (Group 2). Matching criteria included prescribed CDK4/6i, treatment indication (adjuvant or metastatic), age (≥ 65 years, 45–64 years, and < 45 years), and race. The primary outcome was safety, assessed by adverse drug reactions, dose reductions, and discontinuations. **Results:** 82 patients were reviewed, median age 54 years old. Half (41 patients, 50%) were prescribed abemaciclib, 21 (25.61%) palbociclib, and 20 (24.39%) ribociclib. 41 patients receiving concomitant GLP-1 RA and CDK4/6i (Group 1) were matched to 41 patients receiving a CDK4/6i without GLP-1 RA (Group 2). Of those in Group 1, 20 were prescribed a GLP-1 RA for diabetes and 18 for obesity. Median BMI was 32.76 kg/m² (range, 28.44–36.28 kg/m²) in Group 1 compared to 26.32 kg/m² (range, 23.74–28.05 kg/m²) in Group 2. Semaglutide and tirzepatide were the most prescribed GLP-1 RAs. 38 patients (51.35%) in Group 2 experienced an ADR associated with CDK4/6i compared to 36 patients (48.65%) in Group 1 (p-value, 0.457). Median time to first documented ADR was 14 days (range, 8–21 days) in Group 2 compared to 18 days (range, 11–36 days) in Group 1 (p-value, 0.086). 24 patients (55.81%) in Group 1 experienced a GI ADR compared to 19 patients (44.19%) in Group 2 (p-value, 0.269). **Conclusions:** Patients receiving CDK4/6i without GLP-1 RA experienced earlier onset and a numerically higher incidence of ADRs compared with those receiving concomitant GLP-1 RA and CDK4/6i therapy, though differences did not reach statistical significance. Ongoing analyses of treatment adherence and progression-free survival will be reported out at a later date. Larger, multi-center studies are warranted to further characterize safety and potential pharmacologic interactions between GLP-1 RAs and CDK4/6i. Research Sponsor: None.

Fovinaciclib versus placebo combined with fulvestrant for advanced breast cancer after endocrine therapy: A randomized, double-blind phase 3 trial.

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Background: Approximately 70% breast cancer (BC) patients have hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative disease. Fovinaciclib is a novel, potent, oral selective cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor. A multicenter, randomized, double-blind, placebo-controlled phase 3 trial was conducted to compare fovinaciclib versus placebo plus fulvestrant in patients with advanced BC that relapsed or progressed on previous endocrine therapy. **Methods:** Eligible patients were randomly assigned (1:1) to receive 200 mg fovinaciclib (fovinaciclib arm) or placebo (placebo arm) orally once daily on days 1–21 in 28-day cycles. All patients also received intramuscular fulvestrant 500 mg (cycle 1: days 1 and 15; subsequent cycles: day 1). Premenopausal or perimenopausal patients also received subcutaneous goserelin 3.6 mg (day 1). The primary endpoint was blinded independent central review (BICR)-assessed progression-free survival (PFS). Secondary endpoints included other efficacy endpoints and safety. Exploratory endpoints included patient-reported outcomes. **Results:** A total of 319 patients were randomized to the fovinaciclib ($n = 160$) or placebo arm ($n = 159$). Baseline characteristics were balanced. Interim analysis at 9-month median follow-up (data cutoff date May 11, 2023) showed significant PFS benefit from adding fovinaciclib ($p = 0.0001$). Sustained PFS benefit of greater extent (median 14.0 months versus 5.6 months, hazard ratio 0.48, 95% confidence interval 0.36–0.65) was observed at updated analysis at 23-month follow-up (data cutoff date August 30, 2024). Trends of the PFS benefit were observed in all subgroups. Consistent improvements were observed in investigator-assessed PFS and objective response rate, disease control rate, clinical benefit rate, duration of response, and time to progression according to BICR or investigator's assessments. At updated analysis, all patients in the fovinaciclib arm and 148 (93.7%) in the placebo arm reported at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs were hematological toxicities. TEAEs leading to study drug discontinuation were reported in 9 (5.6%) and 2 (1.3%) patients in the respective arms. No grade ≥ 3 venous thromboembolism or interstitial lung disease was reported. The two arms showed similar overall longitudinal profiles of global health status, function domains and symptom domains assessed with the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire. **Conclusions:** Adding fovinaciclib to fulvestrant conferred statistically significant and clinically meaningful PFS benefit and consistent improvements in other survival outcomes, along with manageable safety. These findings support fovinaciclib as a later-line option. Clinical trial information: NCT05438810. Research Sponsor: Avanc Pharmaceutical Co., Ltd.

Should CDK4/6 inhibitor plus endocrine therapy be standard of care for ER-low (1–10%) HR+/HER2– metastatic breast cancer? A multicenter registry cohort.

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Background: ER-low (1–10%) HR+/HER2– metastatic breast cancer (MBC) is increasingly recognized as a distinct clinical subgroup with limited endocrine sensitivity, yet ER-low-specific evidence to guide optimal first-line treatment is sparse. We assessed real-world effectiveness of CDK4/6 inhibitor (CDK4/6i) plus endocrine therapy (ET) in ER-low MBC and benchmarked outcomes against contemporaneous ER-high disease treated with the same approach. **Methods:** We performed a multicenter cohort study using a prospective institutional registry of women with HR+/HER2– MBC who initiated CDK4/6i (palbociclib/ribociclib/abemaciclib) plus an aromatase inhibitor or fulvestrant between January 2018 and October 2024, with follow-up through December 2024. ER expression by immunohistochemistry was categorized as low (1–10% or Allred 3–4), intermediate (10–66% or Allred 5–6), or high (>66% or Allred 7–8). Primary endpoints were progression-free survival (PFS) and overall survival (OS), analyzed by Kaplan–Meier/log-rank methods and multivariable Cox regression adjusting for age, ECOG performance status, progesterone receptor status, disease extent, CDK4/6i choice, and other clinicopathologic factors. **Results:** Among the 540 women with advanced HR+ HER2– breast cancer, 75% received CDK4/6i+ET in the first-line setting; ER-low tumors comprised 4.8% (n=26). ER-low disease had poor outcomes on CDK4/6i+ET with median PFS 2.9 months (95% CI 1.2–4.7) and median OS 12.6 months (95% CI 7.24–18.0), versus ER-high median PFS 23.3 months (95% CI 18.8–27.8) and median OS 49.7 months (95% CI 40.6–54.9) (log-rank $p<0.001$). ER-low status remained independently associated with inferior PFS (HR 10.6, 95% CI 5.02–22.4; $p<0.001$) and OS (HR 4.66, 95% CI 3.03–7.95; $p<0.001$) compared with ER-high after adjustment. Within the ER-low patients, the poor outcome was universally observed regardless of ET partner (AI vs fulvestrant), disease extent (visceral vs bone only), ECOG and HER2 status (low vs 0). **Conclusions:** ER-low HR+/HER2– MBC demonstrated very poor outcomes with CDK4/6i+ET, suggesting CDK4/6i plus AI/ET should not be assumed to be an effective default “standard HR+” approach for this subgroup. Given reported clinicopathologic and molecular similarities between ER-low/HER2– tumors and triple-negative breast cancer, ER-low-dedicated prospective trials and evaluation of TNBC-oriented strategies (including prioritization of chemotherapy-based regimens and TNBC clinical trial enrollment) are urgently needed. Research Sponsor: None.

Optimizing denosumab treatment strategies to balance skeletal-related events for prevention and osteonecrosis of the jaw risk in metastatic breast cancer patients: A Korean nationwide target trial emulation.

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Background: Administration of bone-modifying agents (BMAs) is essential for reducing the incidence of skeletal-related events (SREs) in breast cancer bone metastases patients. As denosumab showed superior effect for prevention of SREs compared to zoledronic acid, denosumab is commonly used BMA in this setting; however, the optimal administration interval and treatment duration of denosumab remain unclear. **Methods:** This study utilized the Health Insurance Review and Assessment Service (HIRA) database and emulated a target trial using the clone-censor-weight approach. Among the overall breast cancer population, 2,023 metastatic breast cancer patients who received regular denosumab administration were identified during Jan 2009 to Aug 2023. We examined the administration patterns and duration of denosumab therapy and evaluated their associations with the incidence of skeletal-related events (SREs) and osteonecrosis of the jaw (ONJ). **Results:** During follow-up, approximately 23% of patients continued regular denosumab administration at intervals of less than 8 weeks. Patients who received denosumab for ≥ 25 months exhibited a low risk of skeletal-related events (SREs) (3.42–6.15%, according to treatment compliance); however, the cumulative risk of osteonecrosis of the jaw (ONJ) increased to 19.47% (95% confidence interval [CI], 13.79–26.75) at 4 years of follow-up. Among patients treated with denosumab for 13–24 months, the risk of SREs was comparable to that observed in those treated for ≥ 25 months (5.15–6.77% vs. 6.15%), while the risk of ONJ remained relatively low (10.02–10.19%, depending on compliance). In contrast, patients who received denosumab for less than 12 months demonstrated a substantially higher risk of SREs, reaching 19.44% (95% CI, 6.47–45.69). Shorter administration intervals were associated with increased ONJ risk but did not significantly affect SRE prevention. **Conclusions:** This nationwide real-world study is the largest to date to evaluate the optimal duration and administration interval of denosumab in metastatic breast cancer patients with bone metastases. To effectively prevent SREs while minimizing the risk of ONJ, a denosumab treatment duration of 13–24 months appears to offer the most favorable benefit-risk balance and may be considered an optimal treatment strategy in clinical practice. Research Sponsor: None.

Real-world insights into bone marrow carcinomatosis in metastatic breast cancer: A retrospective analysis from two large university breast cancer centers.

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Background: Bone marrow carcinomatosis (BMC) is a rare but severe manifestation of metastatic breast cancer (mBC) characterized by diffuse bone marrow infiltration and hematologic dysfunction. Data on incidence, clinical presentation, and treatment outcomes remain limited. **Methods:** This bicentric retrospective real-world study included breast cancer patients diagnosed with BMC between 2010 and 2023 at two German university centers. BMC was diagnosed using bone marrow biopsy and/or leukoerythroblastic blood smear in the presence of cytopenia. Clinical characteristics, systemic treatments, and overall survival (OS) were analyzed descriptively. Survival was estimated using Kaplan–Meier method. **Results:** During the study period, 1,399 patients presented with mBC at one of two participating centers. Among these, 37 were diagnosed with BMC, corresponding to an incidence of 2.6% (0.5% of all breast cancer cases). Median age was 58 years (range 30 – 76). Most patients had hormone receptor (HR)–positive HER2–negative disease (89%). At BMC diagnosis, anemia occurred in 84%, thrombocytopenia in 76%, and pancytopenia in 57% of patients. Median OS after BMC diagnosis was 12.0 months (95% CI: 6.0, 38.0). Patients with bone-only metastases showed longer survival compared with those with additional visceral involvement (median OS not reached vs. 9 months). In HR–positive HER2–negative disease, patients receiving endocrine-based therapy including CDK4/6 inhibitors demonstrated numerically longer survival compared with chemotherapy-based approaches; however, subgroup sizes were small and analyses exploratory. **Conclusions:** BMC is an uncommon but clinically relevant manifestation of mBC associated with substantial morbidity and limited prognosis. This largest European real-world cohort highlights heterogeneous treatment approaches and outcomes. Endocrine-based strategies combined with targeted agents appear feasible in selected patients. Multicenter registries and prospective studies are needed to optimize diagnostic and therapeutic strategies in this patient group. Research Sponsor: None.

Real-world data of the analyzed cohort of patients with BMC.

No of patients	IHC subtype n (%)	Metastatic status at initial BC presentation n (%)	Metastatic site at BMC diagnosis n (%)	Diagnostic method n (%)	Median time to BMC in months (range)	Initial treatment for BMC n (%)
	a) HR pos/HER2neg b) HER2 pos c) TNBC	a) M0 b) M1	a) visceral b) brain c) bone +/- other d) bone only	a) BM biopsy / smear b) blood smear	a) after mBC diagnosis b) after initial BC diagnosis	a) combined CT b) mono CT c) ET+CDK4/6i d) ET only e) Anti HER2 f) BSC
37	a) 33 (89) b) 4 (11) c) 0 (0)	a) 16 (43) b) 21 (57)	a) 22 (60) b) 1 (3) c) 37 (100) d) 11 (30)	a) 26 (70) b) 11 (30)	a) 28 (0-107) b) 58 (0-249)	a) 3 (8) b) 20 (54) c) 6 (16) d) 1 (3) e) 1 (3) f) 1 (3) Other: 5 (14)

Final results of a phase II study of utidelone capsule, the first solid oral microtubule stabilizer, in metastatic breast cancer patients.

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Background: Attempts to develop oral microtubule inhibitors have not made significant progress in decades. Utidelone is a novel microtubule inhibitor insensitive to P-glycoprotein, enabling higher oral bioavailability and response against multidrug-resistant tumors. Utidelone injection (UTD1) has been approved for metastatic breast cancer (mBC) in China in 2021; utidelone capsule (UTD2) is the first solid oral formulation of microtubule stabilizer in clinical stage globally. Our previous phase I study of UTD2 showed promising activity with no DLTs being observed in late line metastatic solid tumors, and 75 mg/m²/d*5 was recommended as monotherapy dose (ASCO 2025). PopPK analysis indicated that AUC of UTD2 of 75 mg/m²/d reached 80%-125% of the AUC of UTD1. The absolute bioavailability of UTD2 vs. UTD1 was 35.1%. Here we report the final results of a phase II study of UTD2 in combination with capecitabine (CAP) in mBC. **Methods:** This is a single-arm, multi-center phase II trial. The key inclusion criteria included patients with metastatic breast cancer, refractory to anthracycline or taxane treatment, ≤ 4 lines of prior chemotherapy, ECOG score of 0-1 and an expected survival of ≥ 12 weeks. Eligible patients received UTD2 at 60mg/m²/d*5 in combination with CAP at 1000mg/m² bid*14 in a 21-day cycle. The primary endpoint was ORR; the secondary endpoints included PFS and safety. **Results:** By data cutoff on October 8, 2025, the recruitment had been completed. 50 mBC pts were enrolled with 72% of HR+/HER2-, 24% of TNBC, and 2% of HR+/HER2+. Twenty-one (21) pts (42%) had received ≥ 3 lines of treatment. 100% of the patients had received taxane or anthracycline and 86% had visceral metastases. Forty-four (44) pts were evaluated for efficacy with the best responses of 27 PR and 12 SD. The confirmed ORR was 52.3% (95%CI 36.7, 67.5) and DCR was 88.6% (95%CI 75.4, 96.2). Median PFS was 8.25 (95%CI 5.36, 10.58) months and median DoR was 7.62 months (95%CI 4.17, NE) (median treatment cycles was 9.0), demonstrating better efficacy than UTD1 +CAP (ORR 40.4%, CBR 53.9%, PFS 7.72 months, Lancet Oncol 2017) in mBC pts. The most prominent ≥ Grade 3 TEAEs was diarrhea (28%). However, the incidence of peripheral neuropathy (PN) was significantly decreased compared with UTD1+CAP (Grade 3 PN only 2% vs 25.1%) while maintaining the characteristic of low hematological toxicity (only 10% for both ≥ Grade 3 Neutropenia and Leukopenia). Treatment related discontinuations occurred in only 2 pts (4%). **Conclusions:** This study demonstrated excellent efficacy of UTD2+CAP in mBC pts. The safety profile with significantly decreased PN and low hematological toxicity highlighted another advantage of this regimen. Utidelone capsule is anticipated to dramatically improve medication convenience and enhance patient compliance. Clinical trial information: NCT05700084. Research Sponsor: Beijing Biostar Pharmaceuticals Co., Ltd.

ADAPT-T-DXd: Multi-institutional real-world study of dose-adapted trastuzumab deruxtecan in HER2-positive and HER2-low metastatic breast cancer.

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Background: Trastuzumab deruxtecan (T-DXd) has demonstrated substantial efficacy in HER2-positive and HER2-low metastatic breast cancer (MBC) at a standard dose of 5.4 mg/kg in the DESTINY trials. But high treatment cost remains a major barrier to access in low/middle-income countries. We evaluated the clinical activity and safety of dose-adapted T-DXd in a multi-institutional real-world Indian cohort, where dose modification was primarily driven by financial constraints. **Methods:** This retrospective analysis included 63 patients with HER2+ or HER2-low MBC treated with dose-adapted T-DXd across multiple Indian centers. Dose-adapted T-DXd refers to the administration of T-DXd at doses lower than the standard 5.4 mg/kg dose in DESTINY trials. Dose selection was based on affordability. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints were progression-free survival (PFS), duration of response (DoR), and safety. An evaluable cohort (n = 53) was defined as patients receiving ≥ 2 cycles of therapy. DoR measured from treatment initiation to radiologic progression or last drug exposure. **Results:** The median age was 57 years; 42.9% had hormone receptor-positive disease. HER2 subtypes included HER2 3+ (63.5%), HER2 2+/ISH+ (11.1%), and HER2-low (22.2%). Patients had received a median of three prior lines of therapy. The median administered dose of trastuzumab deruxtecan was 3.7 mg/kg, corresponding to 68% of the standard dose. At a median follow-up of 8.3 months, the objective response rate (ORR) was 58.7% (95% CI, 46–71%) in the full cohort and 66.0% (95% CI, 53–79%) in the evaluable cohort. The highest ORR was observed in HER2 3+ disease (76.5%). Median progression-free survival was 5.3 months (95% CI, 4.2–6.4) in the full cohort and 7.1 months (95% CI, 5.8–8.4) in the evaluable cohort. Median duration of response was 8.3 months, with 40–45% of responses ongoing at data cutoff. Grade ≥ 3 neutropenia occurred in 9.0% of patients, and interstitial lung disease occurred in 7.0%; no grade 5 pulmonary events were observed. Dose reductions due to toxicity were uncommon. **Conclusions:** Dose-adapted trastuzumab deruxtecan demonstrated clinically meaningful activity with a manageable safety profile in patients with HER2-positive and HER2-low metastatic breast cancer in a real-world setting. The shorter median PFS likely reflects reduced dose intensity, limited follow-up and real-world heterogeneity, rather than loss of intrinsic drug activity. These findings support further prospective evaluation of dose-adapted strategies to improve treatment accessibility in resource-limited settings. Research Sponsor: None.

Quality of life and treatment tolerability of Bria-IMT + CPI in metastatic breast cancer.

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Background: Bria-IMT is an allogeneic whole cell immunotherapy expressing tumor associated antigens and GM-CSF to stimulate adaptive and innate immunity. The phase 3 Bria-ABC trial (NCT06072612) evaluates Bria-IMT + retifanlimab vs physician's choice in MBC w/ no meaningful therapeutic options. Characterization of on-trial pt experience, including quality of life (QoL) and tolerability, remains clinically relevant yet underreported. We evaluated QoL and toxicity to assess feasibility of home self administration. **Methods:** EORTC QLQ-C30 at baseline (BL) and subsequent visits. Raw item responses were aggregated into domain scores. Changes quantified as absolute point differences; domain scores defined as medians of constituent items. Lower functional/symptom and higher global scores indicate better outcomes. Wilcoxon matched pairs test assessed change from BL. Missing QoL data handled by observed cases approach. QoL evaluated at BL, V3, V6, and V9. TWiST and TOX summarized descriptively. TOX defined as cumulative time w/ grade ≥ 3 TEAEs w/o progression; TWiST as time w/o grade ≥ 3 toxicity or progression. TOX and TWiST constitute component health states for planned QTWiST analysis pending mature OS. **Results:** At submission, 251 pts screened, 173 randomized, 147 treated. 75% Caucasian, 20% other, 5% not reported; median 6 prior lines (2-15); ECOG 2-6%; intracranial mets 9%; 42% HR+, 37% TNBC, 12% HER2+. Median 5 QoL assessments/pt completed. 127 pts completed ≥ 2 assessments. Paired data available at V3 52%, V6 17%, V9 6%. Global health medians BL 5.0, V3 5.0, V6 5.0, V9 4.5. Score maintenance/improvement: @V3 63% (p=0.7), V6 62%, V9 71%. Functional domains: role (BL 1.5, V3 2.0, V6 2.0, V9 2.0; maintenance 62.7% [p=0.02], 52.4%, 71.4%). Physical (BL 1.0, V3 2.0, V6 2.0, V9 2.0; maintenance 68.7% (p=0.002), 47.6% (p=0.03), 71.4%), cognitive (BL 1.5, V3 1.5, V6 1.5, V9 1.5; maintenance 63.6%, 61.9%, 85.7%). Emotional (BL 1.5, V3 1.5, V6 1.5, V9 1.5; maintenance 75.8% (p=0.9), 81.0%, 85.7%). Social (BL 1.5, V3 1.5, V6 2.0, V9 2.5; maintenance 58.5%, 75.0%, 57.1%). Symptoms: nausea/vomiting (1.0 throughout; maintenance V3 73%, V6 86%, V9 86%), fatigue median 2.0 all timepoints; maintenance 61%, 67%, 71%), pain (BL/V3 1.5, V6/V9 2.0; maintenance V3 57% [p=0.03], V6 62% [p=0.9], V9 86%). TWiST and TOX restricted mean 3.12 mo and 0.63 mo, respectively; 83.2% and 16.8% of observed follow-up. Pts w global health maintenance demonstrated longer median TWiST v deterioration (4.3 v 2.7 mo). ECOG stable in 78% (n=99). **Conclusions:** Heavily pretreated MBC pts in Bria-ABC demonstrated stable global health and key functional domains. Findings support sustained QoL in advanced disease. TWiST demonstrates meaningful benefit w/o significant toxicity. Ongoing follow up will further characterize durability of pt-reported outcomes and clinical correlation. Results support decentralized care and potential home self administration. Clinical trial information: NCT06072612. Research Sponsor: None.

Survival with Bria-IMT + CPI in advanced metastatic breast cancer at 12 and 24 months.

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Background: Metastatic breast cancer (MBC) remains limited by resistance and cumulative toxicity in heavily pretreated patients. Bria-IMT combines a whole-cell vaccine (SV-BR-1-GM) with anti-PD-1 (CPI) to enhance tumor antigen presentation and overcome immune exhaustion. SV-BR-1-GM is an irradiated breast cancer cell line engineered to secrete GM-CSF, promoting HLA class I and II antigen presentation and T-cell activation. We identified a subset with durable clinical benefit and biologic correlates. **Methods:** Phase I/II evaluating the Bria-IMT regimen (SV-BR-1-GM with CPI (pembrolizumab or retifanlimab). In the phase II portion, pts were randomized 1:1 to CPI initiation at cycle 1 (C1) or delayed start at cycle 2 (C2). Two SV-BR-1-GM formulations were administered: IFN γ -stimulated (IF γ) or unstimulated ($\neq$ IF γ). Baseline circulating tumor cells (CTCs) and delayed-type hypersensitivity (DTH) responses to SV-BR-1-GM were assessed as biomarkers. Progression free survival (PFS) and overall survival (OS) were analyzed using Kaplan Meier (KM). Subgroup comparisons (CPI sequencing, IP formulation, DTH status, and baseline CTC status) are exploratory. **Results:** 32 phase 2 pts were randomized: median age 61 (range 41-80); median prior lines 6 (range 2-13); PFS 3.5 mo (95% CI 3.0 - 4.2); OS 9.5 mo (95% CI 7.0 - 17.4). Among CPI C1 vs C2 starts: median OS 13.3 v 7.4mo (HR 0.8; 95% CI 0.4-1.9, p = 0.6); OS KM probability at 12 mo 47% v 58%. Median OS w $\neq$ IF γ v IFN γ IP =16.6 v 9.1 mo (HR 0.58; 95% CI 0.2-1.4, p = 0.23); OS KM at 12 mo 52.4% v 27.3%. DTH+ v DTH- median OS 11.9 v 4.7 mo (HR 0.0009; p = <0.001), OS KM @12 mo 48% v 0%. CTCs <5 v > 5 at baseline had median OS 16.6 v 5.5 mo (HR 0.005; 95% CI 0.0003-0.09, p < 0.001), OS at 12 mo 49% vs 33%. Among long term survivors @12mo, OS probability 44.0% (95% CI 26.2-59.7%) and @24 mo 26% (95% CI 12.1-42.4%). Median follow up 25.8 with PFS 5.4 mo. 5 received $\neq$ IF γ formulation v 1 w IFN γ . All 6 (3 with CPI @C1, 3@C2) experienced delayed type hypersensitivity reaction to inoculation. 67% of long responders matched HLA at >1 allele, 33% no match. Grade $\geq$ 3 AEs in 47% of pts, most common injection site rxn, nausea, fatigue; no tx related D/C; no unexpected safety signals. **Conclusions:** In heavily pretreated MBC, Bria-IMT demonstrated a tolerable safety profile and the emergence of a long-term survivor cohort. Durable survival was observed beyond 12 and 24 months. Differential survival favoring Ph3 formulation, DTH positivity, lower baseline CTC burden, and early CPI sequencing was observed. These findings support prospective validation of DTH and CTC as predictive biomarkers and the continued use of the Ph3 IP formulation in the ongoing phase 3 study Bria-ABC (NCT06072612). Clinical trial information: NCT06072612. Research Sponsor: None.

Health-related quality of life.

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Background: Trials typically pool patient-reported outcomes across demographics, assuming baseline differences reflect normal variation. When adequate enrollment permits disaggregation, nuanced patterns emerge across quality-of-life domains. **Methods:** Individual participant data meta-analysis of 15 breast cancer trials (N=12,656). HRQoL domains (Physical, Emotional, Social, Role, Cognitive) and breast symptoms assessed via EORTC QLQ-C30/FACT-B at baseline, treatment, and post-treatment. Comparisons: Hispanic vs Not-Hispanic; White vs Asian vs Black vs Other. Dual approach: 1) direct between-group comparisons, 2) pooled within-group trajectories revealing between-group mean differences and absolute changes. **Results:** Population: 2.3% Black, 9.6% Hispanic, 19.9% Asian. Baseline disparities were substantial and domain-specific. Hispanic demonstrated higher cognitive functioning (MD 2.72, $p<0.05$). Black had superior role functioning versus White (84.11 vs 67.19, MD -7.80, $p<0.001$); all minority groups scored lower on emotional functioning (Black MD -4.76, Asian MD -3.34, Other MD -1.88, all $p<0.001$). During treatment, Hispanic maintained physical (MD 1.99, $p<0.05$) and role functioning (MD 3.67, $p<0.05$); Asian showed less role decline (MD 2.61, $p<0.01$). All groups experienced similar symptom improvement and cognitive decline. Post-treatment divergence: Black patients' breast symptoms worsened (change +1.27) while Asian showed highest improvement (change -2.09, $p<0.05$). Hispanic cognitive advantage eroded (MD -1.77, $p<0.05$), and treatment resilience disappeared. Uniform 60% attrition across all groups. **Conclusions:** Equal treatment response does not equal equity when groups enter with disparate baselines and experience differential post-treatment trajectories. Post-treatment divergence was striking: Black patients' symptoms worsened while Asian improved most—invisible in binary White vs Not-White comparisons. Hispanic treatment resilience disappeared in survivorship and cognitive advantages eroded. Uniform 60% attrition demonstrates recruitment, not retention, is the barrier requiring redirection of diversity initiatives. Even pooling 15 trials, Black and Hispanic representation remained inadequate. Equal treatment perpetuates existing disparities from unequal starting points or creates new disparities through differential recovery. Trial equity requires adequate diverse enrollment and interventions addressing pre-enrollment disparities and post-treatment survivorship needs. Research Sponsor: None.

Potential BMI-dependent overall survival differences in postmenopausal breast cancer patients treated with CDK4/6 inhibitors: A Mayo Clinic platform study.

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Background: CDK4/6 inhibitors with endocrine therapy are widely used for HR+/HER2–metastatic breast cancer (BC). While studies have shown similar progression-free outcomes across agents, overall survival (OS) data are limited. Since OS is a definitive endpoint and BMI may influence outcomes, this study examines BMI-dependent OS differences among CDK4/6 inhibitors. **Methods:** A retrospective cohort study was conducted using the Mayo Clinic Platform full AMC1 dataset. Postmenopausal women with BC receiving palbociclib/ribociclib/abemaciclib plus aromatase inhibitor (AI) were included. Patients with prior use of fulvestrant, anthracyclines, radiation therapy, GnRH agonists, or history of MACE, heart failure, myocardial infarction, or stroke before BC diagnosis were excluded. Patients were stratified by BMI and CDK4/6 inhibitor. The primary outcome was 5-year OS. **Results:** Among 1,989 patients (palbociclib: 868; ribociclib: 465; abemaciclib: 656), palbociclib was associated with significantly worse OS compared to ribociclib in BMI <25 (HR 2.91; 95% CI: 1.76–4.79; P < 0.01) and BMI ≥30 (HR 1.91; 95% CI: 1.21–3.01; P < 0.01). Compared to abemaciclib, palbociclib showed worse OS: BMI <25 (HR 1.73; P < 0.01), BMI 25–30 (HR 1.56; P < 0.01), and BMI ≥30 (HR 1.82; P < 0.01). No significant OS differences were observed between ribociclib and abemaciclib. Palbociclib patients were older, particularly in BMI <25 (Cohen’s D = 0.39 vs. ribociclib; 0.27 vs. abemaciclib) and BMI ≥30 (0.28 vs. ribociclib; 0.23 vs. abemaciclib). In the BMI 25–30 group, palbociclib group was also older than ribociclib group (Cohen’s D = 0.26). **Conclusions:** In postmenopausal BC patients on AIs and CDK4/6 inhibitors, palbociclib was associated with worse OS in BMI < 25 and BMI ≥ 30 groups, while ribociclib and abemaciclib showed similar outcomes across BMI groups. Palbociclib patients were older than those on other drugs, which may partially confound results; however, in the BMI 25–30 group, despite similar age differences, no survival difference was observed between palbociclib and ribociclib, suggesting age alone may have limited impact. These findings indicate a potential interaction between BMI and drug choice, and highlight the need for prospective studies to confirm and adjust for these variables. Limitations include the observational design and inability to perform multivariable regression analyses to adjust for confounders. Research Sponsor: None.

Overall survival comparisons by CDK4/6 inhibitor and BMI subgroup.			
Comparison	BMI Group	Hazard Ratio (95% CI)	P-value
Palbociclib vs Ribociclib	<25	2.91 (1.76 – 4.79)	< 0.01
	25 – 30	1.34 (0.87 – 2.071)	0.17
	≥30	1.91 (1.21 – 3.01)	< 0.01
Palbociclib vs Abemaciclib	<25	1.73 (1.29 – 2.32)	< 0.01
	25 – 30	1.56 (1.09 – 2.23)	< 0.01
	≥30	1.82 (1.15 – 2.88)	< 0.01
Ribociclib vs Abemaciclib	<25	1.27 (0.81 – 1.99)	0.29
	25 – 30	0.87 (0.54 – 1.43)	0.59
	≥30	1.05 (0.63 – 1.75)	0.85

Baseline circulating tumor cells and association with early resistance in patients with metastatic breast cancer undergoing palbociclib therapy.

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Background: Palbociclib has significantly improved outcomes in metastatic breast cancer (MBC); however, a substantial proportion of patients experience early treatment resistance. Reliable biomarkers to identify high-risk patients prior to therapy initiation remain limited. Our previous work has demonstrated that circulating tumor cell (CTC) and ctDNA monitoring is associated with poor prognosis in MBC (ASCO 2025 #1042; AACR 2025 #3613). Here, we report new findings of the association between baseline CTC level and timing of resistance in patients receiving palbociclib. **Methods:** This study included 178 patients with ER+/HER2- MBC treated with palbociclib at the Robert H. Lurie Cancer Center between 2016 and 2025 (IRB: NU16B06), all of whom developed treatment resistance. Time to resistance was defined as the interval from treatment initiation to first documented resistance; the median follow-up period was 8.0 months. Patients were stratified a priori into early resistance (≤ 6 months; $n = 71$) and later resistance (> 6 months; $n = 107$). Baseline CTCs were enumerated prior to treatment using FDA-approved CELLTRACKS system (Menarini). Associations between baseline CTC levels and time to resistance were assessed using Spearman rank correlation, treating CTC as a continuous variable and analyzing early and later resistance groups separately. **Results:** Among patients with early resistance, the median time to resistance was 3.25 months (range, 0.16–6.0), compared with 16.0 months (range, 6.5–57) among those with later resistance. Patients with early resistance exhibited higher baseline CTC levels on average than those with later resistance (mean CTC: 36.7 vs 25.8), although CTC distributions were highly right-skewed with substantial overlap between groups. Within the early resistance group, 29 of 71 patients had baseline CTC ≥ 5 , with markedly higher mean CTC levels compared with patients with CTC < 5 (88.6 vs 0.8). In contrast, baseline CTC ≥ 5 was not associated with timing of resistance among patients with later resistance. Using Spearman rank correlation, higher baseline CTC levels were significantly associated with earlier resistance among patients with early resistance ($\rho = -0.24$, $P = 0.043$), whereas no association was observed in patients with resistance occurring beyond 6 months ($\rho = 0.04$, $P = 0.71$). **Conclusions:** Baseline CTC levels were associated with the timing of treatment resistance in patients with metastatic breast cancer receiving palbociclib, with a significant inverse correlation observed exclusively among patients experiencing early resistance within 6 months. These new findings suggest that elevated baseline CTC burden reflects aggressive disease biology underlying rapid treatment failure. Time-dependent assessment of CTC may provide clinically relevant insights into early resistance risk and inform clinical decision-making. Research Sponsor: None.

Prognostic impact of digitally quantified tumor-infiltrating lymphocytes in HR+/HER2- metastatic breast cancer treated with CDK4/6 inhibitors.

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Background: Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors plus endocrine therapy are the first-line treatment for hormone receptor (HR)-positive/HER2-negative metastatic breast cancer(MBC). Prognostic biomarkers are needed to guide treatment decisions. Although Tumor-infiltrating lymphocytes (TILs) have been studied in breast cancer, their prognostic value in HR+/HER2- MBC remains unclear. Therefore, we aimed to assess the prognostic value of TILs in this patient population. **Methods:** We retrospectively analyzed patients with HR+/HER2- MBC receiving CDK4/6 inhibitors (palbociclib, ribociclib, or abemaciclib) plus endocrine therapy at Gangnam Severance Hospital, Seoul, Republic of Korea, from 2017 to 2025. We included 180 of 326 treated patients who met prespecified criteria. TILs were assessed according to the International Immuno-Oncology Biomarker Working Group guidelines using the digital pathology software QuPath (v0.6.0). Stromal TILs were quantified in two representative regions of interest (ROIs; each approximately 1,000 μm wide) using the formula $\text{TIL (\%)} = [\text{immune cell area} / (\text{annotation area} - \text{tumor cell area})] \times 100$, and the values were averaged across ROIs. Patients were classified into high- and low-TIL groups using the median TIL as the cutoff. Progression-free survival (PFS) and overall survival (OS) were compared using Kaplan-Meier analyses and log-rank tests. Hazard ratios (HRs) were estimated using Cox proportional hazards models. **Results:** Among 180 patients, the median age was 53.9 years (range, 28.0–87.5) and the median follow-up was 32.4 months (range, 4.6–104.4). Median PFS was 23.2 months (98 progression events) and median OS was 32.4 months (28 death events). Using a median TIL cutoff of 7.31%, 90 patients were classified into each group. The high-TIL group showed numerically longer PFS than the low-TIL group (median 35.2 vs. 28.1 months, 95% confidence interval [CI] 25.6–not reached[NR] vs. 22.7–42.0; log-rank $p=0.15$; HR 0.75, 95% CI 0.50–1.12; Cox $p=0.154$). For OS, the high-TIL group had significantly longer survival (median NR in both groups; log-rank $p=0.028$; HR 0.41, 95% CI 0.18–0.93; Cox $p=0.033$). In the primary breast tumor subset ($n=111$), similar trends were observed for PFS (median 42.2 vs 27.6 months; 95% CI 24.8–NR vs 19.3–61.4; log-rank $p=0.072$; HR 0.62, 95% CI 0.36–1.05; Cox $p=0.075$) and OS (median NR in both groups; log-rank $p=0.073$; HR 0.41, 95% CI 0.15–1.13; Cox $p=0.083$). **Conclusions:** Higher TIL levels may be associated with more favorable outcomes in patients with HR+/HER2- MBC treated with CDK4/6 inhibitor-based therapy. In contrast, patients with low TILs, who may derive less benefit, could be considered for alternative targeted therapies or chemotherapy. These findings suggest TILs may have prognostic value in this setting and warrant confirmation in further prospective, multicenter studies. Research Sponsor: None.

Analysis of information received and perceived by patients with metastatic breast cancer: Results of the Croyances et Réalités 3 French survey.

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Background: Despite therapeutic advances, metastatic breast cancer (mBC) and its treatments substantially impact quality of life. This impact, as well as prognosis and treatment strategies, varies by histological subtype. The Croyances et Réalités 3 (R3) survey, building on the 2015 and 2020 editions (R1 and R2), provides a longitudinal perspective on how French mBC patients perceive information and the support they receive. **Methods:** R3 was a multicenter, cross-sectional mirror survey involving patients with recurrent or *de novo* mBC (HR+/HER2-, HER2+, Triple-negative (TN)), and oncologists who completed paired questionnaires. Subgroup analyses were prespecified by histological subtype. **Results:** The survey was completed by 331 patients with mBC and 56 oncologists, enabling robust patient–physician comparisons with 80% mirroring. Mean patient age was 64 and 37% lived alone. Only 10% were still in the workforce while 58% were retired. The mean medical consultation duration was 40 minutes and in 26% of cases, was followed by a consultation with a nurse. Patients showed good understanding of their histological subtype, with 62% able to report it correctly (vs 37% in R2). Communication metrics also improved: 86% of patients felt their physician took time to explain, 79% felt listened to, and 69% reported good comprehension, closely matching physicians' perceptions (>80%). For 28% of patients, the treatment decision was shared, while 35% would like to be more involved. Supportive care and disease information brochures were the most common resources handed out (60% and 47% respectively). Uptake of supportive care increased to 65% overall (53% in R2). Psychologist (48% vs 36% in R2), dietitian (44% vs 26%), oncology aesthetician (35% vs 26%), and adapted physical activity (28% vs 18%) use increased. Among patients who did not seek supportive care, 37% stated that it was not offered to them, while 38% stated that they did not wish to receive it. Regarding impact of the disease on daily life, patients with HER2+ and TN mBC reported greater physical burden, including general fatigue and pain with significant impact (HER2+: 52%, TN: 50% vs HR+/HER2-: 33%), and reported greater use of supportive care (HER2+: 67%+, TN: 72% vs HR+/HER2-: 49%). The use of patient associations remained limited, at 11%. **Conclusions:** This current study R3 documents meaningful progress—patients' knowledge of their disease has improved, and oncologists have enhanced communication and supportive care delivery. However, despite recent improvements, supportive care remains underutilized, while the burden of the disease and its treatments remain substantial, underscoring the need to formalize care pathways that systematically integrate supportive care. Further progress is needed to improve shared decision-making, a recognized patient priority. Research Sponsor: PFIZER SAS.

Data-driven precision prognostic stratification in breast cancer leptomeningeal metastasis: The BC-LGPA model and treatment refinement.

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Background: Breast cancer leptomeningeal metastasis (BCLM) lacks data-driven prognostic models integrating diagnostic certainty with molecular features, resulting in empirical treatment limitations. **Methods:** We analyzed 403 BCLM patients (Nov 2013–Nov 2025) from four centers, constructing the Breast Cancer Leptomeningeal Graded Prognostic Assessment (BC-LGPA) based on diagnostic criteria (CSF cytology, symptoms, MRI patterns) and molecular subtype, validated externally. **Results:** The median overall survival (OS) was 7.5 months. As the first data-driven prognostic classification for BCLM, the BC-LGPA integrates diagnostic certainty scores (0–2) and molecular scores (0–1). ECOG performance status and extracranial metastases were excluded owing to collinearity with neurological symptoms and because leptomeningeal metastasis itself constitutes the primary survival-limiting factor. The model stratifies patients into high-risk (0 points, 4.7 months), intermediate-risk (1–2 points, 8.0 months), and low-risk (3 points, 16.6 months) groups (training $p=0.001$; validation: 4.1 vs. 7.9 vs. 16.0 months, $p=0.003$). Key innovations include: (1) Granular diagnostic stratification into Class A (cytology-proven), B (clinical-radiological), and C (incidental-radiological), with subclasses A1/A2/A3, B1/B2, and C1/C2/C-special; (2) Ultra-indolent entity identification: Class C-special (localized calvarial-meningeal disease without diffuse LM) shows exceptional median OS of 68.0 months, representing a distinct clinical entity unsuitable for conventional prognostic models; (3) Treatment refinement: Intrathecal therapy improved survival in Class A and Class B-Linear subgroups, whereas focal radiotherapy demonstrated no independent benefit, including in Class C2 (31 patients, $p=0.794$), challenging empirical RT practices. **Conclusions:** BC-LGPA establishes the first data-driven BCLM prognostic framework, correcting treatment recommendations through subgroup efficacy analyses to guide precision management and clinical trial design. Research Sponsor: None.

The scoring criteria of the BC-LGPA.					
Prognostic Factor		Score	Criteria Definition		
Diagnostic Certainty			CSF cytology	Neurological symptoms	MRI
	Class A (Cytology-proven)	0	+	+ / -	+ / -
	Class B (Clinico-radiological)	1	- / NA	+	+
	Class C* (Incidental radiological)	2	- / NA	-	+
Molecular Subtype	TNBC	0	ER -	PR -	HER2 -
	non-TNBC	1		ER/PR + and/or HER2 +	
Total score = Diagnostic Certainty score + Molecular Subtype score					
NA: Not Available; * Localized calvarial-meningeal disease were excluded.					

Clinicopathologic features, treatment patterns, and outcomes in young women with metastatic breast cancer: A National Cancer Database analysis.

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Background: Young women with metastatic breast cancer (MBC) represent a distinct and understudied population and often present with aggressive disease features. However, population-level studies characterizing clinicopathologic features, treatment patterns, and outcomes in this group remain limited. **Methods:** The National Cancer Database (NCDB) was queried to identify women diagnosed with MBC. Patients were stratified by age (<40 vs ≥ 40 years). Baseline characteristics were compared using chi-square tests. Overall survival (OS) was assessed using Kaplan–Meier analysis and compared using log-rank tests. Multivariable Cox regression was performed to evaluate independent associations with OS. **Results:** Among 59,213 women with MBC, 4,406 (7.4%) were aged <40 years. Median follow-up was 25.3 months (IQR 9.3–42.1). Compared with women ≥ 40 , young women had more grade III tumors (61.0% vs 50.4%), lymphovascular invasion (44.2% vs 31.7%), and liver metastases (35.3% vs 23.5%). Young women were also more likely to receive chemotherapy (44.6% vs 21.7%), immunotherapy (44.2% vs 27.2%), radiation (39.3% vs 29.8%), and surgery of the primary tumor (26.7% vs 13.3%), whereas receipt of hormonal therapy was lower compared to their older counterparts (56.9% vs 54.8%). Receptor subtypes in young women were distributed as follows: HR+/HER2+ (22.6%), HR+/HER2- (50.8%), HR-/HER2+ (11.0%) and TNBC (15.5%). Young women demonstrated longer median OS compared with those ≥ 40 (68.7 months [95% CI 65.2–74.6] vs 37.1 months [95% CI 36.4–37.7]). TNBC had the worst OS among receptor subtypes ($p < 0.0001$), with more than three-fold mortality risk compared with HR+/HER2- (HR 3.65, 95% CI 3.22–4.15). Metaplastic histology was associated with inferior OS compared to IDC (HR 3.11, 95% CI 1.72–5.64), and Black race was associated with worse OS compared to White race (HR 1.65, 95% CI 1.47–1.87). Receipt of radiation (HR 0.75, 95% CI 0.67–0.84), immunotherapy (HR 0.59, 95% CI 0.53–0.66), hormonal therapy (HR 0.42, 95% CI 0.38–0.47), and surgery to the primary site (HR 0.42, 95% CI 0.37–0.49) were associated with improved OS, whereas chemotherapy was not associated with OS. Most patients had a single metastatic site (55.5%), among which bone was the most common site (59.8%), followed by liver (18.4%), lung (7.7%), and brain (1.6%). Compared to bone-only metastases, brain (HR 2.04, 95% CI 1.17–3.56), lung (HR 2.08, 95% CI 1.58–2.74), and distant lymph node involvement (HR 1.54, 95% CI 1.18–2.00) were associated with worse OS. **Conclusions:** In this largest population-level study to date, young women with MBC presented with more aggressive disease features, yet demonstrated better OS compared with older patients. Survival outcomes were associated with receptor subtype, histology, and metastatic site. These findings provide valuable insights to guide clinical management of young women with MBC. Research Sponsor: None.

Temporal changes in mortality among adults with breast cancer and diabetes mellitus in the United States.

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Background: Breast cancer and diabetes mellitus represent major and intersecting public health challenges in the United States. Although breast cancer mortality has declined over recent decades, the growing prevalence of metabolic comorbidities, particularly diabetes, may offset these gains. National patterns of mortality among individuals with both conditions remain incompletely defined. We evaluated long-term trends and demographic disparities in breast cancer– and diabetes–associated mortality from 1999 to 2023. **Methods:** We conducted a retrospective population-based analysis using the CDC Wide-Ranging Online Data for Epidemiologic Research (WONDER) Multiple Cause of Death database (1999–2023). Decedents aged 45–85+ years with breast cancer (ICD-10: C50) and diabetes mellitus (ICD-10: E10–E14) listed as underlying or contributing causes of death were included. Age-adjusted mortality rates (AAMRs) were calculated using the 2000 U.S. standard population. Trends were evaluated using Joinpoint regression to estimate annual percent change (APC) with 95% confidence intervals (CI). Analyses were stratified by age, sex, race/ethnicity, census region, and urbanization. **Results:** Between 1999 and 2023, 78,253 deaths occurred among adults aged 45–85+ years with breast cancer and diabetes mellitus (1.6% male, 98.4% female). Overall AAMRs increased modestly from 2.64 to 2.84. Females consistently exhibited higher mortality than males (5.00 vs 0.13 in 2023). Non-Hispanic Black individuals had the highest AAMRs (5.61), whereas non-Hispanic American Indian/Alaska Native, Asian, and Native Hawaiian/Pacific Islander populations had the lowest (2.05). Mortality counts were greatest in the Southern region and lowest in the Northeast. Nationally, AAMRs declined from 2004 to 2018 (APC –1.82%; 95% CI, –2.12 to –1.51; $P < 0.001$), followed by a sharp increase from 2018 to 2021 (APC 12.30%; 95% CI, 6.64 to 18.25; $P < 0.001$), with subsequent stabilization. In contrast, males demonstrated a steady increase throughout the study period. **Conclusions:** Breast cancer– and diabetes–associated mortality declined for more than a decade but reversed sharply after 2018, highlighting the vulnerability of patients with metabolic comorbidity. Persistently higher mortality among women and non-Hispanic Black individuals and the disproportionate burden in the Southern United States underscore important disparities. These findings emphasize the need for integrated oncologic and metabolic risk management strategies and renewed attention to chronic disease control in breast cancer survivorship. Research Sponsor: None.

Real-world analysis of the association between new-onset depression and outcomes in metastatic breast cancer.

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Background: Depression is prevalent in patients with advanced cancers and it may influence the disease course and treatment. While depression is associated with worse survival in solid tumors, real-world data quantifying its impact on mortality and healthcare utilization patterns in metastatic breast cancer (MBC) are limited. We utilized a global de-identified database to evaluate the association of new-onset depression with overall survival (OS) and care utilization.

Methods: We conducted a retrospective cohort study using the TriNetX global network. We identified adult women with MBC and survival greater than 6 months from diagnosis. Two cohorts were defined: (1) patients with first instance of depression 1-month to 3-years after MBC diagnosis, and (2) patients without depression before or during this period. Propensity score matching was performed (1:1) to balance baseline demographics, comorbidities, tumor receptor status, and previous cancer therapies. Outcomes included OS, palliative care utilization, ED visits, and Inpatient Hospitalizations over follow-up of 5 years. **Results:** We matched 2,753 patients per cohort with well-balanced baseline characteristics (mean age 60.1 ± 13.2 years). Depression was associated with shorter median OS (1,703 days vs not reached; HR 1.28, 95% CI 1.17–1.40, $p < 0.001$) and 6.7% absolute increase in mortality risk (38.1% vs 31.4%). Patients with depression demonstrated significantly higher care utilization: with increased hospitalization (HR 1.52, CI 1.39–1.67), increased ED Visits (HR 1.41, 95% CI 1.30–1.52), and increased use of palliative care visits (HR 1.65, 95% CI 1.49–1.83). Subgroup analysis showed that those treated with common anti-depressants had lower median OS and higher care utilization, with a larger effect size and more statistical significance for SSRIs than SNRIs. **Conclusions:** In this large real-world cohort, new-onset depression in women with MBC was associated with significantly worse survival and increased emergency department, inpatient, and palliative care utilization. This finding may suggest a higher symptom burden or earlier recognition of complex needs. Exposure to common antidepressants was associated with lower OS and higher healthcare utilization, which may suggest residual confounding in the form of depression severity or MBC disease burden. Prospective studies are needed to further understand this relationship. These findings underscore the critical need for integrated psychosocial oncology screening. Research Sponsor: None.

Breast cancer incidence and mortality in LGBTQ+ populations compared with cisgender heterosexual individuals: A comparative epidemiologic synthesis.

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Background: Breast cancer incidence and mortality by sexual orientation and gender identity remain poorly characterized. We aimed to systematically review comparative studies in LGBTQ+ populations versus cisgender heterosexual comparators. **Methods:** We conducted a PRISMA 2020–guided systematic review evaluated breast cancer incidence and mortality in LGBTQ+ populations versus cisgender heterosexual comparators. PubMed, Embase, and Scopus were searched from inception to January 2026. Population-based cohort, registry, and health system studies reporting comparative incidence or mortality were eligible. Two reviewers independently screened records. Of 189 records, 105 were excluded at title/abstract, 84 underwent full-text review, and 8 studies were included. Due to heterogeneity in SOGI ascertainment, comparators, and effect measures, results were synthesized qualitatively. **Results:** Among transgender populations, breast cancer incidence varied by reference group. In a nationwide cohort, trans women had higher incidence vs cis men (SIR 46.7) but lower vs cis women (SIR 0.3), while trans men showed the inverse pattern (vs cis women SIR 0.2; vs cis men SIR 58.9). In a U.S. health system cohort, incidence was similar for FTM vs cis women (0.4% vs 0.5%) but higher for MTF vs cis men (0.2% vs 0.004%). Among sexual minority women, incidence did not differ from heterosexual women in UK Biobank (HR 0.63–0.93) or Nurses’ Health Study (aIRR 1.19; 95% CI, 0.92–1.53). Mortality data were sparse; one national linkage found higher breast cancer–specific mortality in same-sex partnered women (HR 3.24; 95% CI, 1.01–10.37). **Conclusions:** Breast cancer incidence in transgender populations is comparator-dependent: trans women have higher incidence vs cis men but lower vs cis women, with the inverse pattern in trans men; incidence among sexual minority women is similar to heterosexual women. Research Sponsor: None.

Comparative studies.					
Study (Year)	Data Source / Country	SGM Population	Comparator	Outcome	Key Estimate (95% CI)
Yang 2025	UF Health IDR, USA	FTM	Cisgender women	Incidence	RR ≈ 0.72 (0.4% vs 0.5%)
de Blok 2019	Nationwide registry, Netherlands	Trans women	Cisgender women	Incidence	SIR 0.30 (0.20–0.40)
de Blok 2019	Nationwide registry, Netherlands	Trans men	Cisgender women	Incidence	SIR 0.20 (0.10–0.50)
Brown 2014	VHA cohort, USA	Transgender veterans	Expected population	Incidence	SIR ~1 vs cis women; >1 vs cis men
Underwood 2023	UK Biobank	WSWM	WSEM	Incidence	HR 0.93 (0.79–1.10)
Underwood 2023	UK Biobank	WSEW	WSEM	Incidence	HR 0.63 (0.37–1.07)
Huang 2024	Nurses’ Health Study, USA	Lesbian women	Heterosexual women	Incidence	aIRR 1.19 (0.92–1.53)
Cochran 2012	NHIS mortality linkage, USA	Same-sex partnered women	Different-sex partnered	Mortality	HR 3.24 (1.01–10.37)
Chan 2025	NCDB, USA	TGD breast cancer cases	Cisgender cases	Overall survival	5-yr OS: 84.6% vs 91.7% (P=0.04)

The role of FOXM1 in regulating immune memory in triple-negative breast cancer and targeting FOXM1 to develop a therapeutic vaccine.

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Background: Triple-negative breast cancer (TNBC) is an aggressive malignancy with limited therapeutic options and poor long-term outcomes. Although immune checkpoint blockade has improved survival for a subset of patients, durable responses remain uncommon, underscoring the need for strategies that enhance tumor immunogenicity and immune memory. We recently identified a novel function of the transcription factor FOXM1 in promoting an immune-suppressive tumor microenvironment (TME) in TNBC by regulating stress ligands and the STING pathway. This study investigates the role of FOXM1 in shaping antitumor immune memory and leverages FOXM1 targeting to identify tumor antigens for therapeutic peptide vaccine development. **Methods:** FOXM1 was knocked out in TNBC cell lines using CRISPR/Cas9, and syngeneic mouse models were utilized to evaluate tumor-immune interactions. Single-cell RNA sequencing (scRNA-seq) evaluated immune landscape remodeling following FOXM1 loss. Immunopeptidomics was performed to identify tumor-associated antigens enriched following FOXM1 loss. Candidate peptides were functionally validated using dendritic cell-based antigen presentation assays and patient-derived peripheral blood mononuclear cells (PBMCs). Clinical relevance was evaluated using TNBC patient datasets and immunotherapy response cohorts. **Results:** scRNA-seq of syngeneic tumors revealed that FOXM1 deletion reshaped the immune microenvironment, with increased CD8⁺ T cell and NK cell infiltration and expansion of memory T cell populations. Tumor-intrinsic FOXM1 suppressed antitumor immunity by down-regulating MHC-I and the stress ligand ULBP1, disrupting signaling pathways required for NK and CD8⁺ T cell-mediated cytotoxicity. FOXM1-deficient tumors conferred durable protection upon tumor rechallenge, consistent with long-term immune memory. Analysis of patient datasets demonstrated that elevated FOXM1 and DNMT1 expression, coupled with reduced STING and ULBP1 levels, correlated with poorer survival and reduced responsiveness to immunotherapy. Leveraging enhanced antigen presentation in FOXM1-depleted cells, immunopeptidomics identified 275 differentially presented tumor antigens. Dendritic cell pulsing of the top 15 enriched peptides induced robust T cell responses in patient-derived PBMCs, supporting their immunogenicity and its potential to serve as bona fide candidates for a therapeutic vaccine tailored for TNBC patients. **Conclusions:** These findings establish FOXM1 as a clinically relevant regulator of immune evasion and immune memory in TNBC. Importantly, the identification of immunogenic peptides provides a strong rationale for the development of a peptide-based therapeutic vaccine, either as a monotherapy or in combination with immune checkpoint blockade, to improve long-term disease control in patients with TNBC. Research Sponsor: None.

Rare histologic subtypes of triple-negative breast cancer: The impact of immunotherapy on outcomes for metastatic disease.

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Background: The addition of immunotherapy (IO) to chemotherapy (chemo) has significantly improved survival for patients with PD-L1-positive, metastatic triple-negative breast cancer (mTNBC), establishing chemo+IO as the standard first-line treatment in this population. However, the impact of IO on real-world outcomes of rare histologic subtypes of TNBC, such as metaplastic and lobular, as well as inflammatory presentation, are unknown. **Methods:** We conducted a retrospective study analyzing data from the US National Cancer Database (NCDB). Patients diagnosed with *de novo* stage IV TNBC who received chemo alone or chemo+IO between 2019 and 2022 (after FDA approval of IO for mTNBC) were included. mTNBC was classified as ductal, lobular, inflammatory, metaplastic, or other by the NCDB. Overall survival (OS) was assessed using the Kaplan-Meier method and multivariable Cox regression models controlled for sociodemographic and clinicopathologic factors. **Results:** A total of 6,711 patients with *de novo* mTNBC were identified (mean age 59.2 years), with a median follow-up of 19.8 months. Ductal histology was the most common (74.2%), followed by inflammatory (8.7%), metaplastic (4.5%), and lobular (3.6%) cases. Overall, 40.0% of the patients received chemo+IO. Immunotherapy use was the highest in mTNBC with inflammatory presentation (46.8%), followed by ductal (40.0%), lobular (37.5%), and metaplastic (37.2%) subtypes ($P = 0.002$). Among patients who received chemo+IO, the median OS time was the longest in ductal mTNBC (30.3 months) compared to the lobular (23.5 months) and metaplastic (22.9 months) subtypes and inflammatory presentation (16.5 months) (log-rank test $P < 0.001$). In the adjusted models, inflammatory mTNBC had a significantly higher risk of mortality than ductal cases treated with chemo+IO (adjusted hazard ratio [aHR], 1.96; 95% CI, 1.31–2.92); lobular (aHR, 1.59; 95% CI, 0.84–3.00) and metaplastic (aHR, 1.10; 95% CI, 0.44–2.71) subtypes also had a higher mortality risk, though the differences were not statistically significant due to small group sample sizes. Among patients who received chemo alone, inflammatory presentation (aHR, 2.10; 95% CI, 1.58–2.80) and lobular subtype (aHR, 1.67; 95% CI, 1.03–2.70) also had a higher risk of mortality than the ductal subtype. **Conclusions:** In this real-world analysis, patients with inflammatory, lobular, and metaplastic *de novo* mTNBC continued to experience inferior survival outcomes despite the use of chemo+IO. Our findings highlight persistent disparities in mortality outcomes and support the need for biomarker-driven strategies and dedicated clinical trials for these rare subtypes and inflammatory mTNBC. Research Sponsor: National Institute on Aging; T32AG000243.

Homologous recombination deficiency signature (HRDsig+) in older women with advanced breast cancer (ABC).

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Background: The identification of homologous recombination deficiency (HRD) may expand targeted therapy options in the management of advanced breast cancer (ABC). However, the frequency of positive HRD signature (HRDsig+) status in older women with ABC is not widely known. We explored the prevalence of HRDsig+ status, and its co-occurrence with other genomic alterations (GAs). **Methods:** Comprehensive genomic profiling (CGP) was performed on 6,221 cases of patients ≥ 65 years old with ABC to assess GA including base substitutions, short insertions and deletions, copy number changes and rearrangements and fusions. Microsatellite instability (MSI) status, tumor mutation burden (TMB), genomic ancestry, and trinucleotide signature were determined from the sequencing data. HRDsig status, provided as a clinical service, was determined by measuring large scale copy number changes and DNA repair errors. **Results:** Of the 6,221 cases, 662 (10.6%) were HRDsig+. Compared to the HRDsig- cases, HRDsig+ cases more frequently had genomic alterations (GA) associated with DNA repair, including *BRCA1* (13.7% vs 1.2%; $p<.0001$), *BRCA2* (22.8% vs 1.1%; $p<.0001$) and *RAD21* (25.1% vs 14.6%; $p<.0001$). When compared to HRDsig- cases, HRDsig+ cases had more frequent *PTEN* GA (16.3% vs 9.9%; $p<.0001$) *MTAP* loss (5.6% vs 2.7%; $p<.0001$), and TMB >10 mutations/Mb (12.7% vs 9.3%; $p=.015$). HRDsig- ABC cases had more frequent *PIK3CA* GA (47.6% vs 20.4%; $p<.0001$), *ERBB2* (10.9% vs 6.0%; $p<.0001$), *ESR1* (11.0% vs 5.3%; $p<.0001$) and *CDH1* (24.6% vs 6.5%; $p<.0001$). MSI-H status (0.3% vs 0.8%) and PD-L1 low 1-49% (36.1% vs 30.1%) were similar in both groups (NS). **Conclusions:** Among older adults with ABC, HRDsig+ status was identified in over 10% of patients undergoing CGP. Those with HRDsig+ more frequently had GAs in tumor suppressor genes involved in HRD, including *TP53*, *BRCA1*, *BRCA2*, and *RAD21*. The association of HRDsig+ with high TMB could provide the rationale for future trials with combination of PARP inhibitors with immunotherapy. Research Sponsor: None.

HRD signature status and associated genomic alterations in older women with advanced breast cancer.

	HRDsig positive (N=662)	HRDsig negative (N=5559)	P-value
MSI-H	0.3%	0.8%	NS
TMB >10 mut/Mb	12.7%	9.3%	0.015
PD-L1 low positive (1-49%)	36.1%	30.1%	NS
<i>BRCA1</i>	13.7%	1.2%	$<.0001$
<i>BRCA2</i>	22.8%	1.1%	$<.0001$
<i>ERBB2</i>	6.0%	10.9%	$<.0001$
<i>ESR1</i>	5.3%	11.0%	$<.0001$
<i>PIK3CA</i>	20.4%	47.6%	$<.0001$
<i>TP53</i>	73.1%	40.4%	$<.0001$

AI-driven H&E plasma cell to predict pathological complete response in IO-treated triple-negative breast cancer (Yale; NCT02489448).

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Background: Pathological complete response (pCR) remains difficult to predict in triple-negative breast cancer (TNBC) patients treated with immune checkpoint inhibitors due to limited validated biomarkers. While tumor-infiltrating lymphocytes (TILs) are prognostic in TNBC, they are commonly treated as a composite population. Plasma cells are central to humoral immunity and can influence antitumor response through antibody production, antigen presentation, and T-cell modulation. However, the independent and cooperative prognostic role of plasma cells, either alone or in spatial interaction with other immune cells has not been systematically evaluated, particularly in TNBC. Here, we evaluated the value of plasma cells to predict pathological complete response using AI-based analysis of routine H&E slides. **Methods:** We analyzed 239 stage I–III TNBC patients across four cohorts. Models were trained on KEYNOTE-522 regimen treated patients (D1, N=130) and validated in both the Yale TNBC immunotherapy trial cohort (D2, N=65; NCT02489448) treated with durvalumab (anti-PD-L1 antibody) and University Hospital cohort (D3, N=25) treated with pembrolizumab. Plasma cells and lymphocytes were automatically detected on whole-slide H&E images using deep learning-based nuclear segmentation and tumor region classification. Quantified metrics included immune cell density, tumor-infiltrating plasma cell (TIP) ratios, and spatial features capturing plasma cell clustering and interaction with lymphocytes. Density-based classifiers were trained on D1 and evaluated for pCR prediction. **Results:** Plasma cell density alone predicted pCR with higher accuracy than lymphocyte density across both validation cohorts. In D2, plasma cell density achieved an AUC of 73.2 compared with 62.9 for lymphocyte density. Similarly, in the external institutional cohort (D3), plasma cell density outperformed lymphocyte density (AUC 69.2 vs 60.8, respectively; Table 1). These findings demonstrate the superior predictive value of plasma cell density over conventional lymphocyte-based measures for pCR in immunotherapy-treated TNBC. **Conclusions:** Plasma cells demonstrate independent and cooperative predictive value in immunotherapy-treated TNBC. AI-derived plasma cell density and spatial interaction features improve pCR prediction and survival stratification beyond conventional lymphocyte-based metrics. Research Sponsor: None.

Comparison of plasma cell performance compared to lymphocytes on holdout set D2 (Yale TNBC clinical trial NCT02489448) and D3.

	Holdout 1	Holdout 2
	Yale NCT02489448 (N=64), D2	UH Hospital (N=25), D3
M _{plasma}	73.2	69.2
M _{lymph}	62.9	60.8

JSKN016, a first-in-class anti-TROP2/HER3 bispecific antibody-drug conjugate (ADC), in patients (pts) with HER2-negative locally advanced or metastatic breast cancer: Results from a phase I study.

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Background: TROP2 and HER3 are frequently overexpressed in most of solid tumors. JSKN016 is a first-in-class bispecific ADC targeting TROP2/HER3, site specifically conjugated to topo-isomerase I inhibitor via a cleavable linker (DAR₄). Glycan conjugation provides high stability and minimizes off-target toxicity. **Methods:** JSKN016-101 (NCT06592417) is a first-in-human, dose-escalation and expansion study in China, enrolling patients with advanced solid tumors to receive JSKN016 monotherapy. This analysis focused on the HER2-negative BC cohort. **Results:** As of December 22, 2025, JSKN016 was escalated to 8 mg/kg IV Q3W without reaching the maximum tolerated dose. A total of 82 HER2- BC pts were enrolled: 50 TNBC and 32 HR+/HER2- BC, treated at 4 mg/kg (n=14), 6 mg/kg (recommended phase II dose [RP2D]; n=65), and 8 mg/kg (n=3). Overall, 98.8% (81/82) had stage IV disease including 13.4% (11/82) with brain metastases. Median age was 50 (TNBC) and 52y (HR+/HER2- BC); ECOG PS 1 was reported in 78.7% and 76.7%, respectively. All TNBC pts had prior taxane-based chemotherapy, 28.0% had received ≥3 prior systemic regimens. All HR+/HER2- BC pts had progressed after ≥1 endocrine therapy with CDK4/6 inhibition and ≥1 chemotherapy. Among 47 efficacy-evaluable TNBC pts, objective response rate (ORR) was 61.7% (by INV and IRC). At RP2D (n=31), ORR was 64.5% (INV) and 61.3% (IRC), with disease control rates (DCR) of 83.9% and 90.3%. The median PFS was 7.9 months (95%CI: 5.5, NE) by IRC and 7.6 months (95%CI: 4.1, NE) by INV. Among 30 efficacy-evaluable HR+/HER2- BC pts, ORR was 50.0% (INV) and 53.3% (IRC); at RP2D (n=29), ORR was 51.7% (INV) and 55.2% (IRC), with DCR of both 100%. The median PFS was 11.1 months (8.3, NE) by IRC and was not yet mature by INV. With a median follow-up of 8 months, grade 3 or above TRAEs occurred in 25.6% (21/82) pts, with no G₄ or 5 events reported. The most common G₃ TRAEs were neutrophil count decreased (6.1%), amylase increased (4.9%), white blood cell count decreased (4.9%), stomatitis (3.7%), asthenia (2.4%), lymphopenia (2.4%). The incidence of TRAEs was 9.8%. Only one TRAE (G₃ conjunctivitis) led to treatment discontinuation. No interstitial lung disease (ILD) was reported. **Conclusions:** JSKN016 demonstrated robust antitumor activity with good safety profile in pts with HER2-negative BC. The results support further development of JSKN016 as monotherapy or in combination. Clinical trial information: NCT06592417. Research Sponsor: None.

Efficacy of JSKN016 in HER2-BC at 6 mg/kg Q3W.

Assessed by	TNBC (N=31)		HR+/HER2- BC (N=29)	
	INV	IRC	INV	IRC
uORR, % (95% CI)	64.5 (45.4, 80.8)	61.3 (42.2, 78.2)	51.7 (32.5, 70.6)	55.2 (35.7, 73.6)
DCR, % (95% CI)	83.9 (66.3, 94.5)	90.3 (74.2, 98.0)	100 (88.1, 100)	100 (88.1, 100)
mPFS, mos (95% CI)	7.6 (4.1, NE)	7.9 (5.5, NE)	NR	11.1 (8.3, NE)
6-months PFS rate, %	57.7 (38.5, 72.9)	68.4 (47.9, 82.2)	74.0 (53.0, 86.7)	84.5 (63.8, 93.9)

Real-world effectiveness and safety of first-line pembrolizumab plus chemotherapy in patients aged ≥ 65 years with metastatic triple-negative breast cancer.

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Background: Patients aged ≥ 65 years constitute a substantial proportion of individuals with metastatic triple-negative breast cancer (mTNBC), but remain underrepresented in clinical trials due to comorbidities and concerns regarding treatment tolerability. While pembrolizumab combined with chemotherapy (P+C) has been established as a standard first-line treatment for mTNBC with a combined positive score ≥ 10 , real-world evidence on its safety and effectiveness in older patients remains limited. **Methods:** This multicenter observational real-world study (RWS), CEBCC-101, retrospectively analyzed clinical data from 178 female patients with mTNBC treated with P+C in routine clinical practice. Patients were stratified according to age at treatment initiation (< 65 vs. ≥ 65 years). Baseline characteristics, treatment modifications (including dose reductions and treatment delays), adverse events (AEs; graded according to CTCAE v5.0) and clinical outcomes were assessed. Clinical endpoints included progression-free survival (PFS), overall survival (OS) and objective response rate (ORR) evaluated according to RECIST 1.1. Survival outcomes were estimated using the Kaplan–Meier method and compared between age groups using the log-rank test. **Results:** Among 178 patients, 57 (32.0%) were aged ≥ 65 years. Median age in the older cohort was 72.4 years (mean 72.3 ± 4.7). Patients ≥ 65 years had a significantly higher prevalence of relevant comorbidities compared with younger patients (71.9% vs. 39.7%; $p < 0.001$) and more frequently presented with visceral metastases (78.9% vs. 61.2%; $p = 0.029$), driven primarily by a higher incidence of lung metastases (59.7% vs. 42.2%; $p = 0.043$). Rates of chemotherapy dose reductions at treatment initiation or during therapy, treatment delays due to AEs and treatment discontinuation due to toxicity were comparable between age groups. ORR did not differ significantly between patients ≥ 65 and < 65 years (52.6% vs. 55.4%; $p = 0.767$). Median PFS was 9.1 months (mo) in patients ≥ 65 years versus 8.3 mo in younger patients ($p = 0.594$). Median OS was 22.1 mo and 19.5 mo, respectively ($p = 0.985$). The incidence of grade ≥ 2 AEs, including pulmonary, neurological, dermatological events and fatigue was similar across age groups. **Conclusions:** In this RWS, patients aged ≥ 65 years with mTNBC treated with first-line P+C achieved clinical outcomes and safety profiles comparable to those of younger patients, despite a higher burden of comorbidities and more frequent visceral disease. These findings suggest that chronological age alone should not be a limiting factor for immunochemotherapy and underscore the importance of treatment decisions based on clinical fitness. Broader incorporation of geriatric assessment into routine oncology practice may further optimize patient selection and outcomes. Research Sponsor: None.

Real-world evaluation of CXCL9/10 with PD-L1 and TMB as predictors of pembrolizumab benefit in triple-negative breast cancer (TNBC).

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Background: Pembrolizumab is approved for TNBC; however, current biomarkers PD-L1 and tumor mutational burden (TMB) have limited predictive accuracy and show weak correlation with clinical benefit. We evaluated whether chemokines (CXCL9 and CXCL10) that recruit cytotoxic T cells into the tumor microenvironment (TME) may improve prediction of pembrolizumab benefit beyond PD-L1 and TMB. **Methods:** TNBC tumors (n=3662) were profiled by next-generation sequencing (592 NextSeq; WES/WTS NovaSeq; Caris Life Sciences, Phoenix, AZ). Chemokine expression was classified as high vs low based on 50th percentile. Immune cells were estimated using WTS deconvolution (Quantiseq). PD-L1 was assessed by immunohistochemistry (22C3 ≥10%), and TMB by nonsynonymous mutations/Mb (high ≥10). Real-world median overall survival (mOS) was derived from insurance claims and calculated from pembrolizumab initiation to last contact. Associations were tested using chi-square and Mann-Whitney U with multiple comparison adjustment ($q < 0.05$). **Results:** CXCL9/10-high expression showed increased fraction of CD8⁺ T, dendritic cells and higher IFN- γ signatures (CXCL9-high vs low: 1.3% vs 0%, 3.1% vs 2.8%, -0.09 vs -0.47; CXCL10-high vs low: 1.1% vs 0%, 3.1% vs 2.7%, -0.1 vs -0.46), respectively all $q < 0.05$. Among patients treated with pembrolizumab (n=750), CXCL9/10-high expression was associated with improved mOS (CXCL9-high: 24.5 months (m) vs 15.8 m; CXCL10-high: 23.4 m vs 17 m; all $p < 0.05$) compared to CXCL9/10-low; PD-L1+ tumors had improved mOS (24.3 m vs 18.6 m, $p = 0.007$) compared with PD-L1-negative; and TMB-low tumors had numerically improved mOS (21.7 m vs 17.5, $p = 0.08$) compared with TMB-high. Combining CXCL9/10 with PD-L1 or TMB identified subgroups of tumors with PD-L1-negative and TMB-high expression that showed better OS with pembrolizumab (Table). In multivariable cox analysis, adjusting for TMB and PD-L1, CXCL9 [HR 0.67 (95% CI 0.54-0.83)] and CXCL10 [HR 0.79 (95% CI 0.64-0.97)] remained independent predictors of pembrolizumab benefit, all $p < 0.05$. **Conclusions:** In this large real-world study, PD-L1 but not TMB predicted pembrolizumab benefit in TNBC. CXCL9/10-high define an immune-active TME and are independent predictors of pembrolizumab response. When integrated with PD-L1 and TMB, these chemokines help identify additional patients with TNBC who may derive benefit from pembrolizumab, supporting their inclusion as biomarkers in prospective studies. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

PD-L1	Chemokine	CXCL9 mOS (in months) (95% CI)	p	CXCL10 mOS (in months) (95% CI)	p
+	High	25.7 (22.1 - 32.1)	<0.01	25.7 (22.2 - 34.1)	<0.01
-	High	26.9 (17.8 - 39.2)		21.7 (17.5 - 28.2)	
+	Low	18.5 (11.9 - NR)		20.7 (13.3 - 30.1)	
-	Low	15.8 (12.2 - 19.2)		16.7 (13.1 - 21.5)	
TMB					
Low	High	25.0 (22.1 - 30.1)	<0.01	23.7 (20.9 - 28.2)	<0.01
High	High	20.6 (17.5 - 37.1)		19.5 (16.3 - NR)	
Low	Low	18.3 (14.1 - 21.3)		18.6 (15.7 - 22.2)	
High	Low	6.6 (3.6 - 13.7)		7.6 (5.1 - 16.2)	

Single cell spatial profiling for identification of organ-specific immune features in the peritumoral microenvironment of triple-negative breast cancer with liver metastases.

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Background: Breast cancer liver metastasis (BCLM) is associated with poor prognosis. Prior studies have described liver metastases as immune-cold, yet the mechanisms underlying this phenotype remain incompletely understood. We hypothesized that the peritumoral microenvironment, in addition to the tumor itself, contributes to the distinct immunobiology of BCLM. **Methods:** We performed imaging mass cytometry (IMC) with a 42-antibody panel on TNBC tissues from primary breasts (PB) (n = 22) and liver metastases (LM) (n = 26). For each case, one region of interest (ROI) from tumor bed and one from peritumoral tissue were profiled. Cell segmentation was performed using DeepCell. Single-cell phenotyping and clustering were conducted using Scanpy with lineage markers. Functional marker expression was analyzed and differences between PB and LM were assessed using non-parametric tests with Benjamini-Hochberg false discovery rate (FDR) correction. Spatial analysis was performed using Squidpy with Wilcoxon testing and FDR correction across all tested interaction pairs. **Results:** IMC analysis resolved 407,160 cells into distinct immune, stromal, and tumor cell clusters across compartments. Within tumor beds, PB and LM exhibited largely similar functional marker expression and spatial organization, indicating minimal tumor-intrinsic divergence. In contrast, peritumoral tissues diverged substantially between PB and LM. Peritumoral tissues in PB demonstrated M2 macrophage dominance while LM exhibited M1 macrophage dominance. The comparative analysis of peritumoral tissues revealed that cancer cells in LM demonstrated significantly increased spatial proximity to CD8 T cells compared to PB with concurrent upregulation of PD-L1 on macrophages and NK cells, alongside elevated PD-1 expression on multiple immune cell types, indicating that CD8 T cells are potentially exhausted despite their physical presence. Additionally, CCR7, CD6, and CXCL13 were significantly elevated across all cell types in LM, while PB demonstrated higher expression of CD44, CXCR3 and CXCL12, indicating broad immunophenotypic differences in peritumoral tissues. Spatial analysis further revealed that CD4 T cells maintained closer proximity to cancer cells, M1 macrophage, and stromal populations in PB, indicating distinct spatial organization between sites. **Conclusions:** Single-cell spatial profiling reveals that organ-specific tumor and immune biology in TNBC BCLM is encoded primarily within the peritumoral tissue rather than the tumor bed itself. Our findings reveal a paradoxical phenotype in BCLM where CD8 T cells successfully infiltrate and localize near cancer cells but show features consistent with functional impairment. These findings support further investigation of immunotherapy in TNBC BCLM and biomarker validation. Research Sponsor: 2024 Cedars-Sinai Cancer Center Developmental Funds.

Trends in immunotherapy use and survival outcomes by metastatic pattern in metastatic triple-negative breast cancer.

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Background: KEYNOTE-355 demonstrated that adding pembrolizumab to chemotherapy improved progression-free and overall survival (OS) vs chemotherapy alone in patients with metastatic TNBC (mTNBC) and PD-L1 CPS ≥ 10 . Approved in 2020, this regimen transformed advanced TNBC management. However, the benefit of immunotherapy (IO) according to metastatic site remains underexplored given the varied immune environments between organs, with the liver being particularly immune-suppressed. **Methods:** We conducted a retrospective analysis of 2022 NCDDB data for female patients diagnosed 2016–2021 with de novo mTNBC. OS was defined as months from diagnosis to death/last contact. Patients were stratified by first-line therapy (chemotherapy alone vs chemotherapy + IO) and metastatic pattern (isolated liver/lung/bone/brain; multiple sites). IO type was not specified. P-values were calculated by chi-squared/Fisher's exact tests as appropriate. Hazard ratios (HR) were estimated by a univariate Cox model. **Results:** 2329 patients with de novo mTNBC were included in our study. Median age was 59 years, median follow-up time was 42 months. 1723 (74%) received chemotherapy alone and 606 (26%) received chemotherapy + IO. The proportion of patients receiving IO increased each year between 2016 and 2021 (3.3% – 34.3%). Overall, patients treated with chemotherapy + IO had better OS compared to chemotherapy alone (HR = 0.58, 95% CI, 0.51–0.65, $P < 0.001$). Isolated lung metastasis was the most common pattern ($n=402$, 20.9%), followed by bone ($n=374$, 19.4%), liver ($n=246$, 12.8%), and brain metastasis ($n=14$, 0.7%). 892 (46.3%) patients had multiple metastatic sites. Patients with isolated lung, liver or bone metastases had better OS vs those with multiple metastatic sites (lung, HR 0.54, [95% CI 0.47–0.62]; liver, HR 0.62, [95% CI 0.53–0.73]; bone, HR 0.69, [95% CI 0.60–0.79]). Kaplan–Meier analysis showed superior OS with chemotherapy + IO vs chemotherapy alone across lung, liver, bone, and multiple metastases subgroups (log-rank $P < 0.0001$, $P = 0.0003$, $P = 0.0017$, $P < 0.0001$, respectively); brain metastasis analysis limited by small sample size (Table 1). **Conclusions:** In this large real-world mTNBC cohort, IO adoption increased post-KEYNOTE-355 approval and associated with an overall 42% lower mortality risk vs chemotherapy alone. Additionally, increased IO adoption correlated with increased survival over time. The survival benefit of IO was preserved across different metastatic sites of disease. Research Sponsor: None.

Overall survival in mTNBC patients by metastatic site and treatment modality.

Met site	Treatment	N	Median survival, months	24-mo survival, %	36-mo survival, %
Lung	Chemo + IO	57	32.1	60.6	49.4
	Chemo	220	15.9	38	24.8
Liver	Chemo + IO	47	27.7	52.4	37.7
	Chemo	141	15.5	33.4	18.7
Bone	Chemo + IO	67	23.5	49.2	26.3
	Chemo	221	13.2	29.7	19.8
Multiple	Chemo + IO	155	16.4	36.3	26.4
	Chemo	593	8.7	18.1	10.3

Long-term responders to sacituzumab govitecan in metastatic triple-negative breast cancer: Real-world outcomes and predictors from a multicenter Italian cohort.

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Background: Sacituzumab govitecan (SG) has reshaped the treatment landscape of metastatic triple-negative breast cancer (mTNBC), demonstrating superior survival outcomes compared with standard chemotherapy in the ASCENT trial. Despite the overall poor prognosis of mTNBC, a subset of patients experiences remarkably durable responses and prolonged survival, far exceeding the median progression-free survival (PFS) observed in pivotal trial. However, the clinical characteristics and prognostic determinants of these "long-term responders" (LTRs) remain poorly defined, and real-world evidence specifically addressing this population is currently lacking. This multicenter study aims to characterize outcomes and identify potential predictors of long-term benefit from SG in a real-world setting. **Methods:** This multicenter observational analysis included 271 patients with mTNBC treated with SG across 18 Italian cancer centers, within a study incorporating both retrospective and prospective cohorts (NCT02284581). LTRs were defined as patients achieving a real-world PFS (rwPFS) ≥ 9 months. The primary endpoint was rwPFS, while secondary endpoints included real-world overall survival (rwOS) and objective response rate (ORR). Survival outcomes were estimated using the Kaplan-Meier method, and independent prognostic factors were identified using Cox proportional hazards models. **Results:** Seventy-four of 271 patients (27.3%) were identified as LTRs. Within this cohort, median rwPFS was 14 months (95% CI: 13.3–16.3) and median rwOS was 25.6 months (95% CI: 21.0–NR). The ORR was 68.9% (all partial responses; n=51), while 29.7% of patients (n=22) achieved stable disease. On multivariable analysis, previous therapy with immune checkpoint inhibitors (ICI) was independently associated with a reduced risk of progression (HR 0.47; 95% CI: 0.22–0.98; p=0.04). De novo metastatic disease also showed a trend towards a lower risk of progression (HR 0.44; 95% CI: 0.16–1.17; p=0.10). Conversely, treatment with SG in the third line compared with the second line was associated with a higher risk of progression (HR 2.04; 95% CI: 1.02–4.07; p=0.04). No significant association were observed for brain metastases (p=0.37), BRCA mutation status (p=0.33), or visceral involvement (p=0.27). **Conclusions:** In real-world setting, more than 25% of mTNBC patients experience a durable benefit from SG. Prior exposure to immunotherapy and earlier use of SG in the second-line setting were associated with a higher likelihood of LTR, while de novo disease showed a favourable trend. Notably, the presence of brain or visceral metastases did not preclude prolonged benefit. These findings suggest that a subset of patients with mTNBC may derive sustained clinical benefit from SG and support its use earlier in the treatment sequence. Clinical trial information: NCT02284581. Research Sponsor: Gilead Sciences.

Progression-free survival as a surrogate endpoint for overall survival in metastatic triple-negative breast cancer: A systematic review and meta-analysis.

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Background: Overall survival (OS) remains the gold standard endpoint in metastatic triple negative breast cancer (mTNBC), but its assessment is confounded by post progression therapies and prolonged follow up. Progression-free survival (PFS) is frequently used as a primary endpoint; however, its validity as a surrogate for OS in mTNBC remains uncertain. We conducted an updated systematic review and meta analysis to evaluate the strength and reliability of PFS as a surrogate endpoint for OS across contemporary RCTs. **Methods:** We searched PubMed, Embase, Cochrane Library, and major oncology conference proceedings through January 2026 for randomized controlled trials evaluating systemic therapies in metastatic or unresectable TNBC. Eligible trials reported hazard ratios (HRs) for both PFS and OS. Trial level correlations between $\log(\text{HR_PFS})$ and $\log(\text{HR_OS})$ were assessed using weighted Spearman correlation and weighted linear regression, with sample size based weights. Certainty of evidence was assessed using a modified GRADE framework. **Results:** Twenty-seven treatment comparisons from 29 trials (8,527 patients) met inclusion criteria. Across all comparisons, PFS demonstrated a strong correlation with OS (weighted Spearman $\rho = 0.80$; 95% CI, 0.55–0.91), with a moderate surrogate relationship ($R^2 = 0.64$). The regression slope (0.66; 95% CI, 0.46–0.87) indicated attenuation of OS benefit relative to PFS. The surrogate threshold effect corresponded to an HR PFS of 0.96. Eight trials (30%) showed concordant PFS and OS benefit, while 44% demonstrated PFS improvement without significant OS gain. Surrogacy was strongest in phase III trials ($R^2 = 0.71$). Treatment class analyses revealed strong surrogacy for immune checkpoint inhibitors ($R^2 = 0.95$) and platinum based chemotherapy ($R^2 = 0.87$), but weak correlation for AKT pathway inhibitors ($R^2 = 0.31$). Overall certainty of evidence was moderate. Risk of bias assessment using the Cochrane RoB 2.0 tool showed 30% of comparisons at low risk, 56% with some concerns (primarily due to open label design), and 15% at high risk, mainly related to crossover and outcome assessment. **Conclusions:** PFS is a moderate and clinically acceptable surrogate for OS in metastatic TNBC, particularly for immune checkpoint inhibitors and platinum based regimens. However, surrogate validity varies substantially by treatment class, underscoring the need for confirmatory OS data especially for targeted therapies with novel mechanisms. Research Sponsor: None.

Measuring KEYNOTE-522 response from TNBC patient biopsies ex vivo using the E-slice assay.

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Background: The KEYNOTE-522 regimen demonstrated a significant survival advantage of adding neoadjuvant pembrolizumab (pembro) to standard-of-care (SOC) chemotherapy (chemo) in TNBC patients. However, most patients will not benefit from this costly and potentially toxic therapy. A diagnostic test that can stratify responders and non-responders in advance will reduce overtreatment in this population. The E-slice assay is a proprietary 3D human tumor tissue culture platform that enables rapid, personalized drug sensitivity testing. E-slices preserve immune cells in their native state ex vivo, enabling immunotherapy response measurement from tissue resident immune cells. **Methods:** In this prospective clinical study, newly diagnosed triple-negative breast cancer (TNBC) patients scheduled to receive KEYNOTE-522 treatment at MD Anderson Cancer Center were enrolled. E-slices were generated from 14-gauge core biopsies and treated with IgG control, pembrolizumab, or a combination of pembrolizumab with paclitaxel + carboplatin followed by doxorubicin + cyclophosphamide. Diagnostic performance of the E-slice assay was evaluated using sensitivity, specificity, and ROC analysis, with the optimal cutoff determined by the Liu method. Concordance between assay-based predictions and clinical treatment response was assessed using Cohen's kappa, and paired classification differences were tested with McNemar's test. Patient tumor responders were defined solely by pathological complete response (pCR) or not, at the time of surgery, after standard-of-care neoadjuvant chemoimmunotherapy treatment. **Results:** A blinded interim analysis was scheduled after the first 10 patients evaluated in the clinic for pCR. The mean and SD of age were 52.10 ± 12.52 . The mean and SD for E-slice combo response, relative to DMSO @ day12 were 0.68 ± 0.18 . The optimal cutoff point for E-slice combo response was 0.78. The proportion of responders in patients was 0.8 (8/10). The proportion of responders from E-slice combo response was 0.7 (7/10). There was no significant difference based on McNemar's test ($p=1.0$). The concordance rate is 75% (95% CI: 42.81%–94.51%). The sensitivity, specificity, positive predictive value, negative predictive value, and area under ROC curve at cutoff point for E-slice were: 87.5% (95% CI: 47.3%–99.7%), 100% (15.8%–100%), 100% (59%–100%), 66.7% (9.43%–99.2%), and 0.94 (0.82–1.0), respectively. **Conclusions:** E-slice assay predicts TNBC patient responses to pembrolizumab alone or pembrolizumab + chemo by providing drug sensitivity data in a clinically actionable time frame. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

Confusion matrices E-slice combo response.

		E slice Response		Total
		Non-Responders	Responders	
Patient Response	Non-responders	2	0	2
	Responders	1	7	8
	Total	3	7	10

E-slice Responder was defined as E-slice combo response relative to DMSO @ day12 < 0.7816 . Non-responder was defined as ≥ 0.7816 .

Determinants of triple-negative breast cancer among African patients: Early results from The African Cancer Atlas.

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Background: Triple-negative breast cancer (TNBC) is disproportionately common among women of African ancestry and is associated with aggressive clinical behavior and limited therapeutic options. Understanding demographic and contextual determinants of TNBC across African countries is essential to improving prevention, early detection, and precision oncology strategies. Using harmonized data from The African Cancer Atlas (TACA)—an initiative of Yemaachi Biotech, we examined factors associated with TNBC across Côte d'Ivoire, Ghana, Kenya, Nigeria, and Seychelles. **Methods:** We analyzed 236 participants with complete immunohistochemistry data enrolled in TACA. Associations between TNBC and demographic variables were assessed using Wilcoxon rank-sum tests, Fisher's exact tests, and multivariable logistic regression. **Results:** TNBC accounted for 38.1% of breast cancers in the cohort. TNBC had prevalence rates ranging from 21.1% in Kenya to 68.1% in Nigeria ($p < 0.001$). Seychelles exhibited no TNBC cases (0/23). TNBC prevalence among females was 38.5% (89/231), compared with 20.0% (1/5) among the few male participants. Women in Nigeria had markedly higher odds of TNBC compared with Kenya (OR 10.4, 95% CI 3.72–31.4, $p < 0.001$). Women in Ghana also demonstrated increased odds (OR 2.55, 95% CI 1.10–6.12, $p = 0.032$). Age showed no significant association with TNBC (mean age 51.6 years for TNBC vs. 50.2 years for non-TNBC, $p = 0.6$), though the 60–69 age group showed a modestly increased proportion of TNBC (38.1%, OR 0.26, 95% CI 0.07–0.93, $p = 0.042$, relative to 50–59). Education level was significantly associated with TNBC ($p = 0.004$). Women with no formal education had a 59.2% TNBC prevalence (29/49), compared with 26.9% among those with primary education (18/67, OR 0.69, 95% CI 0.26–1.85) and 33.3% among those with higher education (17/51, OR 0.77, 95% CI 0.28–2.14). Family history of cancer was also associated with TNBC ($p = 0.006$). Among women reporting a positive family history, 23.8% had TNBC (15/63), compared with 76.2% with non-TNBC (48/63). **Conclusions:** TNBC prevalence in this multi-country African cohort was high and characterized by substantial geographic variation, with Nigeria demonstrating the highest burden. Lower educational attainment and family history of cancer were also associated with TNBC, independent of country. These findings highlight the importance of considering socio-demographic and contextual factors when designing TNBC-focused screening and treatment strategies and underscore the need for country-specific precision oncology approaches in African settings. Research Sponsor: None.

Immune infiltration features relative to cancer cell clumps as predictors of survival in triple-negative breast cancer.

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Background: Triple-negative breast cancer (TNBC) is an aggressive subtype with poor prognosis. While immune infiltration and abundance have been established as prognostic indicators, we examine how immune spatial organization and tumor geometry jointly influence survival. **Methods:** Whole-slide H&E images from 125 TNBC TCGA cases were analyzed using pathology instance learning models to generate tile-based predictions, which were reconstructed into polygon annotations for tumor epithelium, tumor-infiltrating lymphocytes (TILs), and tertiary lymphoid structures (TLS). From these annotations, we extracted novel spatial features describing abundance, fragmentation, dispersion, shape, and boundary properties of immune and tumor regions, as well as immune-tumor distances, overlap gradients, and boundary engagement. Associations with disease-specific survival (DSS) were assessed using univariate Cox models, and significant features were incorporated into a multivariate Cox model. Kaplan-Meier and correlation analyses were performed for dichotomized features. **Results:** Among all spatial features analyzed, global immune dispersion emerged as a strong indicator of survival. This metric, quantified by the radius of gyration of immune islands, was significantly associated with worse disease-specific survival (DSS) (HR per SD = 1.90; $p = 0.03$) and demonstrated clear Kaplan-Meier separation (log-rank $p = 0.028$). Increased tumor boundary complexity, measured by edge density normalized to tissue area, was also associated with poorer DSS (HR per SD = 1.77; $p = 0.007$). Kaplan-Meier analysis for edge density showed only modest separation (log-rank $p = 0.071$), consistent with a gradual, continuous risk effect rather than a discrete threshold. Similarly, greater intratumoral immune area correlated with adverse DSS (HR per SD = 1.26; $p = 0.020$), supporting the interpretation of intratumoral immune accumulation as a marker of ineffective or dysfunctional immune infiltration rather than protective immunity. In a multivariable Cox model, immune dispersion, tumor boundary complexity, and intratumoral immune area retained concordant effect directions and jointly achieved strong discrimination (C-index ≈ 0.74). Correlation analysis confirmed that the dominant spatial features were non-redundant, with minimal multicollinearity (all variance inflation factors < 1.2). **Conclusions:** In TNBC, survival is not solely dependent on immune abundance and proximity to the tumor region, but on the immune spatial dispersion, aggressive tumor boundaries, and ineffective immune accumulation in the intratumoral space. Novel spatial biomarkers examined here may refine risk stratification beyond conventional metrics. Research Sponsor: MSK Cancer Center Support grant; P30 CA008748; Simons Foundation, and a Breast Cancer Research Foundation; BCRF-17-193.

Impact of protein–energy malnutrition on outcomes of metastatic triple-negative breast cancer patients receiving chemotherapy: A real-world analysis.

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Background: Protein–energy malnutrition (PEM) is common in patients with advanced cancer and is associated with increased toxicity, decreased treatment tolerance, and worse survival across malignancies. Data specific to metastatic triple-negative breast cancer (mTNBC), a biologically aggressive subtype, remain scarce. We evaluated the impact of PEM on outcomes in mTNBC patients receiving chemotherapy. **Methods:** We conducted a retrospective cohort study using de-identified data from TriNetX, a global federated health research network. Females with mTNBC on chemotherapy (paclitaxel, doxorubicin, capecitabine, eribulin, vinorelbine) were identified. PEM was defined using ICD-10 codes along with secondary definitions like BMI (<20). The primary endpoint was overall survival (OS), estimated using the Kaplan-Meier method. Propensity matching was used to adjust for age, race and comorbidities. Two sided $p \leq 0.05$ was used to determine statistical significance. **Results:** A total of 1,644 patients with mTNBC were identified, of whom 761(46.3%) patients had PEM. The mean age was higher in the PEM group compared to the non-PEM group (64.5 vs 63 years, $p < 0.05$). African American patients were more likely to have PEM (37.0% vs 31.4%, $p = 0.02$). After propensity score matching, 595 patients were included in each cohort for analysis. Patients with PEM had significantly worse 1-year OS compared to non-PEM group (65.7% vs 70.8%; HR 0.76, 95% CI 0.62–0.94, $p < 0.05$). At 2 years, survival remained numerically lower in the PEM group (56.2% vs 57.8%; HR 0.92, 95% CI 0.76–1.12), but the difference was not statistically significant. **Conclusions:** In this large real-world cohort of mTNBC, PEM was independently associated with worse 1-year overall survival. These findings underscore the prognostic significance of nutritional status in mTNBC and support routine nutritional assessment and early supportive interventions to improve outcomes in this high-risk population. Research Sponsor: None.

Overall survival (OS) outcomes in matched mTNBC cohorts.

Overall Survival	PEM Group (n=595)	Non-PEM Group (n=595)	Hazard Ratio (95% CI)	P-value
1-Year OS	65.7%	70.8%	0.76 (0.62–0.94)	<0.05
2-Year OS	56.2%	57.8%	0.92 (0.76–1.12)	0.41

Leveraging single-cell trajectory analysis and machine learning to build a robust prognostic classifier for triple-negative breast cancer to pinpoint CCDC171 as a master regulator.

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Background: Triple-negative breast cancer (TNBC) is limited by high heterogeneity and a lack of robust biomarkers for risk-stratified management. While chemotherapy is standard, traditional bulk signatures fail to capture high-resolution cellular transitions driving recurrence. This study integrates scRNA-seq with multi-algorithmic machine learning to identify key regulatory programs. We developed a trajectory-informed prognostic classifier to improve individual risk assessment and uncover potential therapeutic targets in the TNBC tumor microenvironment (TME). **Methods:** We performed single-cell RNA sequencing (scRNA-seq) on 24 TNBC samples to map the cellular landscape and applied pseudotime trajectory analysis to identify dynamic gene programs associated with cell-fate decisions. Prognostic genes derived from trajectory-informed differential expression were integrated with bulk RNA-seq data from TCGA-TNBC and validated in two independent cohorts (GSE58812, GSE135565). A robust prognostic model was constructed using an extensive machine-learning framework combining forward stepwise Cox regression and gradient boosting (Step-Cox[forward] + GBM). Model performance was evaluated using Harrell's C-index and Kaplan-Meier analysis, and predictive utility was assessed in neoadjuvant treatment cohorts. Virtual gene knockout experiments were used to analyze the function of CCDC171. **Results:** We developed an 18-gene prognostic signature that robustly stratified TNBC patients into high- and low-risk groups across multiple cohorts (TCGA: HR = 55.12, $p = 2.9 \times 10^{-12}$; GSE58812: HR = 3.96, $p = 6.3 \times 10^{-4}$; GSE135565: HR = 7.73, $p = 4.0 \times 10^{-3}$). The model outperformed existing prognostic signatures and generalized to non-TNBC breast cancer subtypes. Four genes (CRISP3, PDZK1IP1, CCDC171, IGFL1) were consistently retained across top-performing algorithms. CCDC171 emerged as a central regulator whose expression correlated with poor survival and coordinated a network involving complement activation (C1QB), metabolic reprogramming (CA8), and mitochondrial stress response (MTRNR2L8). In silico knockout of CCDC171 down-regulated these effectors and suppressed oncogenic pathways including PI3K-Akt signaling, ECM interaction, and platinum resistance. **Conclusions:** Our study presents a TNBC prognostic model grounded in TME cellular dynamics and machine learning, with superior predictive accuracy and cross-subtype applicability. CCDC171 is identified as a novel master regulator of a multi-effector network driving tumor aggressiveness, offering a potential therapeutic target. This integrative framework supports risk-stratified management and personalized therapy in breast cancer. Research Sponsor: None.

VISTA: Targeted combination immunotherapy for suppression of breast cancer metastasis and recurrence.

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Background: Triple-negative breast cancer (TNBC) has limited treatment options and poor outcomes, with ~12% 5-year overall survival in stage IV. In early-stage TNBC (II/III), recurrence remains substantial among patients without pathological complete response after chemo-immunotherapy. Current PD-1/PD-L1 inhibitors show limited efficacy in metastatic TNBC (median OS ~23 months) and infrequent durable responses. Novel immune targets are urgently needed to overcome resistance and prevent metastasis. V-domain Ig suppressor of T-cell activation (VISTA) is a next-generation checkpoint with distinct biology, enriched in tumor-infiltrating immune cells in TNBC. **Methods:** Comprehensive bioinformatic analyses of VSIR (VISTA) and ligands were performed across multi-cohort TNBC datasets spanning early and advanced stages, including pre-treatment, post-treatment, and progression samples. Spatial single-cell profiling of stage III TNBC tumors with recurrence versus non-recurrence was conducted using NanoString CosMx. VISTA expression in tumor tissue and circulating tumor cells (CTCs) was assessed by optimized immunofluorescence and digital pathology. Clinically relevant TNBC mouse models evaluated VISTA-mediated immune modulation alone and combined with chemo- or immunotherapy. **Results:** Single-cell bioinformatic analyses revealed enrichment of VSIR and ligands SELPLG/LGALS9 in post-treatment and progression-stage TNBC versus pre-treatment, observed in tumors and liquid biopsies. VSIR/SELPLG were enriched in progenitor and terminally exhausted immune subsets, whereas early-stage TNBC showed broader immune distribution. Digital pathology identified VISTA in metastasis-initiating tumor cells and dysfunctional immune cells, with induction following anti-PD-1 therapy in TNBC mouse models. Spatial profiling of recurrence-associated tumors showed co-enrichment of VSIR/SELPLG with inhibitory receptors TIM3, LAG3, and TIGIT across immune niches in recurrence-associated tumors. VISTA targeting with a novel antibody, HMBD-002, enhanced anti-tumor immunity, synergized with chemo- and immunotherapy, and suppressed recurrence and metastatic burden in preclinical models. **Conclusions:** VISTA is a treatment-emergent checkpoint associated with T-cell exhaustion, recurrence, and metastasis in TNBC. Its enrichment in exhausted T-cell niches, metastasis-initiating tumor cells, and CTCs post-chemo-immunotherapy supports its role in adaptive resistance. VISTA expression in tissue and liquid biopsy CTCs represents a clinically actionable biomarker for patient selection and response monitoring. These data provide strong rationale for early-phase clinical trials of combination VISTA blockade with ICIs in high-risk early-stage TNBC with residual disease and metastatic TNBC after prior ICI exposure. Research Sponsor: None.

Clinical and translational analysis of a phase Ib/II combination of atezolizumab, cobimetinib, and eribulin (ACE) to demonstrate inflammatory and metabolic programs define divergent response states.

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Background: Inflammatory breast cancer (IBC) is a rare, aggressive subtype with poor outcomes and limited immunotherapy data. Preclinical studies suggest MAPK inhibition enhances antitumor immunity and synergizes with checkpoint blockade. We report results from a phase Ib/II trial of atezolizumab (A), cobimetinib (C), and eribulin (E) in metastatic IBC with integrated molecular profiling. **Methods:** Patients (pts) with metastatic/recurrent IBC received ACE (cohort 1, n=17). Following cobimetinib supply discontinuation, an exploratory cohort received AE (cohort 2, n=10). Primary endpoint: objective response rate (ORR) per RECIST v1.1. Secondary endpoints: safety, progression-free survival (PFS), overall survival (OS), and correlative genomic, transcriptomic, spatial immune, and circulating tumor DNA (ctDNA) analyses. **Results:** ACE achieved ORR 50% (7/14; 3 patients were unevaluable for response), disease control rate (DCR) 71% (10/14), median PFS 3.7 months (mo), and median OS 10.6 mo, with 2 exceptional responders achieving >5-year survival. AE showed limited activity (ORR 10%, median OS 7.8 mo). No grade 4/5 toxicities occurred. Molecular profiling revealed distinct response states: responders demonstrated immune-activated, epithelial-like transcriptional programs with CD8+ T-cell infiltration; non-responders exhibited metabolically hyperactive, immune-excluded phenotypes with KRAS pathway activation, T-reg enrichment, CD8+ T-cell exclusion, VEGFA/GSDMB upregulation, and elevated ctDNA. **Conclusions:** ACE demonstrated encouraging activity in metastatic IBC with durable benefit in two pts. Resistance was associated with metabolic reprogramming and stromal immune exclusion, supporting rational development of metabolism-targeting, stroma-modifying, or T-reg/macrophage-directed combinations in this high-risk population. Clinical trial information: NCT03202316. Research Sponsor: None.

Sequence of similar-payload ADCs: Does it make sense in real-world HER2-low advanced breast cancer?—The Portuguese national study.

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Background: New-generation Antibody-Drug Conjugates (ADC) have expanded treatment options for HER2-low advanced breast cancer (ABC), regardless of hormone receptor (HR) status. Sacituzumab govitecan (SG) and trastuzumab deruxtecan (T-DXd) are used sequentially in clinical practice, but real-world data on efficacy, sequencing and potential cross-resistance are limited. We aimed to evaluate efficacy, sequencing patterns and predictors of outcome in a national real-world cohort of HER2-low ABC. **Methods:** We conducted a multicenter, retrospective real-world cohort study including patients with HER2-low ABC treated sequentially with SG and T-DXd, regardless of sequence, across 14 Portuguese centers. Eligible patients initiated the first ADC between 2023 and 2025 and received ≥ 1 cycle of both ADCs. The primary endpoint was progression-free survival (PFS), evaluated for the first (PFS1) and second ADC (PFS2). Secondary endpoints included objective response rate (ORR), primary resistance to the second ADC (PFS2 ≤ 3 months) and safety. PFS was analyzed using time-to-event methods. For exploratory analyses, PFS1 and PFS2 were dichotomized at the median and associations with longer PFS were assessed using chi-square tests. Predictors of PFS2 were explored in an exploratory multivariable Cox regression model. **Results:** Sixty-four patients were included; 36 (56%) had HR-positive disease and 28 (44%) were HR-negative. Median age at ADC1 initiation was 51 years (27–79). T-DXd was used as the first ADC (ADC1) in 34 (53%) patients and was more frequently administered as ADC1 in HR-positive disease. A total of 22 (34%) patients received ≥ 1 intermediate line, mainly chemotherapy (91%). Median PFS1 was 8.9 months (95% CI 5.8–9.7) and median PFS2 was 2.7 months (95% CI 2.1–3.2). PFS2 was consistently shorter than PFS1 across subgroups, independent of treatment line, with 43 (70%) patients presenting primary resistance to the second ADC. ORR to ADC2 was 3%. No significant differences in PFS1 or PFS2 were observed by ADC sequencing. Longer PFS1 was not associated with improved PFS2 ($p=0.44$). In the multivariable model, none of the evaluated variables, including the use of ≥ 1 intermediate line between ADCs, were significantly associated with longer PFS2 (all $p>0.05$). No new safety signals were observed; rates of dose reductions and interruptions were consistent with known safety profiles of SG and T-DXd. **Conclusions:** In this national real-world cohort of HER2-low ABC, clinical benefit from a second ADC was limited, with shorter PFS and frequent early progression, irrespective of sequencing order. Importantly, no baseline clinical factors predicted PFS2. These findings may suggest clinically relevant cross-resistance between ADCs with similar payloads and highlight shared resistance mechanisms as a key challenge in optimizing ADC sequencing. Research Sponsor: None.

Clinical impact and temporal evolution of mutational signatures in metastatic lobular breast cancer.

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Background: Invasive lobular carcinoma (ILC) has distinct genomic features, including frequent *CDH1* alterations, yet the mutational processes shaping metastatic ILC and their prognostic significance remain poorly defined. We evaluated mutational signatures inferred from targeted sequencing in a large single-center cohort of metastatic ILC and their association with outcomes. **Methods:** Patients were included if they had ILC histology on early-stage breast biopsy/surgical pathology, and/or *CDH1* mutation on metastatic site biopsy and MSK-IMPACT sequencing from a metastatic site. For survival analyses, only biopsies performed within 2 months of metastatic diagnosis were included. Clinicopathologic data were abstracted from electronic medical records. Single base substitution (SBS) signatures were inferred using SigMA; cases with ≤ 5 SBS were excluded. Overall survival (OS) was estimated using Kaplan–Meier and compared by dominant signature using the log-rank test. **Results:** 654 patients were included. 467 (71%) had hormone receptor-positive (HR+)/HER2-, 56 (8.6%) had HER2+, and 65 (9.9%) had triple negative disease at metastatic diagnosis. Among 307 (47%) with ILC variant data available, 139 (45%) had classic type, 65 (21%) had pleomorphic, 45 (15%) had mixed, and 58 (19%) had other ILC variants. 385 patients (59%) had MSK-IMPACT testing on a tissue biopsy performed within 2 months of metastatic diagnosis. Among them, the most prevalent mutations included *CDH1* (85%), *PIK3CA* (47%), *TP53* (21%), *TBX3* (16%), *PTEN/AKT1* (14.5%), *FOXA1* (12%), *ERBB2* (12%), *KMT2C* (9.9%), *CBFB* (9.9%), *ARID1A* (9.6%), *MAP3K1* (8.8%), and *NF1* (7.5%). 320/385 (83%) MSK-IMPACT tests had ≥ 5 SBS and were analyzable for mutational signature. The dominant mutational signature was APOBEC in 44%, clock-like (aging) in 38%, Signature 3 (homologous recombination deficiency) in 12%, Signature 17 in 5.6%, and Signature 8 in 1%. Median OS in the total cohort was 4.4 years (95%CI 4.1–4.8) and differed significantly by dominant mutational signature (log-rank $p=0.001$). Median OS for those with APOBEC-dominant disease was 3.1 years (95%CI 2.5–3.7) and for those with clock-like (aging) signature was 4.4 years (95%CI 3.8–6.5). Among 61 patients who had paired samples analyzable for mutational signature within 2 months of metastatic diagnosis and at another timepoint following metastatic diagnosis, the prevalence of APOBEC as the dominant mutational signature increased (29/61 [48%] to 36/61 [59%]), whereas clock-like (aging) decreased (25/61 [41%] to 17/61 [28%]). **Conclusions:** Dominant APOBEC mutational signature at metastatic ILC diagnosis was associated with shorter OS, with differences observed between APOBEC- and aging-dominant tumors. Serial testing demonstrating increasing APOBEC dominance over time supports mutational signatures as dynamic, clinically relevant features of metastatic ILC. Research Sponsor: Lisa Bonchek Adams Memorial Fund.

Phase II study of olaparib plus ATR inhibitor ceralasertib in patients with metastatic breast cancer and germline BRCA1/2 pathogenic variants who progressed on prior PARP inhibitor therapy.

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Background: PARP inhibitors (PARPi) olaparib and talazoparib improve objective response rate (ORR) and disease-free survival (DFS) compared with chemotherapy in patients with metastatic breast cancer and germline BRCA 1/2 pathogenic variants (gBRCA 1/2 PVs). Although the ORR is approximately 60%, about 40% of patients do not respond, and nearly all responders eventually develop progressive disease. Therefore, new strategies to overcome PARPi resistance are needed. Preclinical studies suggest that ATR inhibition combined with olaparib may restore PARPi sensitivity. Phase I studies have shown that olaparib (Ola) plus the ATR inhibitor ceralasertib (Cerala) is safe and have established the recommended phase II dose. This prospective phase II study evaluated the ORR of Ola plus Cerala in patients with metastatic breast cancer with gBRCA 1/2 PVs who previously progressed on PARPi therapy. **Methods:** Eligible patients had metastatic breast cancer (HER2- negative), prior PARPi exposure, and no more than two prior lines of chemotherapy. After informed consent, all patients underwent the baseline research biopsy of a metastatic lesion and provided blood samples for exploratory analysis aimed at identifying mechanisms of PARPi resistance. Treatment consisted of olaparib 150 mg orally twice daily on days 1–28 plus ceralasertib 80 mg orally twice daily on days 1–14 of each 28-day cycle. The primary endpoint was ORR per RECIST 1.1. Secondary endpoints included safety, DFS, and duration of response. Exploratory endpoints focused on biomarker analysis of PARPi resistance. This abstract reports the primary end point. **Results:** Fifteen patients were enrolled. The median age was 39 years. Eight patients had hormone receptor-positive disease; 6 of these had received endocrine therapy before first-line PARPi. Two patients achieved a partial response (PR) and two had stable disease (SD), resulting in an ORR of 13.3% and a clinical benefit rate of 26.7%. No grade 4 toxicities were observed. Grade 3 adverse events included anemia (N=5), neutropenia (N=1), decreased white blood cell count (N=1), lymphopenia (N=1), and thrombocytopenia (N=1). **Conclusions:** The combination of olaparib plus ceralasertib is well tolerated and demonstrates clinical activity in patients with metastatic breast cancer with gBRCA 1/2 PVs who have progressed on prior PARPi therapy. A study of this combination in the first-line setting may help determine whether ATR inhibition can overcome or delay PARPi resistance. Biomarker analysis to identify mechanisms of resistance are ongoing and will be reported separately. Clinical trial information: NCT04090567. Research Sponsor: CPRIT; Astra Zeneca.

A phase II study evaluating treatment discontinuation of dual anti-HER2 therapy in metastatic HER2-positive breast cancer after five years of sustained complete response (FREEDOME-trial).

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Background: Dual anti-HER2 therapy with trastuzumab (T) and pertuzumab (P) has transformed outcomes in HER2-positive metastatic breast cancer (mBC), with approximately 20% of patients maintaining response beyond 8 years based on CLEOPATRA trial data. Current practice continues anti-HER2 therapy indefinitely in responding patients, despite lack of evidence supporting necessity of lifelong treatment in long-term responders. This approach is associated with cumulative financial burden, and quality of life impact from indefinite therapy requirements. No prospective data exist regarding optimal duration of anti-HER2 therapy in long-term responders, nor are there validated biomarkers to guide treatment discontinuation decisions. Minimal residual disease (MRD) assessment has shown promise in other malignancies for identifying patients at low risk of recurrence. This study addresses an unmet need for evidence on safety of treatment discontinuation in long-term responders.

Methods: This prospective, multicenter, single-arm phase II trial enrolls patients with HER2-positive mBC who have maintained CR for ≥ 5 years on dual anti-HER2 therapy (T plus P). Target enrollment is 40 patients based on Fleming's single-stage design to detect median progression-free survival (mPFS) >12 months with 80% power ($\alpha=0.05$). Key eligibility criteria include: confirmed HER2-positive mBC, sustained CR by RECIST 1.1 for ≥ 5 years, normal tumor markers (CA125, CEA, CA15-3), and no evidence of progression on baseline PET-CT. Patients with concurrent malignancies requiring systemic therapy are excluded. Following enrollment, participants discontinue T+P therapy but should continue endocrine therapy (if given). Surveillance includes PET-CT at baseline, 3, 6, 12 months, then annually; annual mammography/ultrasound per institutional standards; and blood collection for tumor markers at baseline, 3, 6, 12 months, then annually. Patients resuming anti-HER2 therapy upon progression remain on study for survival assessment. Primary endpoint is mPFS post-discontinuation. Secondary endpoints include 6-month PFS, 12-month PFS, and median overall survival. Exploratory analyses examine tumor markers as predictive biomarkers. Kaplan-Meier methodology will estimate survival probabilities with 95% confidence intervals. As of January 2026, one site is open for recruitment. Minimal residual disease analysis is planned and will be submitted to the IRB committee for approval. Study completion is anticipated by 2031 with interim analysis planned after 2 years. Clinical trial information: MOH_2025-12-27_015564. Research Sponsor: None.

A phase 1b/2 study of QLS1304, a novel, highly potent, and selective dual inhibitor of KAT6A/6B, plus endocrine therapy (ET) in patients (pts) with estrogen receptor–positive (ER+), human epidermal growth factor receptor 2–negative (HER2–) breast cancer (BC).

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Background: QLS1304 is a novel, highly-potent, and selective dual inhibitor of KAT6A/6B. KAT6A acetylates histone H3 at the 23rd lysine residue, thereby modulating gene transcription, and implicated in ER+/HER2– BC. QLS1304 showed potent efficacy in standard of care resistant, KAT6A-high and *ESR1*-mutant ER+/HER2– BC patient-derived xenograft model, whether administered as a monotherapy or combination therapy (*Cancer Res (2025) 85 (8_Supplement_1): 457*). In the ongoing phase 1 trial, QLS1304 monotherapy showed an acceptable safety profile and potential anti-tumor activity in pts with BC. This study aimed to evaluate the safety and preliminary efficacy of QLS1304 + ET combination (fulvestrant or QLC1401, a novel oral selective ER degrader) ± CDK4/6 inhibitor (CDK4/6i) in pts with ER+/HER2– locally advanced or metastatic (LA/M) BC. **Methods:** This multicenter, open-label, phase 1b/2 trial consists of phase 1b combination dose-escalation and phase 2 dose-expansion. The phase 1b study will enroll pts with LA/M ER+/HER2– BC, who have received prior ET plus CDK4/6i, utilizing the Rolling-Six design. There are 2 cohorts: Cohort 1A QLS1304 + fulvestrant and Cohort 1B QLS1304 + QLC1401. Three dose levels of QLS1304 are planned, which are 4 mg/d, 8 mg/d, and 12 mg/d. The dose of QLC1401 is 150 mg, which is the recommended phase 2 dose (RP2D) of monotherapy. Both QLS1304 and QLC1401 are orally administered in a 28-day cycle. A total of 12~18 pts per cohort are planned to be enrolled, which might be adjusted based on the occurrence of dose-limiting toxicities (DLTs) during the first cycle. The primary endpoints are safety, tolerability, and RP2D of QLS1304 combined with fulvestrant/QLC1401. In phase 2, 1~2 dose levels of QLS1304 will be explored in 5 cohorts. In Cohort 2A (QLS1304 + fulvestrant) and Cohort 2B (QLS1304 + QLC1401), pts with LA/M ER+/HER2– BC who received prior ET plus CDK4/6i will be enrolled. In Cohort 2C (QLS1304 + CDK4/6i + letrozole), pts with LA/M ER+/HER2– BC with no prior therapy will be enrolled. In Cohort 2D (QLS1304 + CDK4/6i + fulvestrant), adjuvant ET-resistant or ET+CDK4/6i pretreated LA/M ER+/HER2– BC pts will be enrolled in 2 subgroups. In Cohort 2E (QLS1304 + CDK4/6i + QLC1401), adjuvant ET-resistant, treatment naïve, or ET+CDK4/6i pretreated LA/M ER+/HER2– BC pts will be enrolled in 3 subgroups. Doublet combination will be firstly explored, which will support the dose selection of triplet combination. In triplet cohorts 2C–2E, 6 pts will be enrolled in a safety run-in to assess the preliminary safety profile in each cohort. Expansion will be started after safety confirmation. A total of 316~366 pts will be enrolled. The primary endpoint of phase 2 is ORR per RECIST v1.1. Patient enrollment is currently ongoing. Clinical trial information: NCT07235176. Research Sponsor: Qilu Pharmaceutical Co. Ltd.

TUC-TOC phase II trial (NCT05955170): Tucatinib in combination with oral etoposide (VP16) and trastuzumab in patients with metastatic HER2-positive breast cancer (HER2+ mBC).

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Background: Patients with HER2-positive metastatic breast cancer (HER2+ MBC) have limited therapeutic options after progression on tucatinib–trastuzumab–capecitabine. There is a need for later-line regimens combining chemotherapy with dual HER2 targeting. TUC-TOC was designed to evaluate the efficacy and safety of tucatinib combined with oral etoposide (VP16) and trastuzumab in this setting. Oral VP16 was selected because (i) topoisomerase II inhibitors are rarely used in HER2+ MBC, (ii) TOP2A and ERBB2 are frequently co-amplified, and (iii) it enables an almost all-oral regimen. A prior retrospective analysis suggested favorable activity and tolerability of VP16 plus trastuzumab in heavily pretreated HER2+ MBC (PMID: 35565244).

Methods: TUC-TOC (NCT05955170) is an open-label, multicenter, academic phase II trial. Eligible patients have histologically-confirmed HER2+ MBC with disease progression on tucatinib–trastuzumab–capecitabine or a contraindication to capecitabine, measurable disease per RECIST v1.1, and adequate cardiac function. Patients with brain metastases are eligible unless urgent local treatment is required. The study includes a safety run-in followed by an expansion phase. In the safety run-in, six patients received oral VP16 50 mg/d on days 1–14 of a 3w cycle, tucatinib 300 mg PO BID, and trastuzumab 600 mg SC q3w. The primary endpoint of this phase was the rate of dose-limiting toxicities (DLTs). The primary endpoint of the expansion phase is the objective response rate (ORR), defined as the best overall response within 24 weeks according to RECIST v1.1. Secondary endpoints include PFS, OS and safety. A total of 55 evaluable patients is planned. As of 01.2026, the safety run-in phase has been completed and enrollment into the expansion phase is ongoing. Clinical trial information: NCT05955170. Research Sponsor: pfizer; Women's Cancer Institute of Institut Curie.

HER2-positive central nervous system (CNS) surveillance: A study of the feasibility of randomizing women and men with HER2-positive metastatic breast cancer to CNS surveillance versus no surveillance.

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Background: Breast cancer (BC) is the second most common primary tumour to metastasise to the brain (Aragon-Ching, 2017). Clinical data have demonstrated that BC brain metastases (BCBM) are an increasing clinical problem (Akshara, 2024). Improved systemic treatment of extracranial disease has prolonged survival (DESTINY-Breast9, 2025); coupled with more CNS imaging, this likely contributes to rising BCBM incidence (Frisk, 2012; Pedrosa, 2018). HER2+ BC has a predilection for the CNS (Sun, 2022), and real-world data from the ESMÉ programme report BCBM incidence in metastatic BC (MBC) (Darlix, 2019). Cumulative incidence at 12 months after MBC diagnosis in a cohort of 16,703 MBC pts was 16.8% and 32.4% for HER2+ /HR+ and HER2+ /HR- respectively; at 24 months, 29.2% and 49.0%, respectively. Given the high risk of CNS disease in HER2+ MBC, associated morbidity/mortality (Riecke, 2023) and the evidence that there may be a survival and quality of life advantage for early asymptomatic detection (Hurvitz, 2019; Laakmann, 2020), surveillance strategies for early detection need evaluation. **Methods:** This is a multi-centre, randomised study in pts with HER2+ MBC without prior CNS disease. The study is testing the feasibility of randomising pts to CNS screening vs none. The study is recruiting male/female pts, aged ≥ 16 years with HER2+ BC with visceral metastases who are currently on HER2 directed therapies. It excludes pts with a history/clinical symptoms of CNS disease, unable to undergo MRI, or with bone only MBC. Pts following a baseline MRI brain, to exclude occult disease, are randomised 1:1 to 6 monthly MRI brain with contrast for a year or no CNS imaging. Primary endpoint: feasibility of randomising HER2+ MBC pts with no CNS disease to surveillance vs no surveillance. Secondary endpoints: proportion of pts with occult CNS disease at baseline, proportion developing occult CNS disease during surveillance and proportion developing symptomatic CNS disease during the study. The management of detected CNS disease on study will be documented. Further qualitative research through a series of interviews/focus group discussions will explore reasons why pts either agree/refuse randomization, to identify challenges with study implementation and delivery. **Statistics:** A maximum of 193 pts are to be approached; with 69 pts agreeing to be consented to the study for a larger study to be deemed feasible (based on $\alpha=5\%$ and power 90%). Recruitment will halt at 69 consented/193 approached, whichever is reached first. REC/IRAS project ID: 341272. Research Sponsor: Make 2nd Count; Pfizer; Breast Cancer Ireland; NIHR-BRC research fellowship (for T.B); Clatterbridge Cancer Centre Charity (for T.B); The Grace Trust (for T.B).

A single-arm, phase II study of sequential therapy with curative intent in de novo HER2+ metastatic breast cancer: The SAPPHO study.

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Background: Due to dramatic improvements in neoadjuvant and adjuvant HER2-directed therapy (tx), most patients (pts) with early HER2+ breast cancer are cured. As a result, over half of pts newly diagnosed with HER2+ metastatic breast cancer (MBC) now present with *de novo* stage IV disease. Anti-HER2 tx has also significantly extended survival for pts with HER2+ MBC, with a subgroup of exceptional responders alive many years (yrs) after diagnosis. However, the paradigm for HER2+ MBC remains non-curative, and pts receive tx indefinitely with significant toxicities and costs. The SAPPHO study is investigating whether an intensification approach of sequential, non-cross resistant anti-HER2 tx followed by tx discontinuation is associated with long-term disease control in pts with HER2+ MBC. **Methods:** SAPPHO is an open-label, phase II, single-arm trial testing a sequential regimen of non-cross resistant, HER2-targeted tx with curative intent in pts with *de novo* HER2+ MBC. Eligible pts must have biopsy-proven, *de novo* MBC with high HER2 expression (3+ by immunohistochemistry). Pts with brain metastases are eligible upon receipt of local tx. Treatment consists of an induction regimen (trastuzumab-pertuzumab-taxane [THP] x 4 cycles, followed by trastuzumab deruxtecan [TDXd] x 6 cycles, followed by trastuzumab emtansine [TDM1]-tucatinib x 4 cycles), followed by a maintenance regimen (HP-tucatinib for 1 yr). Given results from DESTINY-Breast09, the sequence of TDXd-P x 6 cycles followed by THP x 4 followed by TDM1-tucatinib x 4 can be chosen as alternative induction tx per investigator and patient choice. Pts who remain progression-free after completing maintenance will stop all anti-HER2 tx. Endocrine tx will be continued for pts with hormone receptor+/HER2+ tumors. Tumor specimens from breast and a metastatic site are collected at baseline and the end of induction. Serial plasma samples for ctDNA analysis are collected at baseline, during treatment, and during follow-up. The primary endpoint is the probability of being progression-free and off anti-HER2 tx 4 yrs from the start of induction. With a sample size of 72 pts, the study is designed to have 91% power to reject the null hypothesis that the probability of being off anti-HER2 tx and progression-free is less than 24%, with an alternative hypothesis of 40%. Key secondary endpoints are overall survival, overall response rate by modified RECIST 1.1 after induction, and safety. Correlative endpoints include the relationship between ctDNA dynamics and outcomes. Patient-reported outcomes will be analyzed, including quality of life, illness intrusiveness, financial toxicity, anxiety, distress about cancer progression, perception of benefit and risk of progression. SAPPHO began enrollment in Q3 2024, and the study is open at 4 US sites within the Translational Breast Cancer Research Consortium (NCT05721248). Clinical trial information: NCT05721248. Research Sponsor: Pfizer.

ReDiscover-2, a phase 3 study of zovegalisib (zovega, RLY-2608) + fulvestrant (fulv) versus capivasertib (capi) + fulv as treatment for locally advanced or metastatic *PIK3CA*-mutant HR+/ HER2- breast cancer following recurrence or progression on or after treatment with a CDK4/6 inhibitor.

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Background: *PIK3CA* mutations constitutively activate PI3K α and drive ~40% of HR+/HER2- breast cancer (BC). The PI3K inhibitors alpelisib and inavolisib and the AKT inhibitor capi are approved therapeutic options; however, they are limited by significant toxicity, notably hyperglycemia, rash, and diarrhea, due to non-selective targeting of the pathway. Zovega is a pan-mutant-selective allosteric PI3K α inhibitor designed to optimize dose intensity and target inhibition with reduced toxicity and improved tolerability. The first-in-human ReDiscover study of zovega demonstrated encouraging antitumor activity with a median progression-free survival (PFS) of 10.3 mo (95% CI: 7.2, 18.4) across a range of *PIK3CA* genotypes and a favorable safety profile when combined with fulv in patients with *PIK3CA*-mutated HR+/HER2- advanced BC previously treated with a CDK4/6 inhibitor. Based on these findings, zovega in combination with fulv is being studied in this phase 3 study, ReDiscover-2 (NCT06982521), in *PIK3CA*-mutated HR+/HER2- advanced BC following recurrence or progression on or after a CDK4/6 inhibitor. **Methods:** ReDiscover-2 is a global, multicenter, open-label, randomized phase 3 study comparing the efficacy and safety of zovega + fulv to capi + fulv in patients with *PIK3CA*-mutated HR+/HER2- advanced BC. Approximately 540 patients will be randomized 1:1 to receive zovega (400 mg BID with food) + standard-dose fulv or capi (400 mg BID, 4 days on and 3 days off, with or without food) + fulv. Randomization will be stratified by *PIK3CA* mutation type, visceral disease, and geographic region. The primary endpoint is PFS assessed by blinded independent central review in patients having tumors with *PIK3CA* kinase domain mutations and in all patients. Overall survival is a key secondary endpoint within the same populations. Key eligibility criteria: ≥ 18 years of age with ECOG performance status of 0-1; confirmed diagnosis of HR+/HER2- locally advanced or metastatic BC with radiological or objective evidence of recurrence or progression; presence of one or more oncogenic *PIK3CA* mutations without evidence of *AKT* or *PTEN* alterations; measurable disease per RECIST v1.1 or evaluable bone-only disease; previous treatment for HR+/HER2- advanced BC with at least 1 and no more than 2 lines of endocrine therapy (ET) (prior fulv is allowed) or 1 prior line of CDK4/6 inhibitor therapy; HbA1c $< 7.0\%$ (< 53 mmol/mol) and fasting plasma glucose < 140 mg/dL (Type 1 diabetes or Type 2 diabetes requiring antihyperglycemic medication are excluded); no prior PI3K, AKT, or mTOR inhibitors. ReDiscover-2 (NCT06982521) is open for enrollment. For information: clinicaltrials@relaytx.com. Clinical trial information: NCT06982521. Research Sponsor: Relay Therapeutics.

HERTHENA-Breast04: A phase 3, randomized, open-label study evaluating the efficacy and safety of patritumab deruxtecan (HER3-DXd) versus treatment of physician's choice in hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) unresectable locally advanced or metastatic breast cancer.

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Background: There is an unmet therapeutic need for patients with HR+/HER2– metastatic breast cancer who experience disease progression and recurrence after first-line standard of care treatment with a CDK4/6 inhibitor (CDK4/6i) and endocrine therapy (ET). The main therapy options, for those patients who are not considered suitable for additional ET-based therapy, are chemotherapy and antibody–drug conjugates (ADCs). Human epidermal growth factor receptor 3 (HER3) is overexpressed in HR+/HER2– breast cancer and is associated with poor prognosis and drug resistance. Patritumab deruxtecan (HER3-DXd) is a novel ADC composed of a fully human anti-HER3 IgG1 antibody linked to a cytotoxic topoisomerase I inhibitor via a stable tetrapeptide–based linker that is selectively cleaved within tumor cells. In the phase 2 ICARUS-Breast01 study, HER3-DXd showed clinically meaningful antitumor activity and manageable safety in patients with HR+/HER2– advanced breast cancer who progressed on CDK4/6i treatment and 1 line of chemotherapy. The phase 3, multicenter, open-label, HERTHENA-Breast04 study (NCT07060807) evaluates efficacy and safety of HER3-DXd monotherapy vs treatment of physician's choice (TPC) in participants with HR+/HER2– advanced breast cancer after progression on 1 line of CDK 4/6i treatment. **Methods:** Participants must be aged ≥ 18 y and have centrally confirmed HR+/HER2– (per most recent ASCO/CAP guidelines: HER2 IHC 0 or 1+ or IHC 2+/in situ hybridization negative) unresectable locally advanced or metastatic breast cancer. Participants must have experienced disease progression or recurrence following prior treatment with a CDK4/6i and ET and must be eligible for at least 1 TPC option, as determined by the investigator. Participants must have measurable disease per RECIST v1.1 and ECOG PS of 0 or 1. Participants who have received prior chemotherapy or are candidates for an additional line of ET-based therapy in the advanced setting are ineligible for the study. Participants are randomized 1:1 to Arm 1 or 2, with ~500 participants assigned to each arm. Participants in Arm 1 will receive HER3-DXd 5.6 mg/kg IV on day 1 Q3W, and participants in Arm 2 will receive TPC consisting of 1 of the following options: paclitaxel, nab-paclitaxel, capecitabine, liposomal doxorubicin, or trastuzumab deruxtecan. Treatment will continue until disease progression, unacceptable toxicity, or participant withdrawal. The dual primary endpoints are PFS per RECIST v1.1 by BICR and OS. Secondary endpoints are ORR and DOR per RECIST v1.1 by BICR, safety, and patient-reported outcomes. Imaging assessments occur Q6W from randomization through week 60 and Q12W thereafter. Enrollment began in 2025. Clinical trial information: NCT07060807. Research Sponsor: Daiichi Sankyo Company, Limited and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Camizestrant plus ribociclib in hormone receptor–positive/HER2-negative advanced breast cancer: The phase II CADILLAC trial.

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Background: CDK4/6 inhibitors combined with endocrine therapy (ET) are the standard first-line treatment for hormone receptor–positive (HR+)/HER2–negative (HER2–) advanced breast cancer (ABC). Secondary endocrine resistance includes patients (pts) relapsing after ≥ 2 years of adjuvant ET during treatment or within 12 months of discontinuation but does not distinguish according to adjuvant ET duration; thus, whether HR+ tumors progressing after prolonged adjuvant ET (≥ 5 years) constitute a biologically and prognostically distinct entity remains unclear. Next-generation oral selective estrogen receptor degraders (SERDs) provide more potent estrogen receptor (ER) degradation and have demonstrated superiority over standard ET in pts with previously treated endocrine-resistant ABC. We hypothesized that camizestrant plus ribociclib as first-line therapy may improve outcomes versus historical ribociclib plus aromatase inhibitor (AI) or fulvestrant in HR+/HER2– ABC relapsing after long-term adjuvant ET. **Methods:** CADILLAC (NCT07195227) is an international, multicenter, open-label, single-arm, external historical-controlled phase II trial. A total of 150 pts with HR+/HER2– ABC who have not received systemic treatment for advanced disease will be enrolled from Spain, Germany, and China. Key eligibility criteria include: (a) ≥ 18 years; (b) histologically confirmed unresectable locally recurrent or metastatic breast cancer; (c) evaluable disease as per RECIST v1.1; (d) prior adjuvant ET duration ≥ 5 years, including ≥ 2 of AI (with a cap of 30% pts with an ET-free interval ≥ 12 months); and (e) ECOG performance status 0–1. Pts will receive camizestrant 75 mg orally once daily continuously in 28-day cycles, combined with ribociclib 600 mg orally once daily on days 1–21 of each 28-day cycle, until unacceptable toxicity, disease progression, death, or discontinuation for other reasons, whichever occurs first. The primary endpoint is progression-free survival (PFS). Key secondary endpoints include overall response rate (ORR), clinical benefit rate (CBR), quality of life assessed by EORTC QLQ-C30 and QLQ-BR42 questionnaires, and safety according to NCI-CTCAE v5.0. PFS, ORR, and CBR will be locally assessed by investigators per RECIST v1.1 and compared with outcomes from a historical control cohort of at least 150 pts treated with ribociclib plus AI or fulvestrant. The null hypothesis is defined as a median PFS ≤ 20.3 months, whereas the alternative hypothesis corresponds to a median PFS ≥ 28.7 (target hazard ratio 0.707). The primary hypothesis will be tested using a stratified log-rank test at one-sided 5% significance level with 70% power. An effective total of 157 PFS events across arms is required. Interim efficacy and safety analyses are planned once the first 50 pts have completed ≥ 6 months of treatment. Enrollment will not be paused during this interim analysis. Clinical trial information: NCT07195227. Research Sponsor: AstraZeneca; Novartis.

A phase 1/2 study of EP0062 (vosilasarm), a first-in-class oral selective androgen receptor modulator (SARM), in combination with standard-of-care endocrine therapy +/- targeted therapies in patients with advanced or metastatic AR+/ER+/HER2— breast cancer.

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Background: EP0062 (vosilasarm), a first-in-class, oral, non-steroidal, Selective Androgen Receptor Modulator (SARM) acts as a potent tissue-selective AR agonist, suppressing growth and proliferation of multiple endocrine-sensitive or -resistant AR+/ER+/HER2- breast cancer (BC) cell lines and patient-derived xenograft (PDX) models. Pre-clinically, AR activation—rather than AR suppression—exerts potent antitumor activity in AR+/ER+ breast malignancies, including those resistant to endocrine therapy and CDK4/6 inhibitors. EP0062 has been shown to inhibit the growth of AR+/ER+ BC PDX models as a single agent, and in combination with palbociclib, everolimus or elacestrant. Phase 1 of this study reported promising safety and evidence of clinical benefit with EP0062 monotherapy in advanced AR+/ER+/HER2- BC. The ongoing Phase 2 cohorts described here are the first clinical evaluation of a SARM in combination with various standard of care therapies in patients that have previously received a CDK4/6 inhibitor. **Methods:** The Phase 2 cohorts will include up to 75 post-menopausal women, ≥ 18 years, ECOG ≤ 1 , with locally advanced/metastatic, endocrine-sensitive (> 2 y adjuvant or > 6 mo treatment prior to recurrence), AR+/ER+/HER2- BC, that is measurable per RECIST v1.1, or non-measurable with an evaluable bone component. AR positivity is defined as $\geq 10\%$ AR nuclei staining by IHC. Patients may have previously received ≤ 2 lines of endocrine therapy (including CDK4/6 inhibitor), and ≤ 1 line of chemotherapy in the advanced/metastatic setting. Treatment arms are as follows: Arm 1: EP0062 + elacestrant (mandatory ESR1 mutation); Arm 2: EP0062 + exemestane + everolimus; Arm 3: EP0062 + fulvestrant + abemaciclib. A 3+3 safety run-in will confirm the combination dose for each cohort before expansion. Starting EP0062 dose was 10 mg BID. The primary objective is to evaluate safety and tolerability. Secondary objectives are to characterise the PK profile and preliminary efficacy. Biomarkers, including CA15-3, PSA, and molecular genetics are also being evaluated. Exploratory objectives are to evaluate potential biomarkers of efficacy, safety and/or PD activity. The study is currently recruiting across the three treatment arms in USA, UK, and Spain. Clinical trial information: NCT05573126. Research Sponsor: None.

OPERA-02: A phase 3 study of palazestrant plus ribociclib as first-line treatment of ER+, HER2- advanced breast cancer.

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Background: Estrogen receptor-positive, human epidermal growth factor 2-negative advanced breast cancer (ER+, HER2- ABC) accounts for nearly 70% of all ABC. The standard first-line treatment for ER+, HER2- ABC is the combination of an aromatase inhibitor (AI) with cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). When combined with AI, the CDK4/6i ribociclib has demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS) in this setting. Despite these advances, resistance to AI + CDK4/6i develops in a substantial proportion of patients (pts), most commonly driven by acquired mutations in the ligand-binding domain of ER α , resulting in constitutive ligand-independent ER activation. Early and sustained suppression of both wild-type and mutated ERs in the first line treatment of ER+, HER2- ABC may enhance endocrine sensitivity, delay resistance to endocrine therapy and improve clinical outcomes. Palazestrant (OP-1250) is an investigational oral, complete estrogen receptor antagonist (CERAN) and selective estrogen receptor degrader (SERD). In early phase studies, palazestrant has shown favorable safety and encouraging antitumor activity as monotherapy (Hamilton et al, 2025) and in combination with ribociclib (Lin et al, 2025), regardless of ESR1 mutation status, including in those previously treated with CDK4/6i. Palazestrant showed no clinically meaningful drug-drug interactions with ribociclib, and the combination safety profile was consistent with the known profiles of each drug. **Methods:** OPERA-02 (NCT07085767) is a phase 3, international, multicenter, randomized, double-blind, study designed to evaluate the efficacy and safety of palazestrant plus ribociclib versus letrozole plus ribociclib in the first line treatment of pts with ER+, HER2- ABC. Approximately 1,000 pts will be randomized 1:1 to either palazestrant plus ribociclib or letrozole plus ribociclib, with matching placebos. The primary endpoint is investigator-assessed PFS; secondary endpoints are OS, PFS by a blinded-independent review committee, overall response rate, duration of response, clinical benefit rate, safety, pharmacokinetics, pt-reported outcomes and PFS2. Eligible pts are adult women, regardless of menopausal status, and men, with de novo or recurrent disease (≥ 12 months after completion of adjuvant endocrine therapy) who have not received prior systemic therapy for ER+, HER2- ABC. Pts must have measurable disease per RECIST 1.1 or evaluable bone disease, ECOG performance score of 0-1, and adequate organ function. Pts with a contraindication to ribociclib are excluded. Pre- or perimenopausal women and men must receive gonadotropin-releasing hormone (GnRH) agonists for gonadal function suppression. The study has been recruiting globally since November 2025. Clinical trial information: NCT07085767. Research Sponsor: None.

ELEGANT: Elacestrant versus standard endocrine therapy (ET) in women and men with node-positive, estrogen receptor-positive (ER+), HER2-negative (HER2-), early breast cancer (eBC) with high risk of recurrence in a global, multicenter, randomized, open-label phase 3 study.

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Background: Adjuvant ET is the standard of care (SOC) for treating ER+/HER2- eBC. Despite advances to optimize adjuvant treatment in high-risk ER+/HER2- eBC, there continues to be risk of local and metastatic recurrence that persists, new therapies with desirable safety profiles are warranted. Elacestrant is a next-generation oral SERD that provides a novel mechanism of action that has shown both SERD (degradative) and SERM (partial agonist) activity that differs from currently available adjuvant ET (Wardell, ERC 2015). In the EMERALD trial, elacestrant significantly prolonged PFS vs SOC ET in the overall population (HR 0.70; 95% CI 0.55–0.88; P=0.0018) and in patients with *ESR1m* tumors (HR 0.55; 95% CI 0.39–0.77; P=0.0005) (Bidard, JCO 2022). In patients with *ESR1m* tumors who received prior ET+CDK4/6i ≥ 12 mo, mPFS with elacestrant was 8.6 vs 1.9 mo with SOC ET (Bardia, CCR 2024). In patients with ER+/HER2- eBC, the SOLTI-1905-ELIPSE and SOLTI-2104-PremiERE trials showed that preoperative elacestrant was associated with a statistically significant mean change of complete cell cycle arrest rate and led to a shift in tumor biology towards a more endocrine-sensitive and less proliferative tumor phenotype in both pre- and post-menopausal women (Vidal, CCR 2025; Bellet, SABCS 2025). Given that elacestrant demonstrated efficacy in mBC regardless of *ESR1m* status relative to SOC ET and has shown biologic activity in eBC, it is hypothesized that elacestrant can prolong invasive breast cancer-free survival (IBCFS) in patients with high-risk eBC who received prior adjuvant ET $\pm$ CDK4/6i. **Methods:** ELEGANT (NCT06492616) is a global, multicenter, open-label Ph3 study designed to evaluate elacestrant vs SOC ET (AI or tamoxifen) in patients with eBC and high risk of recurrence. Patients will be randomized 1:1 to continue SOC ET or to elacestrant for a duration of 5 years. Eligible patients are women/men with ER+/HER2- node-positive eBC who received between 2–5 years of SOC ET $\pm$ CDK4/6i and have ECOG PS ≤ 1 . Patients who received a prior CDK4/6i or PARP inhibitor must have completed or discontinued these treatments. Pre/perimenopausal women and men will be administered a LHRH agonist. Exclusion criteria include stage IV mBC, inflammatory BC, history of prior invasive BC, history of malignancy within 3 years of randomization date, >6 mo continuous interruption of prior SOC adjuvant ET or discontinuation of adjuvant ET >6 mo prior to randomization, and received prior treatment with SERDs. The primary objective is IBCFS. Key secondary objectives are distant relapse-free survival, overall survival, invasive disease-free survival, safety, PROs-QoL, and PK. Planned enrollment is 4,220 patients; recruitment is ongoing. Clinical trial information: NCT06492616. Research Sponsor: Menarini Group.

ADELA: A double-blind, placebo-controlled, randomized phase 3 trial of elacestrant (Ela) + everolimus (EVE) versus elacestrant + placebo 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 the standard-of-care (SOC) in 1L ER+/HER2– aBC; however, tumors eventually develop resistance. Constitutive activation of the PI3K/AKT/mTOR pathway can contribute to endocrine resistance in breast cancer. *ESR1* mutations (*ESR1m*) are a common type of acquired resistance that emerges in 40–50% of patients (pts) 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 pts with ER+/HER2– aBC with *ESR1m* tumors progressing after ET+CDK4/6i. Ela is a next-generation oral SERD that binds and degrades ER α . In the Ph3 EMERALD trial, single-agent Ela improved mPFS vs SOC ET in pts with *ESR1m* tumors (HR 0.55; 95% CI 0.39–0.77; P=0.0005) [Bidard 2022]. Among pts who received prior ET+CDK4/6i ≥ 12 months, mPFS with Ela was 8.6 vs 1.9 months with SOC ET (HR 0.41; 95% CI 0.26–0.63) [Bardia 2024]. The crosstalk between the ER and PI3K/AKT/mTOR pathways provides a rationale for evaluating Ela+EVE (a mTORC1 inhibitor). In the ELEVATE Ph2 trial (NCT05563220), the combination of Ela 345 mg + EVE 7.5 mg showed a clinically meaningful mPFS of 8.3 months (95% CI, 4.0–10.2) in all pts (N=50) with ER+/HER2– aBC who progressed after ET+CDK4/6i, regardless of *ESR1m* status (Rugo, SABCS 2025). Safety was consistent with the known profile of EVE+SOC ET. **Methods:** ADELA (NCT06382948) is an international, multicenter, double-blind, placebo-controlled, randomized Ph3 trial that compares Ela+EVE vs Ela+placebo in pts who have ER+/HER2– aBC with *ESR1m* tumors progressing on ET+CDK4/6i. Eligible pts are adults (≥ 18 years) with ER+/HER2– aBC and centrally confirmed *ESR1m* who received 1–2 prior lines of ET for aBC and progressed on ET+CDK4/6i for aBC after ≥ 6 months. Pts receiving CDK4/6i-based adjuvant therapy are eligible if progression occurred after ≥ 12 months of treatment but < 12 months following CDK4/6i completion. Exclusion criteria include prior chemotherapy for aBC and active uncontrolled/symptomatic brain metastases and/or leptomeningeal disease. Pts will be randomized 1:1 to 28-day cycles of Ela 345 mg + EVE 7.5 mg QD or Ela 345 mg + placebo QD until disease progression or unacceptable toxicity. Pts will receive dexamethasone mouthwash during the first 8 weeks. Stratification factors are visceral metastases (yes vs no) and duration of prior CDK4/6i therapy (≥ 12 vs < 12 months). Primary objective is PFS assessed by BICR. Secondary objectives are investigator-assessed OS, PFS, ORR, CBR, DoR, TTR, best percentage change in tumor burden, safety, HRQoL. Planned enrollment is 240 pts. Recruitment is ongoing across Spain, France, Greece, Italy, Germany, Austria, Czech Republic, United Kingdom, and Brazil. Clinical trial information: NCT06382948. Research Sponsor: Menarini Group; MEDSIR.

ELECTRA: An open-label, multicenter, phase 1b/2 study of elacestrant in combination with abemaciclib in patients with brain metastasis from ER+/HER2– breast cancer.

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Background: Endocrine therapy (ET) + cyclin dependent kinase 4/6 inhibitor (CDK4/6i) is the mainstay for the management of ER+/HER2– mBC as 1st-line therapy. However, tumors eventually develop resistance to ET, leading to disease progression. In the EMERALD phase 3 trial, single-agent elacestrant demonstrated a significantly prolonged progression-free survival (PFS) vs SOC ET (*ESR1m* tumors HR 0.55; 95% CI 0.39–0.77; all pts HR 0.70; 95% CI 0.55–0.88) with a manageable safety profile (Bidard 2022), leading to the first oral SERD approved. In a subgroup analysis in patients with *ESR1m* tumors who had received prior ET+CDK4/6i ≥ 12 months, the median PFS for elacestrant was of 8.6 months vs 1.9 months with SOC ET (HR=0.41; 95% CI, 0.26–0.63) [Bardia CCR 2024]. Currently, there are no approved systemic treatments for patients with ER+/HER2– breast cancer who have brain metastasis. ELECTRA (NCT05386108) is an open-label phase 1b/2, multicenter study evaluating elacestrant in combination with abemaciclib. The phase 1b portion of ELECTRA evaluated the combination of elacestrant with abemaciclib in patients with ER+/HER2– mBC regardless of metastatic site and *ESR1* status. The recommended phase 2 dose (RP2D) of the combination was determined to be elacestrant 345 mg QD with abemaciclib 150 mg BID (Ibrahim ASCO 2024). The phase 2 portion of ELECTRA is ongoing to further characterize efficacy and safety of this combination in patients with brain metastases from ER+/HER2– breast cancer, as both compounds cross the blood-brain barrier (Conlan, 2020; Tolaney, 2020). **Methods:** Phase 2 eligibility includes patients with ER+/HER2– locally advanced or metastatic breast cancer and measurable brain metastasis (≥ 1 active and measurable brain metastasis per RECIST v1.1). Patients must have received prior therapy in the metastatic setting, including ≥ 1 endocrine therapy, ≤ 2 chemotherapy regimens, and 0–2 prior CDK4/6i (excluding abemaciclib). The phase 2 primary objective is ORR per RECIST v1.1; secondary objectives include intracranial response rate, DoR, CBR, PFS, OS, PK, and quality of life. The phase 2 portion of ELECTRA is actively recruiting patients worldwide. Clinical trial information: NCT05386108. Research Sponsor: Menarini Group.

CAPELA: A phase II multicenter open-label randomized study of capecitabine in combination with elacestrant versus capecitabine alone in advanced estrogen receptor (ER)–positive breast cancer (TBCRC 070).

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Background: Endocrine therapy (ET) in combination with targeted treatments can effectively treat metastatic ER-positive (ER+) breast cancer (BC); however, nearly all patients ultimately progress on these therapies, eventually requiring treatment with chemotherapy. Current standard of care, based on older data, is to discontinue ET when starting chemotherapy. Many of these studies used tamoxifen, which has partial agonist activity, in combination with chemotherapy. Newer estrogen-targeting agents, e.g. oral selective ER degraders (SERDs), function as ER antagonists. Preclinical work investigating the combination of SERD and chemotherapy has demonstrated an additive effect of the agents in ER wildtype tumors and a synergistic effect in tumors with *ESR1* mutation (*ESR1m*); this synergy was attenuated with P53 silencing. **Methods:** CAPELA, an investigator-initiated, multicenter, open-label randomized phase II study, is designed to assess the safety and efficacy of capecitabine monotherapy vs. capecitabine + elacestrant in patients with advanced/unresectable ER+ HER2- BC. Eligible patients will have progressed on a CDK4/6 inhibitor and had no prior treatment with chemotherapy for metastatic disease. At least 50% of enrolled patients are required to have *ESR1m* tumors. Patients will be randomized 1:1 to receive capecitabine 1000mg/m² PO BID days 1-14 of a 21-day cycle +/- the oral SERD elacestrant 345 mg PO daily. Randomization will be stratified by prior lines of ET in the metastatic setting (1 vs. >1), visceral disease (yes/no), *TP53* mutation status, and *ESR1m* status. Patients with tumors with an *ESR1m* who are randomized to the monotherapy arm will have the option to crossover to elacestrant monotherapy at the time of progression to evaluate benefit of concurrent vs. sequential use of these agents. The primary endpoint is hierarchical assessment of median progression free survival (mPFS) in 1) the *ESR1m* population and if positive 2) the intention to treat (ITT) population. Secondary endpoints include safety/tolerability, median overall survival (OS), objective response rate, median time to second progression, clinical benefit rate, and patient reported outcomes in the *ESR1m* and ITT populations. PFS and OS in the *ESR1m* not detected population will also be evaluated. Exploratory correlative studies on collected plasma, serum, and archival tissue will also be conducted. The study will enroll 297 patients over an estimated 3 years. The trial will open at 10 sites through the Translational Breast Cancer Research Consortium (TBCRC). Clinical trial information: NCT07222215. Research Sponsor: Menarini-Stemline; Gateway for Cancer Research.

AVATAR: Efficacy of personalized tumorogram-based therapy in breast cancer established from patient-derived organoids.

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Background: Despite therapeutic advances in advanced breast cancer (ABC), predicting drug efficacy for individual patients remains difficult. Patient-derived tumor organoids (PDTOs) could enable drug efficacy testing within a timeframe compatible with clinical decision-making. We hypothesize that personalized treatment based on PDTO-guided tumorograms can improve outcomes for patients with HER2-negative ABC. **Methods:** AVATAR (NCT06459791) is a single-arm multicenter phase II trial assessing tumor response rate within 6 months as the primary endpoint in patients with HER2-negative ABC treated with tumorogram-guided chemotherapy. A biopsy of a tumor lesion is performed and transferred to the laboratory for PDTO establishment. While waiting for the result of the tumorogram, the patient receives standard-of-care treatment. A drug screening of standard-of-care drugs is performed on the PDTO (~5-10 drugs per patient), with selection adapted to the clinical setting. A multidisciplinary team makes therapeutic recommendations based on the tumorogram. A tumorogram is considered informative if it identifies at least one chemotherapy drug that is considered effective in the PDTO model. When possible, patients with an informative tumorogram receive one of the recommended treatments as their next line of therapy. Otherwise, they receive standard treatment. Eligible patients include those with HER2-negative ABC who are treated with chemotherapy (endocrine-resistant for HR+/HER2-), have a performance status of 0-1, and have a tumor lesion that can be biopsied. Patients who have received more than three lines of chemotherapy in the metastatic setting or who have progressive brain or leptomeningeal metastases are excluded. We hypothesize that the prescription of chemotherapy based on an informative tumorogram will be clinically meaningful if the tumor response rate is at least 25% (p_0). With a one-sided α of 9%, a power of 90%, and an alternative hypothesis of 45% (p_1), 39 patients should be treated according to an informative tumorogram, and 110 patients need to be included (assuming a minimum of 40% informative tumorograms and accounting for dropouts). Enrollment began in December 2024 and is ongoing. Clinical trial information: NCT06459791. Research Sponsor: PHRC-I.

Exploratory analysis of prognostic value of ctDNA monitoring among advanced breast cancer with oligometastatic disease: An ancillary biomarker study of JCOG 2110 (JCOG2110A1).

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Background: Oligometastatic advanced breast cancer represents a biologically heterogeneous disease state in which a subset of patients may achieve prolonged disease control or potential cure through the addition of definitive local therapy to systemic treatment. However, conventional imaging has limited sensitivity for detecting minimal residual disease (MRD), and reliable biomarkers to identify patients most likely to benefit from local therapy remain lacking. Circulating tumor DNA (ctDNA) has emerged as a sensitive, minimally invasive marker of tumor burden and treatment response and may provide complementary information beyond radiographic assessment. JCOG2110 is a phase III randomized trial evaluating whether the addition of definitive local therapy (surgery or radiotherapy to all detectable lesions) to systemic therapy improves survival in patients with advanced breast cancer with three or fewer oligometastatic lesions. JCOG2110A1 is an ancillary biomarker study designed to characterize ctDNA dynamics in this clinical setting and to explore the clinical significance of ctDNA-based MRD assessment.

Methods: Eligible patients are those enrolled in JCOG2110 who provide written informed consent prior to initiation of protocol-defined systemic therapy. Plasma ctDNA will be analyzed using Guardant Reveal, a next-generation sequencing-based assay integrating genomic alterations and methylation signatures, and reported as ctDNA positive or negative with quantitative estimates of tumor fraction. Blood samples will be collected longitudinally at predefined timepoints: before systemic therapy, prior to completion of the initial 12-week systemic treatment, and during protocol-specified follow-up aligned with imaging assessments after second registration. In cases of disease progression, ctDNA will be collected at progression and subsequent sampling will be discontinued. The primary endpoint is the proportion of ctDNA clearance and ctDNA level reduction after initial systemic therapy among patients who are ctDNA-positive at baseline. Secondary endpoints include ctDNA positivity at each timepoint, associations between ctDNA kinetics and radiographic tumor prognosis, and correlations with clinical characteristics such as tumor subtype, number of metastatic lesions, and treatment allocation. This study aims to define the detectability and early kinetics of ctDNA in oligometastatic advanced breast cancer and to generate prospective evidence regarding the prognostic and potential predictive value of ctDNA for treatment outcomes and benefit from local therapy. Clinical trial information: jRCTs031230439. Research Sponsor: Guardant Health contracted research fund.

Phase II single-arm trial of low-dose capecitabine in patients with advanced breast cancer.

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Background: Capecitabine is approved for use in both the adjuvant and metastatic settings of breast cancer. The clinical activity of capecitabine was established at the maximum tolerated dose of 1000–1250 mg/m² given on days 1–14 of a 21-day cycle. As seen with other cytotoxic agents, dose escalation may lead to increased toxicity without clear efficacy benefit, while lower, fixed-dose capecitabine maintains antitumor activity with fewer adverse effects, including diarrhea, hand–foot syndrome, mucositis, and neutropenia. This approach is especially important for older and frail patients, who are more vulnerable to toxicity and underrepresented in trials. **Methods:** This single-arm, open-label phase 2 study aims to evaluate the anti-tumor effect of continuous daily oral low-dose capecitabine at 1500mg in 40 patients aged 60 years or older, and/ or considered frail at any age (ECOG 0–2). Frailty is defined by the investigator as an individual at greater risk of complications and poorer outcomes with systemic therapy, secondary to a lower physiologic reserve and higher comorbidities and functional deficits. Eligible patients include those with HER2-negative unresectable or metastatic breast cancer (hormone positive or triple negative) with measurable disease, who have progressed on at least 1 prior line of therapy. Major exclusion criteria include HER2-positive breast cancer, severe hepatic or renal failure, inability to swallow pills, and uncontrolled CNS/leptomeningeal disease. Patients will be evaluated for toxicity every 4 weeks and for response every three cycles using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Therapy will be continued until evidence of disease progression or unacceptable toxicity. The primary objective is the clinical activity of daily low dose capecitabine by overall response rates (ORR) per RECIST. The secondary objectives include progression-free survival (PFS), overall survival (OS), and determining the safety and tolerability of daily low dose capecitabine using the Common Terminology Criteria for Adverse Events (CTCAE) v.6.0. Exploratory analyses include evaluating quality of life, measurement of sarcopenia, geriatric assessment using the CARE (Cancer and Aging Resilience Evaluation) tool before registration and at the end of treatment, and evaluating adherence to capecitabine. Simon's two-stage minimax design will be used with a type I error rate of 0.05 and power of 80%. The null hypothesis response rate of 10% will be tested against a one-sided alternative response rate of 25%. In the first stage, 22 patients will be accrued. If there are 2 or fewer responses in the first 22 patients enrolled, the study will be discontinued. The trial was approved by the Institutional Review Board at the University of Alabama at Birmingham (UAB) and has been accruing since February 2025. 8 of the planned 40 patients have been enrolled. Clinical trial information: NCT06105684. Research Sponsor: Dr. Francisco Robert Award O'Neal Comprehensive Cancer Center (OCCC) University of Alabama at Birmingham.

Phase III trial of brain MRI surveillance in stage IV breast cancer.

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Background: The incidence and prevalence of breast cancer patients who develop brain metastasis is increasing. Intracranial surveillance of asymptomatic stage IV breast cancer patients with brain MRIs is not currently recommended by the National Comprehensive Cancer Network (NCCN) Guidelines. In a previously conducted phase II brain MRI surveillance trial, approximately 25% of patients with stage IV breast cancer, independent of tumor subtype, were found to have newly detected brain metastases on the 6-month follow-up MRI from study entry.

Methods: The study is designed as a randomized phase III, multi-institutional prospective trial evaluating the role of surveillance brain MRIs in neurologically asymptomatic patients with metastatic breast cancer, based on subtypes (triple negative (TN), HER2+, and hormone receptor (HR)+ breast cancer). Following study enrollment, patients will be randomized in a 1:1 fashion to surveillance brain MRIs at baseline and q6 months for 24 months compared to a baseline MRI followed by standard-of-care brain MRI surveillance for symptomatic presentation. Newly diagnosed stage IV patients (within ≤ 60 days of starting systemic therapy for HER2+ or TN or within ≤ 60 days of initiating 1st or 2nd line therapy for HR+/HER2- disease) with an ECOG ≤ 2 and life expectancy ≥ 6 months are eligible. The primary objective is to evaluate the treatment characteristics of brain metastases diagnosed via brain MRI surveillance or standard of care imaging. Secondary objectives include the frequency of asymptomatic brain metastases and leptomeningeal disease, the number and size of brain metastases at diagnosis, quality of life, and overall and brain metastases specific survival following brain metastasis diagnosis in patients randomized to brain MRI surveillance compared to standard of care imaging. A total of 156 patients will be enrolled with an equal distribution of TN, HER2+, and HR+/HER2- subtypes, respectively. Funding: Florida Department of Health. Clinical trial information: NCT07357298. Research Sponsor: Florida Department of Health; 25B01.

Evaluation of the safety and efficacy of TRC003 in metastatic triple-negative breast cancer: A prospective, open-label, multicenter, single-arm exploratory clinical trial.

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Background: TRC003 (also named ^{225}Ac -TR2205) is a novel molecule of targeted alpha therapy (TAT) designed to deliver alpha-particle radiation to cancer cells expressing prostate-specific membrane antigen (PSMA). Compared to beta-particles, alpha-particles have a shorter path length and higher linear energy transfer, resulting in more frequent double-strand DNA breaks and potentially superior antitumor efficacy. In an ongoing pilot study, TRC003 has demonstrated a favorable safety profile and promising activity in patients with prostate cancer. Notably, PSMA expression has been reported in up to 60% of breast cancer neovasculature, with the highest rates observed in triple-negative breast cancer (TNBC). A head-to-head study found valuable insights into the expression of PSMA in TNBC and underscore the potential clinical significance of PSMA PET/CT in enhancing both diagnostic and therapeutic approaches for TNBC. This study aims to investigate the preliminary safety and efficacy of ^{225}Ac -TRC003 in patients with metastatic TNBC (mTNBC). **Methods:** This is a prospective, open-label, multicenter, single-arm study in accordance with ICH GCP guidelines at two centers. The primary objective is to evaluate the safety and tolerability of TRC003. Secondary endpoints include Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DoR), Time to Progression (TTP), progression-free survival (PFS) and overall survival (OS). Key eligibility criteria include: 1) age ≥ 18 years; 2) histologically confirmed mTNBC with documented progression after ≥ 2 prior lines of systemic therapy (including at least 1 line for metastatic disease); 3) presence of PSMA-positive lesions on imaging, without FDG-positive & PSMA-negative target lesions; 4) at least one measurable lesion per Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1; 5) Eastern Cooperative Oncology Group performance status of ≤ 1 ; and 6) adequate bone marrow, renal, and hepatic function. Fifteen eligible participants will be enrolled to receive 7.40 MBq (200 μCi) ($\pm 10\%$) of TRC003 by intravenous infusion every 8 weeks (± 1 week), for up to 8 cycles if clinical benefit is observed. Treatment will continue until disease progression, unacceptable toxicity, or consent withdrawal, meeting any study withdrawal criterion, whichever occurs first. Tumor assessments (contrast-enhanced CT/MRI and bone scan) will be performed every 8 weeks until disease progression is confirmed per RECIST 1.1. Clinical trial information: MR-37-25-039070. Research Sponsor: C Ray Therapeutics (Chengdu) Co., Ltd.

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 heterogeneous group of breast cancers 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, with short overall survival in the metastatic setting. Breast tumors 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 (BCs) that express the androgen receptor (AR). Enzalutamide (enza), an AR-antagonist, has demonstrated activity in AR-positive 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 BCs (Kach et al, Sci Transl Med 2015). Effective therapies for advanced TNBC remain an unmet need, particularly in patients who are ineligible for or progress following a checkpoint inhibitor. This randomized study evaluates the efficacy of enzalutamide or enzalutamide 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 in a 1:1:1 fashion 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 enza arms is superior to TPC; there is 80% power to detect a hazard ratio (HR) of 0.70, corresponding to an increase in median PFS from 3.5 months (mos) with TPC to 5.0 mos with enza-based tx. Secondary endpts include comparisons of PFS among the 3 arms and evaluation of response rate, clinical benefit rate, duration of response, overall survival, safety, and patient-reported outcomes by arm. Exploratory endpts include correlation of tumor and circulating markers (constitutively active AR variants in circulating tumor cells and cfDNA) with tx response. Eligible pts must have: ECOG 0-2, metastatic measurable or evaluable disease (dz), normal organ function, no history of brain mets, < prior lines of chemotx, any # of prior endocrine txs, no prior anti-AR tx, no prior mif, no concurrent CYP17 inhibitor use. Tumors must test ER/PR low or negative, HER2 negative, AR >10%. Pts with PD-L1+ BC must have received prior IO if not contraindicated. As of December 28, 2025, 32 of 201 pts have been enrolled on study. Clinical trial information: NCT06099769. Research Sponsor: Breast Cancer Research Foundation; TBCRC; Astellas; Corcept; The TaTa Sisterhood Foundation; Pfizer.

A randomized phase II study of pembrolizumab plus paclitaxel with or without bevacizumab in PD-L1–positive recurrent triple-negative breast cancer previously treated with perioperative immune checkpoint inhibitors: WJOG16522B (PRELUDE) trial.

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Background: Perioperative pembrolizumab combined with chemotherapy has become a standard of care for patients with early-stage triple-negative breast cancer (TNBC). However, a substantial proportion of patients experience disease recurrence after perioperative immune checkpoint inhibitor (ICI)–based therapy, and the optimal systemic treatment for this population remains undefined. Angiogenesis has been implicated as a potential mechanism of resistance to immunotherapy. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), may enhance antitumor immunity through vascular normalization and modulation of the tumor microenvironment. The PRELUDE trial was designed to evaluate whether the addition of bevacizumab to pembrolizumab plus paclitaxel improves clinical outcomes in patients with PD-L1–positive recurrent TNBC previously treated with perioperative ICIs. **Methods:** PRELUDE is a multicenter, open-label, randomized phase II trial conducted in Japan. Eligible patients have recurrent TNBC with PD-L1 expression (combined positive score ≥ 10 using 22C3) and prior exposure to perioperative ICI-containing chemotherapy. Patients are randomized 1:1 to receive pembrolizumab plus paclitaxel with or without bevacizumab. Pembrolizumab is administered at 400 mg every 6 weeks, paclitaxel at 90 mg/m² on days 1, 8, and 15 every 4 weeks, and bevacizumab at 10 mg/kg on days 1 and 15 every 4 weeks in the experimental arm. Treatment is continued until disease progression or unacceptable toxicity. Tumor assessments are performed according to RECIST v1.1. Exploratory biomarker analyses using tumor tissue and peripheral blood samples are planned. The primary endpoint is progression-free survival. Secondary endpoints include overall response rate, disease control rate, overall survival, and safety. Exploratory endpoints include translational biomarker analyses to investigate mechanisms of response and resistance. Enrollment is currently ongoing. ClinicalTrials.gov: NCT06976944, jRCT2031250076. Research Sponsor: MSD.

Phase Ib randomized open-label trial of sacituzumab govitecan plus nivolumab or sacituzumab govitecan plus nivolumab and relatlimab as second-line therapy metastatic triple negative breast cancer: SIMONE trial.

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Background: The use of immunotherapy beyond first-line setting is not yet routine in the treatment arsenal of patients with metastatic triple-negative breast cancer (TNBC), and this opens an opportunity for clinical trials examining whether adding novel immunotherapy agents to standard of care therapies would benefit patients. Prior studies have combined immunotherapy with standard chemotherapy (Cortes J, NEJM 2022), but combining immunotherapies with antibody-drug conjugates (ADCs) is a strategy worth pursuing given improvement of outcomes of ADCs when compared to standard chemotherapy (Bardia A et al, NEJM 2021). Sacituzumab govitecan (SG), a TROP2-ADC, is currently the standard second-line therapy for patients with metastatic TNBC, and in this study it is being combined with either nivolumab (programmed cell death [PD-1] inhibitor) or nivolumab plus relatlimab (lymphocyte activation gene-3 [LAG3]-inhibitor) due to preliminary data showing that simultaneous PD-1 and LAG3 inhibition enhances the anti-tumor immune response and restores the effector function of exhausted T-cells (Woo S-R et al, Cancer Res 2012; Tawbi HA et al, NEJM 2022).

Methods: This is an ongoing investigator-initiated randomized, open-label, phase Ib study to assess safety and efficacy of SG plus nivolumab (n= 30 patients) or SG plus a fixed dose combination (FDC) of nivolumab and relatlimab (n = 30 patients) in patients with metastatic TNBC; NCT06963905. The study is accruing patients whose tumors are PD-L1 positive (combined positive score >10) and an amendment is under review to also include patients whose tumors are PD-L1 negative on routine testing, with 1 prior line of cytotoxic chemotherapy with or without prior immunotherapy use in the metastatic setting or within 6 months from completion of curative intent treatment. Study treatment will be continued until progression of disease, unacceptable toxicity, death, or withdrawal of consent. Safety will be monitored, and tumor response will be regularly evaluated by RECIST 1.1 criteria every 9 weeks. The primary endpoint includes safety as the incidence of dose-limiting toxicities (DLT) in 3 weeks after C1D1. Secondary endpoints include objective response rate (defined as either complete response or partial response), duration of response, clinical benefit rate (objective response plus stable disease), progression-free survival, and safety with SG plus nivolumab or SG plus nivolumab + relatlimab FDC. Exploratory endpoints include overall survival, and biomarkers of prediction of response and resistance. There will be a follow-up visit after the last study treatment administration or before starting a new anticancer treatment, whichever occurs first, followed by long-term/survival chart review follow-up every three months for 2 years. Clinical trial information: NCT06963905. Research Sponsor: None.

Phase IIa, open-label, multi-center study of the DNA polymerase theta inhibitor ART6043 administered orally in combination with olaparib to patients with HER2-negative breast cancer with a germline BRCA1/2 mutation (randomized expansion of study NCT05898399).

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Background: Microhomology-mediated end joining (MMEJ) repair of DNA double-strand breaks is reliant on DNA polymerase theta (Pol θ). ART6043 inhibits Pol θ and hence MMEJ without affecting other forms of DNA double-strand break repair (DSBR) such as homologous recombination (HR) and non-homologous end joining (NHEJ). MMEJ becomes essential for tumor survival in patients with germline BRCA1/2 mutations being treated with poly adenosine diphosphate ribose polymerase (PARP) inhibitors. Pol θ inhibition is therefore a powerful strategy to target HR-deficient cancers by potentiating the DNA damage induced by PARP inhibition. Combination of Pol θ inhibition with PARP inhibition may also delay or prevent emergence of PARP inhibitor resistance through circumvention of MMEJ-mediated BRCA1/2 gene reversions that restore HR activity. The restricted expression profile of the *POLQ* gene in normal tissues compared with tumor tissues predicts a high therapeutic index for combining Pol θ inhibition with DNA damaging agents without synergistic toxicity. Data from 61 pts dosed in the ART6043 dose escalation as monotherapy and in combination with the PARP inhibitor, olaparib, in a tumor agnostic population were presented at ESMO 2025 (Yap et al 2025). These data showed that ART6043 was well-tolerated alone and with the approved dose of olaparib; good ART6043 exposure with no evidence of drug-drug interaction with olaparib; pharmacodynamic engagement as monotherapy and enhanced with olaparib and promising signals of anti-tumor activity for the combination of ART6043 + olaparib. These data support a randomized expansion of ART6043 + olaparib compared to olaparib alone to demonstrate the first proof of concept for Pol θ inhibition in HR-deficient cancers. **Methods:** In this expansion to study NCT05898399, approximately 80 pts with locally advanced or metastatic HER2 negative breast cancer with a germline BRCA1/2 mutation will be randomized to ART6043 + olaparib vs olaparib (stratified by use of prior platinum). Patients must have received prior chemotherapy and no or ≤ 1 month of prior PARP inhibitor. Patients with hormone receptor positive breast cancer should have been treated with prior endocrine therapy. Patients in the investigational arm will receive ART6043 600 mg once daily with olaparib 300 mg twice daily. Patients on the olaparib-alone arm may cross over to receive ART6043 + olaparib on progression. Key objectives include preliminary efficacy (progression-free survival, objective response rate etc), safety and tolerability. Cell free DNA samples will be collected to assess stratification biomarkers, response and compare the occurrence of resistance mechanisms (eg BRCA reversion) between the two arms. Enrollment will continue until Q4-2027. Clinical trial information: NCT05898399. Research Sponsor: Artios Pharma Ltd.

IvoLoC: A phase II trial of ivonescimab (IVO) in endocrine-refractory hormone receptor (HR)–positive or triple-negative (TN) metastatic invasive lobular carcinoma (mILC).

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Background: ILC accounts for approximately 10–15% of breast cancers and is predominantly hormone receptor–positive (HR+)/HER2–. Patients with endocrine-refractory mILC have poor outcomes, with median progression-free survival (PFS) of less than three months following standard therapies. ILC is biologically distinct from invasive ductal carcinoma, with unique tumor microenvironmental features. Molecular profiling of primary untreated ILC has demonstrated marked heterogeneity, including immune-enriched (IE) and highly vascularized (HV) molecular functional portraits associated with PD-1/PD-L1 signaling and VEGF pathway activation. IVO is a novel bispecific antibody targeting PD-1 and VEGF, designed to enhance antitumor immunity while inhibiting angiogenesis. We hypothesize that dual immune and vascular targeting will improve clinical outcomes in patients with endocrine-refractory HR+/HER2– or TN mILC. **Methods:** Trial Design: IvoLoC (NCT07229417) is a single-center, open-label, phase II study conducted at The University of Texas MD Anderson Cancer Center. Eligible patients include those with HR+/HER2– mILC with progression on prior endocrine therapy, including combinations with CDK4/6, PI3K, AKT, and/or mTOR inhibitors, as well as patients with TN mILC. Patients may have received any number of prior endocrine-based regimens but no more than two prior cytotoxic therapies, including antibody–drug conjugates, in the metastatic setting. IVO is administered intravenously at 20 mg/kg every three weeks until disease progression or unacceptable toxicity. Radiographic assessments are performed every 9 weeks and evaluated per RECIST v1.1. Endpoints: The primary endpoint is 6-month PFS. Secondary endpoints include 12-month PFS, median PFS, objective response rate, disease control rate, duration of response, overall survival, and safety. Exploratory objectives include correlation of outcomes with molecular functional portraits, longitudinal circulating tumor DNA analyses, and integrated genomic and transcriptomic biomarker discovery. Enrollment: The study plans to enroll 29 patients. Accrual is ongoing in the United States. Clinical trial information: NCT07229417. Research Sponsor: Summit Pharmaceuticals.