LBA1000 **Oral Abstract Session**

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

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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, 2023, issue of the *Journal of Clinical Oncology*.

1001 **Oral Abstract Session**

Second-line endocrine therapy (ET) with or without palbociclib (P) maintenance in patients (pts) with hormone receptor-positive (HR[+])/human epidermal growth factor receptor 2-negative (HER2[-]) advanced breast cancer (ABC): PALMIRA trial.

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Background: Cyclin-dependent kinases 4 and 6 inhibitors (CDK4/6i) in combination with ET has become a standard first-line treatment for pts with endocrine-sensitive, HR[+]/HER2[-] ABC. The optimal treatment after progression on a CDK4/6i remains unknown. This study aims to determine if P maintenance with an alternative ET improves the antitumor activity of second-line treatment in this patient population. **Methods:** A total of 198 pts with HR[+]/HER2[-] ABC who had disease progression to first-line P plus ET (aromatase inhibitor or fulvestrant) were included. Pts were eligible if they had clinical benefit to the first-line treatment defined as response or stable disease $\geq$24 weeks, or who had progressed on a P-based regimen in the adjuvant setting with disease progression after at least 12 months of treatment but no more than 12 months following P treatment completion. Pts were randomly assigned (2:1 ratio) to receive P plus second-line ET (letrozole or fulvestrant, based on prior ET) or second-line ET alone. Stratification factors were prior ET and the presence of visceral involvement. Primary endpoint was investigator-assessed progression-free survival (PFS) determined by RECIST v.1.1. Secondary endpoints included overall response rate (ORR), clinical benefit rate (CBR), overall survival, and safety. The 2-sided log-rank test ($\alpha = 0.05$) had an 80% power to detect a hazard ratio $\leq$0.59 in favor of P maintenance. **Results:** Between April 2019 and October 2022, 136 and 62 pts were randomized to receive P+ET and ET, respectively. Pts characteristics were well balanced. Median age was 59 years (range: 33-85), 61.1% were ECOG 0, 61.1% had visceral disease, and 89.9% received aromatase inhibitor + P as first-line treatment for metastatic disease. At median follow-up of 8.7 months and 155 PFS events, median investigator-assessed PFS was 4.2 months (95% CI 3.5–5.8) in the P+ET *vs.* 3.6 months (95% CI 2.7–4.2) in the ET arm (hazard ratio 0.8, 95% CI 0.6–1.1, p=0.206). This result was consistent across all stratification subgroups. 6-month PFS rate was 40.9% and 28.6% for P+ET and ET, respectively. Among 138 pts with measurable disease, no significant differences were observed in ORR (6.4% *vs.* 2.3%) or CBR (33.0% *vs.* 29.5%) for P+ET and ET, respectively. Grade 3-4 adverse events were higher in pts treated with P+ET (45.2% *vs.* 8.3%) and no new safety signals were identified. No treatment-related deaths were reported. **Conclusions:** For HR[+]/HER2[-] ABC pts, maintaining P with a second-line ET beyond progression on prior P-based therapy did not significantly improve PFS compared with second-line ET alone. Planned biomarker analysis may help identify which pts are more likely to benefit from this therapeutic approach. Clinical trial information: NCT03809988. Research Sponsor: Pfizer.

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

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Background: In PADA-1, ER+ HER2- metastatic breast cancer patients who displayed a rising *ESR1* mutation in blood (b*ESR1*mut) during a first-line therapy with aromatase inhibitor (AI) and palbociclib were randomized between keeping the same treatment or switching to fulvestrant (FUL) and palbociclib (PAL) (Bidard, Lancet Oncol 2022). In this analysis, we investigated the kinetics of b*ESR1*mut after randomization, under AI+PAL or FUL+PAL. **Methods:** Patients who had a rising b*ESR1*mut detected and no synchronous disease progression underwent further serial ctDNA analyses at randomization and then every 2 months until disease progression. ctDNA analysis at randomization, i.e. before any change in endocrine therapy, was intended to study the impact of sampling fluctuations – since rising b*ESR1*mut levels were often close to the limit of detection of the assay. b*ESR1*mut detection was performed with droplet digital PCR (Jeannot, Oncogene 2020), while left over samples were subjected to next-generation sequencing, which allowed for b*ESR1*mut typing and clonality assessment (Callens, Anal Chem 2022). **Results:** 172 patients were randomized in PADA-1 after having a rising b*ESR1*mut and no synchronous disease progression. In these patients, b*ESR1*mut had a median mutant allelic frequency of 0.8 % (range 0.1-25.8%) and a median copy number of 14 copies/ml of plasma (4-1033) on the "rising" sample, with no imbalance between randomization arms. Among them, N=75 (46.6%) had no b*ESR1*mut detected at the repeat blood sample at randomization. Of note, these patients had a lower level of bESR1mut at "rising" compared to those who remained b*ESR*1mut+ at randomization (p=0.01). After treatment start, patients who were switched to FUL+PAL experienced a higher rate of b*ESR1*mut clearance at 2 months, compared to those remaining on AI (70.9% vs 32.8%, $p<0.001$). b*ESR1*mut clearance at 2 months was associated with longer PFS (HR=0.36 95%CI=[0.25;0.52], $p<0.001$). The length of b*ESR1*mut clearance was also longer in patients randomized to FUL (median: 7.3 mo 95%CI=[3.7;11.2] vs 1.9 mo 95%CI=[1.8;2.3]; $p<0.001$). At clinical disease progression, N=62 (83%) and N=49 (73%) patients tested positive for b*ESR1*mut in the AI and FUL arms, respectively. Mutation typing in 95 patients with available material revealed that the Y537S mutation was the most prevalent (N=36, 37.9%), while N=25 (26.3%) and N=18 (69.2%) had polyclonal b*ESR1*mut at time of rising b*ESR1*mut and progression, respectively. The mutation type -including Y537S- and the presence of polyclonal b*ESR1*mut at time of rising b*ESR1*mut did not influence patients' survival and hazard ratio between arms. **Conclusions:** b*ESR1*mut ctDNA kinetics support the clinical benefit observed in the FUL+PAL arm over the AI+PAL arm. *ESR1* mutation type and clonality did not impact the benefit of the treatment switch. Clinical trial information: NCT03079011. Research Sponsor: Pfizer; INCA PRT-K (Grant nb PRT-K19-110).

Final overall survival (OS) analysis from the phase 3 TROPiCS-02 study of sacituzumab govitecan (SG) in patients (pts) with hormone receptor–positive/HER2-negative (HR+/HER2–) metastatic breast cancer (mBC).

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Background: Treatment of HR+/HER2– mBC includes sequential endocrine therapy (ET) combined with targeted agents followed by sequential single-agent chemotherapy (CT), which is associated with poor outcomes and quality of life. SG is a Trop-2–directed antibody-drug conjugate approved in multiple countries for pts with metastatic triple-negative breast cancer who received ≥1 prior systemic therapy and in the US for pts with pretreated HR+/HER2- mBC. In the phase 3 TROPiCS-02 study, SG demonstrated a statistically significant OS benefit versus treatment of physician's choice (TPC) in pts with pretreated, ET-resistant HR+/HER2– mBC at the 2nd planned interim OS analysis with 390 events (median, 14.4 vs 11.2 mo; HR, 0.79 [95% CI, 0.65-0.96]; *P*=0.02; Rugo HS, et al. ESMO 2022. LBA76); this is considered the final analysis per the protocol. Here, we report the results of an exploratory analysis of OS from TROPiCS-02 with a longer median follow-up (12.75 mo). **Methods:** Eligible pts withHR+/HER2– mBC who received prior taxane, ET, CDK4/6 inhibitor, and 2-4 prior lines of CT were randomly assigned 1:1 to receive SG (10 mg/kg IV d1 and 8, every 21 d) or TPC until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival by blinded independent central review per RECIST v1.1. Key secondary endpoints included OS and safety. In an exploratory analysis, we evaluated OS by HER2 immunohistochemistry (IHC). **Results:** In total, 543 pts (median prior CT for mBC, 3; visceral metastases, 95%) were randomized to receive SG (n=272) or TPC (n=271). At data cutoff (Dec 1, 2022), 437 OS events had occurred (median follow-up, 12.75 mo), with 47 (8.7%) new deaths in the SG versus TPC groups (22 [8.1%] vs 25 [9.2%]) since the 2nd planned interim analysis. With this extended follow-up, SG continues to demonstrate improved OS versus TPC (median, 14.5 vs 11.2 mo; HR, 0.79 [95% CI, 0.65-0.95]; nominal *P*=0.01). The OS rates (95% CI) for SG versus TPC were 60.9% (54.8-66.4) and 47.1% (41.0-53.0) at 12 months, 39.2% (33.4-45.0) and 31.7% (26.2-37.4) at 18 months, and 25.6% (20.4-31.1) and 21.1% (16.3-26.3) at 24 months. Overall, 92% of pts were evaluable for HER2 status by IHC (HER2 IHC0, n=217; HER2-low, n=283). SG demonstrated improved OS versus TPC in the HER2 IHC0 (median, 13.6 vs 10.8 mo; HR, 0.86 [95% CI, 0.63-1.13]) and HER2-low (median, 15.4 vs 11.5 mo, HR, 0.74 [95% CI, 0.57-0.97) groups. Updated safety will be reported at the time of presentation. **Conclusions:** The final OS analysis of the TROPiCS-02 study confirms the clinically meaningful OS benefit of SG over single-agent CT in pts with pretreated, endocrine-resistant HR+/HER2–mBC. This improvement was independent of HER2-low status. This analysis reinforces SG as an effective and safe treatment for this pt population with limited treatment options. Clinical trial information: NCT03901339. Research Sponsor: Gilead Sciences, Inc.

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

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Background: HER3-DXd is an antibody drug conjugate (ADC) comprised of a fully human anti-HER3 IgG1 monoclonal antibody (patritumab), attached to a topoisomerase 1 inhibitor via a tetrapeptide-based cleavable linker that has shown promising efficacy in pts with HER3-expressing MBC (Krop, 2022). This 3-part Phase 2 study examines efficacy of HER3-DXd across MBC subsets and defines the pt population likely to derive greater benefit (NCT04699630). **Methods:** Part A is reported here (Data cutoff 6Sep2022). Pts had HER2 negative MBC with measurable disease per RECIST v1.1, 0-2 prior chemo and prior endocrine therapy (ET) + CDK4/6 inhibitor for hormone receptor (HR)+ BC, or 1-3 prior chemo for triple negative BC (TNBC). Prior treatment (tx) with anti-HER3 agents and ADCs with exatecan derivatives were prohibited. Pts provided pre-tx tissue to evaluate the association of biomarker expression with progression free survival at 6 months ($PFS_{6months}$). Primary endpoints for Part A are objective response rate (ORR) and $PFS_{6months}$. Secondary endpoints are safety/tolerability, duration of response (DOR), and clinical benefit rate (CBR) (CR, PR or SD $\geq$180 days). **Results:** 60 pts were treated in Part A: median age 57.5 y, 98.3% female; median 5 prior lines of therapy (range 1-15). 32% had TNBC. 48% were HR+. 48% had liver and 32% had lung metastases. HER3 membrane expression was evaluated by overall % membrane positivity at 10X. 47/60 (78%) pts provided evaluable samples at baseline. Among evaluable pts, 64% (30/47) had HER3 expression $\geq$75%, 28% (13/47) had 25-74% expression and 8% (4/47) had $<$25% expression. The median tx duration was 5.2 mos and 21 pts remained on tx at data cut-off. All pts experienced a tx emergent adverse event and 93% of pts experienced a tx related AE (TRAE) with Gr $\geq$3 TRAE in 19 pts (32%). The most common ($\geq$ 25%) any grade TRAEs were nausea (50%), fatigue (45%), diarrhea (37%), vomiting (32%), alopecia and anemia (30% each). 7 pts (12%) experienced a serious AE (SAE), including 4 pts (7%) with a related SAE (interstitial lung disease, nausea/vomiting, pneumonitis, thrombocytopenia). 15% of pts experienced a dose reduction and 23% experienced a dose interruption due to an AE. 3 pts died while on tx, 2 unrelated to tx 1 cause unknown. ORR was 35% (95% CIs 23.1, 48.1) for all pts, and the CBR was 48% (95% CIs 35.2, 61.6). Pts with $\geq$75% HER3 expression had an ORR of 33% and CBR of 50%, pts with HER3 25-74% expression had an ORR of 46% and CBR of 54%. There were 4 pts with HER3 $<$ 25% expression, limiting efficacy assessment. The median DOR was 10.0 mos (95% CIs 5.5, NA). The $PFS_{6months}$ was 60% for all pts, 50% for pts with HER3 $\geq$75%, and 70% for pts with HER3 25-74%. **Conclusions:** HER3-DXd had an acceptable safety profile, and the data further confirm the clinical activity in MBC in heavy pre-tx MBC across the broad range of HER3 expression levels. Parts B and Z are ongoing and data from this report support the potential entry of HER3-DXd into the therapeutic paradigm in MBC. Clinical trial information: NCT04699630. Research Sponsor: Sarah Cannon Development Innovations; Daiichi Sankyo.

1005 **Oral Abstract Session**

Dynamic HER2-low status among patients with triple negative breast cancer (TNBC): The impact of repeat biopsies.

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Background: Trastuzumab deruxtecan (T-DXd) is FDA-approved for HER2-low, but not HER2-0 metastatic triple negative (TNBC) and hormone positive breast cancer. Therefore, identifying HER2-low status is of great clinical importance. Prior studies have shown HER2-low status in TNBC is dynamic, but the correlation between the number of successive biopsies (Bxs) conducted and the likelihood of a HER2-low result is unknown. **Methods:** Patients (pts) were identified from an institutional database including all pts with TNBC treated in a single large academic center between 2017-2022. Only pts with TNBC at diagnosis were included. Bxs without known HER2 status were excluded. Pathological, clinical, and demographic data were extracted. HER2-low was defined as HER2 IHC 1+, or 2+ with non-amplified ISH. The type of Bx was categorized as core Bx, surgical Bx, or metastatic Bx based on the timing and method of Bx acquisition. For the early-metastatic matched analysis, the core Bx was considered the early Bx, unless the core Bx was missing and then the surgical bx was used instead. For cases with several metastatic Bxs the first metastatic Bx was used. **Results:** 529 consecutive pts with TNBC at diagnosis were included. The proportion of pts with HER2-low result increased as the number of successive Bxs increased (60%, 74%, 83%, 87% and 100% when 1 (192 pts), 2 (235 pts), 3 (52 pts), 4 (38 pts), and 5-9 (12 pts) Bxs were conducted, respectively). In women without a prior HER2-low result, about one third converted to HER2-low with each successive additional biopsy (e.g. 322/529 at 1^{st} biopsy, 44/131 on 2^{nd} biopsy, 8/25 at 3^{rd} biopsy, 3/8 at 4^{th} biopsy). HER2 status distribution did not significantly vary between the different types of Bx (58%, 63%, and 54% of pts had a HER2-low result in their core, surgical or metastatic Bx, respectively; p=0.2). Among 246 women with matched core-surgical biopsies, one quarter changed their HER2 status (55% from low to 0, 44% from 0 to low, and 1% from low to 3+). Core-surgical HER2 status conversion rates did not differ between women who had neoadjuvant therapy with residual disease and women who had surgery as their primary intervention. Among women with both matched early-metastatic (70 pts) or two matched metastatic Bxs (39 pts), nearly half (44%) converted their HER2 status (68%, 26% and 6% or 35%, 59% and 6% were converted from low to 0, 0 to low and low to 3+ in the matched early-metastatic or the two matched metastatic Bxs, respectively). **Conclusions:** Our findings show that HER2 status is dynamic in pts with TNBC and support the idea that HER2-low is a spectrum, not a specific entity. We further report the novel finding that for pts with TNBC without a prior HER2-low result, repeat Bxs at progression can increase the chance of obtaining a HER2-low result and provide clinically impactful information. Whether the dynamic HER2 result represents underlying biology or analytic variation remains to be determined. Research Sponsor: None.

An age-specific pooled analysis of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) from DESTINY-Breast01, -02, and -03.

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Background: T-DXd is approved for use in pts with HER2+ unresectable or mBC after a prior anti-HER2-based regimen in the metastatic or (neo)adjuvant setting, based on the randomized phase 3 DESTINY-Breast03 study (Cortes et al. *N Engl J Med* 2022). Older pts with HER2+ mBC tend to have worse efficacy and safety outcomes, regardless of treatment (Evans et al. *Cancer Res* 2021). Outcomes of older pts treated with T-DXd have not been thoroughly examined. Here we report age-specific (<65 vs ≥65 years) efficacy and pooled safety analyses of T-DXd from DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03. **Methods:** DESTINY-Breast01 (data cutoff [DCO], March 26, 2021) and DESTINY-Breast02 (DCO, June 30, 2022) enrolled pts whose disease progressed on trastuzumab emtansine (T-DM1); DESTINY-Breast02 compared T-DXd to chemotherapy of physician's choice. DESTINY-Breast03 (DCO, July 25, 2022) included pts previously treated with trastuzumab and taxane; pts received either T-DXd or T-DM1. **Results:** At baseline, there were 44 (23.9%), 85 (20.9%), and 49 (18.8%) pts ≥65 years of age who received T-DXd in DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03, respectively. At DCO, median pooled treatment duration with T-DXd was 13.1 mo (range, 0.7-44.0) for pts <65 and 12.4 mo (range, 0.7-45.1) for pts ≥65. Key efficacy data are shown in the Table. Any-grade treatment-emergent adverse events (TEAEs), grade ≥3 TEAEs, and serious AEs were observed in 99.6%, 53.6%, and 24.3% of pts <65 and 100%, 65.5%, and 32.2% of pts ≥65, respectively. There were 125 (18.7%) and 45 (25.4%) TEAEs associated with T-DXd discontinuation in pts aged <65 and ≥65, respectively. Any-grade adjudicated drug-related interstitial lung disease/pneumonitis occurred in 11.8% of pts <65 and 17.5% of pts ≥65; grade 5 events occurred in 0.9% and 0.6% of pts <65 and ≥65, respectively. Additional efficacy and safety data will be presented. **Conclusions:** Results from this pooled analysis further demonstrate that T-DXd has a favorable benefit-risk profile in pts ≥65 years, with slightly increased toxicity, as expected. Clinical trial information: NCT03248492, NCT03523585, NCT03529110. Research Sponsor: Daiichi Sankyo Inc. and AstraZeneca.

	DESTINY-Breast01		DESTINY-Breast01		DESTINY-Breast03	
	<65 (n=140)	≥65 (n=44)	<65 (n=321)	≥65 (n=85)	<65 (n=212)	≥65 (n=49)
Median overall survival, mo (95% CI)	28.1 (23.3-36.1)	30.9 (21.9-NE)	NR (35.5-NE)	30.2 (22.3-39.2)	NR (40.5-NE)	NR (26.3-NE)
Median progression-free survival, mo (95% CI)	18.1 (13.8-NE)	19.4 (12.4-NE)	17.9 (14.1-20.8)	16.8 (12.7-NE)	30.4 (22.4-NE)	25.1 (14.1-37.3)
Confirmed objective response rate by blinded independent central review, % (95% CI)	62.1 (53.6-70.2)	61.4 (45.5-75.6)	70.7 (65.4-75.6)	65.9 (54.8-75.8)	78.8 (72.6-84.1)	77.6 (63.4-88.2)
Disease control rate, n (%)	136 (97.1)	43 (97.7)	296 (92.2)	82 (96.5)	205 (96.7)	47 (95.9)

NE; not estimable; NR; not reached.

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

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Background: In metastatic breast cancer (MBC), oral capecitabine prescribed at the FDA approved dose of 1250 mg/m^2 twice daily, 14 days on followed by 7 days off, is associated with poor tolerance and high discontinuation rates. Mathematical models suggest a fixed dose, dose dense (7 days on, 7 days off) schedule may be optimal for capecitabine efficacy. We conducted a randomized trial to compare the efficacy and tolerability of fixed-dose capecitabine, 1500 mg twice daily, 7 days on, 7 days off (FD) to the FDA approved dose and schedule (SD). **Methods:** Females with MBC and any prior lines of endocrine therapy or chemotherapy were included. HER-2 positive patients were allowed with concurrent trastuzumab. Patients were stratified by line of chemotherapy (first or subsequent), measurable disease, and ER status, and randomized 1:1 to either FD or SD. The primary endpoint was 3-month progression free survival (PFS). Additional endpoints included PFS and overall survival (OS). Capecitabine related toxicities were solicited and graded at each visit. **Results:** Between October 2015 and April 2021, 153 patients were enrolled (N=80 FD, N=73 SD). 78% were hormone receptor positive/HER-2 negative, 11% each were HER-2 positive and triple negative. The 3-month PFS was 76% in the FD arm and 76% in the SD arm (HR=1.01; 95% CI, 0.52 to 1.94; p=0.99). Landmark analysis of PFS at 12, 24 and 36 months is reported. Non-proportional hazards were detected, so restricted mean survival time (RMST) was used to report estimates of effect. PFS (restricted mean) at 36 months was 13.9 months in the FD arm versus 14.6 months in the SD arm (hazard ratio for progression or death, 1.31; 95% CI, 0.56 to 1.15; p=0.24). OS (restricted mean) at 36 months was 21.2 months in the FD arm versus 19.6 months in the SD arm (hazard ratio for death, 0.80; 95% CI, 0.55 to 1.81; p=0.27). Toxicity related treatment discontinuation occurred in 21 patients (28.8%) in the SD arm compared to 6 patients (7.5%) in the FD arm (p<0.0006). Grade 2-4 toxicities (Table) occurred more frequently in patients receiving SD capecitabine (49.3%) as compared to FD capecitabine (25.0%) (p=0.0018). **Conclusions:** Fixed dose capecitabine (1500 mg twice daily) on a 7/7 schedule has less toxicity and similar survival when compared to standard BSA-based dosing on a 14/7 schedule in MBC. Clinical trial information: NCT02595320. Research Sponsor: The University of Kansas Cancer Center and the IIT Steering CommitteeNational Institute of General Medical Sciences (P20 GM130423); The University of Kansas Cancer CCSG from the NCI (P30 CA168524)'.

Progression free survival by time; adverse events.

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

CANKADO PRO-React eHealth support in patients with HR+ HER2- metastatic breast cancer receiving palbociclib and endocrine therapy and the affect on time to deterioration of quality of life: Primary outcome analysis of the multicenter randomized PreCycle trial.

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Background: The multicenter, randomized phase IV Intergroup PreCycle trial (NCT03220178) evaluated the impact of CANKADO-based ePRO assessment on quality of life (QoL) in HR+/HER2- locally advanced or metastatic breast cancer (MBC) patients (pts) treated with palbociclib (P) and an aromatase inhibitor or P+fulvestrant. CANKADO PRO-React, an EU- registered medical device, is an autonomous application reacting to changes in pt self- reported QoL. **Methods:** Between 2017 and 2021, 499 pts (median age 59y) from 71 centers were randomized (2:1, stratified by therapy line) between an active (A; CANKADO PRO-React) or an inactive arm (B; inform; limited CANKADO functionality). 412 pts (271 A; 141 B) were available for analysis of the primary endpoint, i.e. time to deterioration (TTD) of QoL (10-point drop on FACT-G), using an Aalen-Johansen estimator for cumulative incidence function of TTD DQoL with 95% pointwise confidence intervals (CI). Secondary endpoints included PFS, OS, and DQoL (QoL deterioration). **Results:** In all pts (ITT-ePRO), a significantly decreased risk (HR 0.6982) for the CANKADO active arm A with 95% CI [0.5059, 0.9635] regarding DQoL was observed (p=0.03). In 1^{st}L pts (n=295), the decreased risk for arm A was 0.7162 (0.4839, 1.06; p=0.09), in 2^{nd}L pts (n=117) 0.6614 (0.3744, 1.168; p=0.2). Absolute pt numbers declined in later visits; until about visit 30, FACT- G completion rates were 80% and higher; mean total scores were similar between arms; the change from baseline showed a linear decline and a nearly constant offset in favor of arm A, particularly in 1^{st} L. No significant differences in clinical outcome were observed between arms: Median PFS (ITT population) was 21.4 (95% CI 19.4-23.7) (A) and 18.7 (15.1.-23.5) months (B); median OS was not reached (A) and 42.6 months (B). **Conclusions:** PreCycle is the first multicenter randomized eHealth trial demonstrating a significant benefit of an interactive autonomous patient empowerment application on QoL in MBC pts receiving oral tumor therapy. Clinical trial information: NCT03220178. Research Sponsor: Pfizer.

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

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Background: Immunotherapy benefit in patients with metastatic breast cancer (MBC) is limited to patients with triple negative breast cancer and PD-L1 expression in the tumor sample. Multi-omics characterization of the anti-cancer immune response in MBC could provide novel insights into the mechanisms behind immune response failure. **Methods:** The AURORA program (NCT02102165) enrolled patients with MBC who received at most one line of treatment in the metastatic setting. RNA sequencing was performed on primary and metastatic lesions. Stromal tumor infiltrating lymphocytes (sTIL) were scored in line with the International Immuno-Oncology Biomarker Working Group for Breast Cancer recommendations. T cell and B cell receptor (TCR and BCR) analysis was performed with MiXCR. Deconvolution of bulk RNA sequencing data was performed using xCell. ImmuneScore-normalized Relative Abundance metastasis/primary Ratios (RAR) of immune cell types were calculated. All comparisons between primary and metastatic lesions were performed on matched samples. Wilcoxon signed-rank tests were used. **Results:** As expected, sTILs decreased from primary to metastatic lesion. However, 9% of metastatic lesions still had $\geq$20% sTILs. Matched RNA expression data was available for 204 patients. Relative abundance of macrophages (RAR 3.3, $p<0.001$) and Th1 cells (RAR 1.5, $p<0.001$) was increased in the metastases, while Treg cells (RAR 0.12, $p<0.001$), CD8+ T cells (RAR 0.32, $p<0.001$) and B cells (RAR 0.32, $p<0.001$) decreased the strongest. Metastases with $\geq$20% sTILs had higher Treg cells ($p<0.001$) and B cells ($p<0.001$) compared to metastases with low sTILs, which had more Th1 cells ($p<0.001$), mast cells ($p<0.001$) and NKT cells ($p<0.001$). De novo metastatic and synchronous primary samples had more BCR ($p<0.001$) and TCR ($p<0.001$) clones in common as compared to non-de novo metastatic cancers. **Conclusions:** sTIL percentage decreased from primary tumor to metastatic lesion. Metastatic lesions with many sTILs ($\geq$20%) were enriched for immune response suppressing regulatory T cells. Research Sponsor: Breast Cancer Research Foundation (BCRF), Fondation Cancer (Luxembourg), NIF Foundation, Barrie and Dena Webb, Candriam, Fondation Futur 21, Sogerim, Think Pink Belgium (SMART Fund), Cognizant Foundation, Fund Friends of BIG, and many individual donors; Pfizer grant for non-drug research and Eurofins Foundation; National Lottery (Belgium).

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

Association of tumor infiltrating lymphocyte quantity with survival in patients (pts) with metastatic breast cancer (MBC) receiving microtubule-targeting agents: Post hoc analysis CALGB 40502 (Alliance).

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Background: Stromal tumor infiltrating lymphocyte (sTIL) quantity is prognostic in primary breast cancer, yet MBC is characterized by lower sTILs. No study has definitively evaluated the association of sTIL quantity with survival outcome in the metastatic (met) setting without checkpoint blockade. CALGB (Alliance) 40502 was a randomized phase 3 trial of 799 MBC pts receiving first-line chemotherapy, comparing paclitaxel, nab-paclitaxel or ixabepilone with or without bevacizumab. We hypothesized that sTILs quantity is associated with outcome in MBC. **Methods:** 582 submitted hematoxylin and eosin slide images from 443 unique pts were evaluable for sTILs in accordance with International TILs Working Group methods. Analysis of sTILs was based on most recent available tissue, with 161/443 (36.3%) having recurrent/met tissue. Using prespecified thresholds of $<5\%$ (low) vs $\geq 5\%$ (high) for sTIL distribution in the met setting, associations between sTILs low/high or as a continuous variable were evaluated with baseline characteristics and outcome. The primary objective was to evaluate the association of sTILs with progression-free survival (PFS) and overall survival (OS), with chemotherapy arm as a covariate. **Results:** High sTILs were more frequent among pts with hormone receptor (HR)-negative disease (64% HRneg vs 34% HRpos, $p<0.001$), with no significant association with treatment arm, age, menopausal status, race/ethnicity, or body mass index (BMI). Among all evaluable slides, mean sTILs were higher for primary tumors than met (mean 13.3% primary vs 8.4% met, p=3e-4). Among non-lymph node met sites, sTILs ranged from 1.3% (bone) to 9.5% (lung). Among 100 unique pts with paired primary and met slides, the primary had significantly greater mean sTILs (10.5% vs 7.7%, p=0.008). For the primary objective, Cox proportional hazard model of sTILs low vs high was significantly associated with worse PFS (HR 1.34; 95% CI 1.1-1.63, p=0.004) and OS (HR 1.32; 95% CI 1.07-1.63, p=0.009) when controlling for treatment arm. When controlling for both treatment arm and HR status, association of sTILs low vs high demonstrated similar trends but did not reach statistical significance for PFS (HR 1.2; 95% CI 0.97-1.47, p=0.09) or OS (HR 1.14; 95% CI 0.91-1.43, p=0.2). There was no significant interaction between sTILs and chemotherapy arm (all p-interaction >0.05). **Conclusions:** Immune activation measured by sTILs is significantly lower in met tumors than primary breast cancer and varies by met site. In this trial, sTILs were associated with progression-free and overall survival in chemotherapy-treated MBC, with a trend toward independent value adjusted for other prognostic features. Clinical trial information: NCT00785291. Research Sponsor: U.S. National Institutes of Health; Alliance Foundation Trials; BMS, Celgene.

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RNA expression levels from peripheral immune cells, a minimally invasive liquid biopsy source to predict response to therapy, survival and immune-related adverse events in patients with triple negative breast cancer enrolled in the GeparNuevo trial.

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Background: The impact of immune checkpoint therapy on the tumor microenvironment including tumor-infiltrating immune cells is well described. However, little is known about the circulating immune repertoire and its association with treatment outcome. Hence, we set out to investigate the RNA phenotype of peripheral immune cells before and during treatment of patients enrolled in the GeparNuevo trial (Loibl S et al. Annals Oncol 2022). **Methods:** The GeparNuevo trial investigated the outcome after neoadjuvant nabP-EC-chemotherapy in combination with the anti-PD-L1 immune checkpoint inhibitor durvalumab versus placebo in patients with non-metastatic triple negative breast cancer. Blood was collected before therapy (baseline), after window, before epirubicin/cyclophosphamide and at end of treatment. RNA from circulating leucocytes of 117 patients was extracted and analyzed using a custom NanoString nCounter CodeSet. Expression of 290 immune-related genes was quantified. The association of RNA expression and signatures with outcome parameters like pathologic complete response (pCR), distant disease-free survival (DDFS), invasive disease-free survival (iDFS), overall survival (OS), and immune-related adverse events (irAEs) were investigated. **Results:** Immune cell type scores representing macrophages and neutrophils significantly increased during treatment, while B cell, T and Th1 cell scores decreased ($p < 0.0001$, respectively) regardless of treatment arm. Multivariate logistic respectively multivariate Cox regression analysis revealed a significant association of each baseline *DPP4* and *MYC* gene expression with pCR, DDFS, iDFS, and OS in patients. *CDK2*, *F5* and *HLA*-DR mRNA expressions were associated with the presence of irAEs. The signature score for *TNFR2* non-canonical *NF-kB* pathway, which is known for its protective capacity, was inversely associated with irAEs in the durvalumab arm (OR = 0.454, 95% CI 0.231-0.892, p = 0.0220). Multiple immune-related signatures at baseline were associated with tumor mutational burden. **Conclusions:** Our study indicates the importance of the peripheral immune phenotype for treatment response and survival. This association between RNA expression levels of circulating immune cells and outcome seems to be not only relevant for patients receiving immune checkpoint therapy, but also for those under standard chemotherapy alone. Clinical trial information: NCT02685059. Research Sponsor: This study was funded by Walter Schulz Stiftung and the clinical trial was funded by AstraZeneca and Celgene; Walter Schulz Stiftung; AstraZeneca, Celgene.

BRACELET-1 (PrEO113): Inducing an inflammatory phenotype in metastatic HR+/HER2- breast cancer with the oncolytic reovirus pelareorep in combination with paclitaxel and avelumab.

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Background: In preclinical studies, the oncolytic reovirus pelareorep promoted an inflammatory tumor microenvironment (TME) by promoting greater infiltration of tumor infiltrating lymphocytes and upregulating PD-1/PD-L1 expression, potentially increasing the efficacy of immune checkpoint blockade. The addition of pelareorep to paclitaxel (PTX) was associated with improved survival (10.4 vs. 17.4 mos., HR = 0.65, p = 0.1) in a prior trial, with the greatest benefit in patients (pts) with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) disease (N = 57; 10.8 vs. 21.0 mos., HR 0.60, p = 0.1). **Methods:** This is a randomized phase 2 study in pts with HR+/HER2- metastatic breast cancer. Patients must have progressed on at least one hormone therapy with a CDK4/6 inhibitor. After a safety run-in for Cohort 3, patients were randomized 1:1:1 to PTX-alone (Cohort 1), PTX + pelareorep (Cohort 2), or PTX + pelareorep + avelumab (Cohort 3). The primary endpoint was overall response rate (ORR) at week 16 according to RECIST v1.1 without formal comparison across groups. Toxicity, progression-free survival (PFS) and overall survival were secondary endpoints. Blood samples were collected at cycle 1-day 1 (C1D1), C2D1 and C4D1, and T-cell receptor sequencing was performed. **Results:** Forty-eight pts were enrolled between June 2020 and June 2022. Median age was 55.5 yrs, range 37-74. Forty pts (83%) had visceral disease. Six pts (12%) previously received everolimus, and 3 alpelisib. Thirteen pts (27%) received prior taxanes in the neo/adjuvant setting. Three pts who withdrew consent prior to starting therapy and 2 pts who discontinued treatment after week 1 were considered non-responders and were censored for PFS. The most common pelareorep-associated toxicities were fever, chills, and flu-like infusion reactions, which were occasionally severe enough to require hospitalization in 5 (15%) pts despite acetaminophen prophylaxis. Nine pts (33%) discontinued pelareorep and 6 (35%) discontinued avelumab due to toxicity. Pelareorep increased T-cell repertoire turnover, with identification and expansion of new and pre-existing T-cell clones by C2D1. **Conclusions:** The addition of pelareorep to PTX is an active regimen with a high 6-month PFS rate worthy of further study. One third of patients discontinued either pelareorep or avelumab due to toxicity, highlighting the need for attentive supportive care. Survival data is maturing. Clinical trial information: NCT04215146. Research Sponsor: Oncolytics.

	Cohort 1 (n = 15)	Cohort 2 (n = 16)	Cohort 3 (n = 17)
ORR at 16 wks	3 (20%)	5 (31.3%)	3 (17.6%)
Disease Control at 16 wks (CR+PR+SD)	7 (46.7%)	10 (62.5%)	12 (70.6%)
Median PFS	6.4 months (95% CI: 2.0,-)	9.6 months (95% CI: 6.5,-)	7.5 months (95% CI: 3.8,-)
6-month PFS rate	62.5% (95% CI: 27.6, 84.2)	92.9% (95% CI: 59.1, 99.0)	73.2% (95% CI: 42.0, 89.4)

LBA1013 **Rapid Abstract Session**

TORCHLIGHT: A randomized, double-blind, phase III trial of toripalimab versus placebo, in combination with nab-paclitaxel(nab-P) for patients with metastatic or recurrent triple-negative breast cancer (TNBC).

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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, 2023, issue of the *Journal of Clinical Oncology*.

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

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Background: Recent guidelines have positioned T-DXd as a preferred treatment in the second line setting for HER2+ metastatic breast cancer (MBC). TTC is the preferred treatment in third line, however little is known on the efficacy of this combination after T-DXd exposure. **Methods:** We conducted a retrospective study in 12 French comprehensive cancer centers. All patients with HER2+ MBC treated with TTC after prior exposure to T-DXd were included. The primary end point was progression-free survival (PFS) in the whole population. Secondary end-points included overall survival (OS), PFS in subgroups and objective response rate. **Results:** Between 08/2020 and 12/2022, 101 patients were included. Median age was 56.4 y.o. (range 30.8 - 84.8). Median number of prior line of treatment for metastatic disease at TTC start was 4 (2 - 15). 82% and 95% of patients had received previous pertuzumab and T-DM1 respectively. The median duration of previous exposure to T-DXd was 8.9 months (1.4 - 31.4) and 82/101 (81%) patients had progressed under T-DXd while 19 had stopped T-DXd for toxicity or other reasons. TTC regimen was given as a 3rd line or 4th line for metastatic disease in 37/101 (37%) and beyond for the remaining patients. TTC was the immediate subsequent therapy to T-DXd for 86/101 pts (85%). With a median follow-up of 8.5 m (95%CI [7.7; 9.4]), 68/101pts (67%) have stopped TTC for progressive disease. Median PFS was 4.7 m (95%CI [3.8; 5.6]) and median OS not reached (95%CI [10.6; NA]) in the whole population. Patients treated with TTC as the immediate subsequent therapy to T-DXd, had a median PFS of 5.0 m (95%CI [4.0; 6.0]) and a median OS not reached (95%CI [11.9; NA]). Best response to TTC, evaluated by investigators in the 87/101 RECIST evaluable patients, was progressive disease, stable disease, partial response and complete response in 34%, 34%, 30% and 2% of patients respectively. At TTC initiation, 39 (39%) of patients had known brain metastases. Out of the 62 patients without known brain metastases at the initiation of TTC, 2 had brain metastases documented as a site of progression during TTC. **Conclusions:** In this large retrospective cohort, TTC shows significant efficacy for patients with HER2+ MBC previously exposed to T-DXd. Data and subgroup analyses will be updated for the meeting. Research Sponsor: None.

1015 **Poster Discussion Session**

Pertuzumab retreatment in patients with HER2-positive locally advanced/metastatic breast cancer: Overall survival results of a phase III randomized trial (JBCRG-M05: PRECIOUS).

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Background: We previously reported that pertuzumab (P) retreatment in combination with trastuzumab (T) + chemotherapy based on physician's choice (C) (PTC) significantly improved investigator-assessed progression-free survival (PFS) compared with T + C (TC) in patients with HER2-positive locally advanced/metastatic breast cancer (LA/MBC) previously treated with P-containing regimens in the phase III PRECIOUS study. Here we report updated OS at the median follow-up of 27.4 mo. **Methods:** Patients previously treated with P-containing regimens as $1^{st}/2^{nd}$-line treatment for LA/MBC were randomly assigned 1:1 to two groups, PTC group and TC group, stratified by estrogen receptor (ER) status, previous treatment duration of P, number of previous chemotherapy regimens, and presence or absence of visceral metastasis. The primary endpoint was investigator-assessed PFS. The key secondary endpoints included OS, independent reviewer assessed PFS and safety. Superiority of PTC to TC will be tested using a log-rank test and a one-sided P-value of less than 0.05 will be considered an indicator of superiority. The distribution of OS will be estimated using the Kaplan-Meier method. In addition, the hazard ratio and one-sided 95% CI of the therapeutic effect between the groups will be calculated using the Cox proportional hazard model. **Results:** Of the 219pts enrolled, 217 (108 PTC, 109 TC) were included in the intent-to-treat analysis. At the data cutoff (Dec 31, 2021), OS and PFS events were 138 (63.6%) and 190 (87.6%), respectively. Updated median OS was significantly longer in the PTC group (median OS 36.2 vs. 26.5 mo.; HR = 0.73 [one side 95%CI upper limit, 0.97]; log-rank test p = 0.0323). In a prespecified subgroup analysis for OS including ER, visceral metastases, number of previous chemotherapy regimen was broadly constant without disease-free interval. Updated median investigator-assessed PFS (5.5 vs. 4.2 mo.; HR = 0.81 [one side 95%CI upper limit, 1.03]; stratified log-rank test p = 0.019) were also significantly better in the PTC group. Median PFS by independent review did not show the difference between two groups (4.4 vs. 4.4 mo.; HR = 1.03 [one side 95%CI upper limit, 1.36]; log-rank test p = 0.561). The serious adverse event rate did not differ between the groups (19.0% vs. 23.1%). There were no new safety signals in the two groups. **Conclusions:** Retreatment of P in combination with TC demonstrated significantly improved OS compared to TC. HER2 dual blockade with PT can contribute to improve survival in patients previously treated with P-containing regimens as $1^{st}/2^{nd}$-line treatment for LA/MBC. Clinical trial information: NCT02514681. Research Sponsor: Chugai Pharmaceutical.

The association of centromere amplification and response to trastuzumab in HER2+ metastatic breast cancer.

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Background: Chromosomal instability and copy number aberration (CNA) burden can be associated with patients' survival in some cancers. Centromeres, chromosomal regions crucial for genomic stability, can be found altered by CNA in tumours but remain largely unexplored due to sequencing technologies. Using whole-genome sequencing (WGS) data from cases of long term, never relapsed HER2+ metastatic breast cancer (MBC) patients, also referred as exceptional responders (ExRs), we aim to better characterise the CNA profiles and underlying long-term survival of this "exceptional" cohort and investigate the centromeric and pericentromeric association with prognosis and treatment response. **Methods:** Two hundred and forty-three HER2+ MBC patients were enrolled in the HER2 Patients Project Database from St Vincent University Hospital, Dublin, Ireland. Eighty-five HER2+ MBC patients were identified as exceptional survivors (ExS) with an OS $>$ 60 months (range 60-248 months), of which 28 never-relapsed and responded exceptionally (ExR) to trastuzumab. Patients with an OS $<$ 60 months (N=158, range 0.2-59 months) were identified as non responders (NR). WGS was performed on 13 ExR tumours (primary or metastases) and matching control at a mean depth of 60X and 30X, respectively. Control-FREEC and CNVkit were used to characterise the CNA profiles and estimate the CNA burden. Samples from 10 NR patients were used for comparison with the ExR. **Results:** WGS analysis revealed that ExR samples are more impacted by gain rather than loss of copy overall, with a median fraction altered by gain of 0.24. No significant difference was observed between the ExR and NR in terms of CNA burden. However, a large fragment on chromosome 9 was amplified in 92% of ExR (12/13) which corresponded to the centromere (chr9q11) and a large heterochromatic block (chr9q12). A higher copy number status of this centromeric region was detected in the ExR, with a gain of at least 1 additional copy compared to the NR tumoral samples ($P<0.001$). The dichotomisation into high versus low copy number of the centromeric region of chromosome 9 was also observed in centromeres of chromosome 17 ($P=0.009$) and chromosome 19 ($P<0.001$). No case of polysomy was detected in our cohort and genes located near the centromeres, such as ERBB2 (amplified in both ExR and NR), were independent of the centromeres copy-number status. **Conclusions:** The identification of the genomic aberrations of these metastatic patients, treated with trastuzumab who never relapsed, increases our understanding of the mechanisms involved in MBC progression. Our results suggest that the centromere co-amplification of chr9q11-q12, chr17p11.1-q11.1 and chr19p11-q11 stratifies patients according to their OS. CNA status of the centromeric regions of chromosomes 9, 17 and 19 may therefore represent a novel prognostic predictor to trastuzumab response and new outcomes for patients. Research Sponsor: Cancer Clinical Research Trust (CCRT) Ireland.

LEONARDA-1: Phase III randomized study of lerociclib plus fulvestrant in patients with HR+, HER2- locally advanced or metastatic breast cancer that has progressed on prior endocrine therapy.

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Background: Lerociclib (GB491), a novel oral CDK4/6 inhibitor with continuously daily dosing, which has demonstrated anti-tumor response and a differentiated safety & tolerability profile in previous clinical trials. The LEONARDA-1 study assessed the efficacy of lerociclib and fulvestrant in endocrine-resistant advanced BC. **Methods:** This is a randomized, double-blind, placebo-controlled phase III study assessing lerociclib in combination with fulvestrant in pre/peri-menopausal or postmenopausal, HR+, HER2- locally advanced or metastatic BC patients (pts) who had relapsed or progressed on prior endocrine therapy (ET). Eligible patients were allowed one prior line of chemotherapy for metastatic disease. Pre-/peri-menopausal pts also received goserelin. Pts were randomized 1:1 to receive lerociclib (150mg po bid, d1-28, q4w) or placebo (P) plus fulvestrant (F). The primary endpoint was investigator-assessed progression-free survival (PFS) based on RECIST v1.1. Secondary endpoints included PFS (assessed by BICR), overall survival (OS), response assessment, safety and tolerability, pharmacokinetic (PK) profile. **Results:** By December 2nd 2022 as data cut-off date, 275 pts were randomized, 137 to receive lerociclib + F and 138 to P + F. Median follow-up time was 7.36 months (range, 0.03-11.93+) for lerociclib + F vs 7.33 months (range, 0.03-11.27) for P + F. Baseline characteristics were well balanced (The median age was 54 years and 53.5 years, 41.6%% and 44.9% were Pre/peri-menopausal, 64.2% and 62.3% had visceral disease, 24.8% and 26.1% were primary resistant to prior ET, 28.5% and 29.0% received one line of chemotherapy for metastatic disease, respectively). At the time of cut-off date, 125 PFS events were observed with a median PFS of 11.07 months for lerociclib + F and 5.49 months for P + F (HR: 0.458; 95% CI: 0.317, 0.661, $P<0.001$ by log-rank test). In patients with measurable disease (n=240, 87.3%), the ORR was significantly higher in lerociclib + F 26.9% (2.5% complete response [CR]) vs 9.9% (0% CR) for P + F. Consistent benefit from lerociclib was seen in pre/peri-menopausal and postmenopausal subjects. The most common adverse events (AEs) for lerociclib + F versus P + F were neutropenia (90.5% vs. 4.3%), leucopenia (86.9% vs. 6.5%), anemia (34.3% vs. 10.1%), thrombocytopenia (19.7% vs. 3.6%), and diarrhea (19.7% vs. 3.6%). Grade 3 or 4 neutropenia was reported in 46.7% pts on lerociclib + F (G3: 41.6%, G4: 5.1%) vs 0% pts on P + F. There was no case of ≥Grade3 diarrhea reported. The discontinuation rate due to AEs was 0.7% on lerociclib + F and 0% on P + F. Serious AEs were reported for 5.8% and 8.0%, respectively. **Conclusions:** Lerociclib at 150mg twice daily plus fulvestrant significantly improved PFS and ORR and demonstrated a favorable tolerable safety profile in pts with HR+ / HER2- endocrine-resistant advanced BC. Clinical trial information: NCT05054751. Research Sponsor: Genor Biopharmaceutical Ltd.

1018 **Poster Discussion Session**

First-line systemic treatment with palbociclib in women aged ≥70 years presenting with hormone receptor-positive advanced breast cancer: Results from the PALOMAGE program.

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Background: Endocrine therapy (ET) combined with a CDK4/6 inhibitor is standard of care for hormone receptors-positive (HR+) advanced breast cancer (ABC). In France, 33% of BC are diagnosed in women aged 70 and older, contrasting with their constant underrepresentation in clinical trials. PALOMAGE, a prospective, observational, longitudinal real-life program, assessed the feasibility of ET combined with palbociclib (PAL), specifically in women aged ≥70 years with HR+ HER2- ABC. **Methods:** Depending on prior treatment for ABC and time of relapse, women were enrolled in two cohorts: ET-sensitive disease (no prior systemic treatment for ABC and no relapse within 1 year after adjuvant ET, cohort A) or ET-resistant disease (relapse on adjuvant ET or < 1 year after completion, or prior treatment for ABC, cohort B). Data collected at baseline and then every 3 months included: sociodemographic, clinical, biological, disease- and treatment-related, response, quality of life (QoL; EORTC QLQ-C30 and ELD14), geriatric (G8 and Geriatric-COre DatasEt [G-CODE]) and safety. Results of feasibility in cohort B (rate of PAL discontinuation at 6 months 28.8%) were reported at SABCS 2021. Here, we report results in cohort A, based on the rate of PAL discontinuation at 18 months for any reason as the primary endpoint. Secondary endpoints included time-to-treatment failure (TTF), progression-free survival (PFS), QoL, and safety. **Results:** For this analysis, 362 patients (from 130 sites) with sufficient data were considered: median age was 78 years (range: 70-94), ECOG was ≥2 in 19.2%, and visceral metastases was present in 39.8%. PAL starting dose was 125 mg, 100 mg, and 75 mg in 80.0%, 14.4%, and 5.6% of patients, respectively, and combined with an aromatase inhibitor in 93.6% or fulvestrant in 6.4%. Baseline scores showed G8 ≤14, ADL ≤5 and IADL ≤3 in 68.2%, 15.5% and 29.4% of patients, respectively. Among the 362 patients, 327 were evaluable for the primary endpoint. With a median follow-up of 20.7 months (95% CI: 18.8-22.0), the 18-month discontinuation rate for PAL was 41.9% (95% CI: 36.6%-47.2%), due to disease progression (20.8%), toxicity (7.7%), patient's choice (6.7%), death (4.6%), or other reason (2.1%). Median TTF and PFS were 22.7 months (95% CI: 19.1–26.0) and 28.1 months (95% CI: 25.6-not reached), respectively. Safety profile showed (360 patients evaluable) 54.4% all grade neutropenia (1.1% febrile neutropenia). Impact of geriatric status on effectiveness and safety will be presented, together with the evolution of QoL. **Conclusions:** In a large real-life population of older women with G8 impaired in two thirds and with ET-sensitive ABC, discontinuation rate of PAL at 18 months was 41.9%, with a median PFS of 28.1 months, consistent with PALOMA2 results. Optimized ET combined with PAL is feasible in unselected older women with HR+ ET-sensitive ABC. Research Sponsor: PFIZER.

Clinico-molecular characteristics associated with outcomes in breast cancer patients treated with CDK4/6 inhibitors: Results from the AURORA Molecular Screening Initiative.

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Background: CDK4/6 inhibitor (CDK4/6i) plus endocrine therapy (ET) is the recommended first line standard of care for patients with estrogen receptor positive (ER+), HER2-negative (HER2-) advanced breast cancer (ABC). However, not all patients derive the same benefit from this treatment. We aimed to identify factors associated with outcome in patients treated with CDK4/6i in a real-world setting. **Methods:** AURORA (NCT02102165) is an international program aimed at studying ABC by performing multi-omics profiling on paired primary tumors and metastases. Here we present exploratory results from AURORA patients treated with first line CDK4/6i + ET. DNA from primary and/or metastatic lesions and germline DNA was sequenced for 411 cancer-related genes. Endocrine resistance was defined according to the 5th ABC international consensus guidelines at the start of the first line. Local histology assessment of the primary tumor was used. Progression-free survival (PFS) was calculated from the start of CDK4/6i treatment until disease progression or death (whichever occurred first). **Results:** We analyzed 339 patients treated with CDK4/6i + ET in the first line. PFS differed significantly among the endocrine resistance subgroups ($p<0.001$). Both *TP53* and acquired *ESR1* mutations were associated with shorter PFS (hazard ratio [HR] 1.59 [95% CI 1.43-6.73], p=0.004 and 3.10 [95% CI 1.16-2.18], p=0.004 respectively). In a multivariable analysis, acquired *ESR1* mutations were significantly associated with worse PFS independently of endocrine resistance status (HR 2.42 [95% CI 1.01-5.79], p=0.048). Mutations in *PIK3CA* were not associated with outcome (HR 0.84 [95% CI 0.63-1.13], p=0.25). No PFS difference was observed between lobular and ductal tumors (HR 1.07 [95% CI 0.66-1.75], p=0.61). **Conclusions:** Endocrine resistance status and *TP53* and acquired *ESR1* mutations were associated with shorter PFS. Factors associated with poor outcome may be used to select patients to test alternative treatment strategies in clinical trials. Clinical trial information: NCT02102165. Research Sponsor: AURORA was funded by Breast Cancer Research Foundation (BCRF) as the main funder; Fondation Cancer (Luxembourg), Fondation contre le Cancer (Belgium), NIF Foundation, Barrie and Dena Webb, Candriam, Fondation Futur 21, Sogerim, Think Pink Belgium (SMART Fund), Cognizant Foundation, Eurofins Foundation, Fund Friends of BIG, managed by the King Baudouin Foundation; Pfizer grant for non-drug research; National Lottery (Belgium).

Subgroup	n (%)	PFS events	Median PFS months (95% CI)
All	339 (100)	194	19.5 (15.9-21.6)
Primary resistant	26 (8)	20	6.6 (3.6-NE)
Secondary resistant	124 (37)	79	14.6 (12.3-19.3)
Endocrine sensitive	93 (27)	48	26.3 (18.6-39.0)
Endocrine Naive	96 (28)	47	27.3 (21.0-40.0)
PIK3CA mutated	137 (40)	73	20.4 (15.6-30.9)
TP53 mutated	79 (23)	54	14.0 (10.8-19.4)
acquired ESR1 mutated*	11 (11)	8	11.7 (3.8-NE)
Lobular	51 (15)	33	19.6 (14.7-26.5)

*Paired samples only (n=96).

Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice (TPC) in patients (pts) with HER2-low, hormone receptor-positive (HR+) unresectable and/or metastatic breast cancer (mBC): Exploratory biomarker analysis of DESTINY-Breast04.

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Background: DESTINY-Breast04 (NCT03734029) showed improved progression-free survival (PFS) and overall survival for T-DXd vs TPC in pts with HER2-low (IHC 1+ or 2+/ISH-negative) mBC. We present exploratory biomarker analysis in pts with HER2-low, HR+ mBC. **Methods:** Biopsy specimens collected from 326 pts after prior treatment were analyzed using RNA-sequencing and intrinsic subtypes estimated by PAM50 gene expression. *ESR1* and *PIK3CA* mutations and known gene alterations associated with resistance to CDK4/6 inhibitors (CDK4/6i) were assessed in baseline (BL) circulating tumor DNA (ctDNA) samples from 414 pts by Guardant OMNI. Association with objective response rate (ORR) and PFS was evaluated. **Results:** Frequencies of BL intrinsic subtypes in the T-DXd and TPC arms were 41.3% and 46.6% for Luminal A, 48.0% and 37.9% for Luminal B, and 9.0% and 11.7% for HER2 enriched, respectively. According to ctDNA results in the T-DXd and TPC arms, respectively, *ESR1* mutations were observed in 51.3% and 54.0% of pts, *PIK3CA* mutations in 36.1% and 41.6% of pts, and at least one CDK4/6i resistance marker (pts with prior CDK4/6i) was detected in 71.5% and 70.2% of pts. Improved T-DXd efficacy was seen regardless of intrinsic subtype (Luminal A, Luminal B, HER2-enriched), *ESR1* mutation, *PIK3CA* mutation, or CDK4/6i resistance markers (Table). **Conclusions:** Greater clinical benefit was consistently observed with T-DXd vs TPC independent of intrinsic subtype, *ESR1* mutation, *PIK3CA* mutation, or known CDK4/6i resistance marker status. Clinical trial information: NCT03734029. Research Sponsor: This study was funded and designed by Daiichi Sankyo, Inc., and AstraZeneca.

Efficacy in biomarker subgroups.

Subgroup	N T-DXd TPC	T-DXd ORR, % (95% CI)	TPC ORR, % (95% CI)	T-DXd PFS, mo (95% CI)	TPC PFS, mo (95% CI)	PFS Hazard Ratio (95%CI)
Luminal A	92 48	55.4 (44.7-65.8)	18.8 (8.9-32.6)	13.0 (10.1-16.4)	7.8 (5.4-12.4)	0.57 (0.36-0.89)
Luminal B	107 39	52.3 (42.5-62.1)	23.1 (11.1-39.3)	8.7 (6.9-11.1)	4.8 (2.7-8.3)	0.60 (0.40-0.92)
HER2 enriched	20 12	65.0 (40.8-84.6)	8.3 (0.2-38.5)	11.0 (6.6-NA)	2.7 (1.4-5.9)	0.15 (0.05-0.40)
***ESR1* mutant**	142 74	54.2 (45.7-62.6)	16.2 (8.7-26.6)	9.8 (8.2-12.0)	6.9 (4.3-10.7)	0.67 (0.47-0.97)
***ESR1* wild-type**	135 63	51.1 (42.4-59.8)	17.5 (9.1-29.1)	10.0 (8.3-12.6)	5.3 (4.0-7.8)	0.43 (0.29-0.62)
***PIK3CA* mutant**	100 57	53.0 (42.8-63.1)	22.8 (12.7-35.8)	9.7 (7.5-12.3)	6.2 (5.3-7.8)	0.60 (0.40-0.91)
***PIK3CA* wild-type**	177 80	52.5 (44.9-60.1)	12.5 (6.2-21.8)	10.0 (8.5-12.2)	4.8 (2.9-8.3)	0.50 (0.35-0.70)
CDK4/6i resistance marker[a] positive	153 73	48.4 (40.2-56.6)	11.0 (4.9-20.5)	9.5 (6.9-10.3)	5.3 (2.9-7.1)	0.56 (0.39-0.80)
CDK4/6i resistance marker negative	61 31	52.5 (39.3-65.4)	22.6 (9.6-41.1)	12.3 (8.4-23.7)	8.4 (5.4-12.8)	0.57 (0.33-1.01)

[a]Included only pts with prior CDK4/6i and ≥1 gene alternation (*CCND1*, *CCNE1*, *CDK6*, *FGFR1/2* amplification; *RB1*, *PTEN*, *RAS*, *AKT1*, *ERBB2*, *FAT1* mutation).

1021 **Poster Discussion Session**

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

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Background: Trastuzumab deruxtecan (T-DXd) was recently approved to treat unresectable/metastatic HER2-low breast cancer. However, patients whose primary tumor is HER2-0 but recurrent/metastatic lesion is HER2-low will lose therapeutic opportunities for T-DXd if a rebiopsy is not performed. In this study, with the largest sample size to date, we aimed to investigate the prevalence of HER2 status conversion. Moreover, it remains debated whether HER2-0 and HER2-low tumors have different prognoses, probably because previous studies did not assess HER2 status entirely based on recurrent/metastatic lesions. Our study aimed to fill this gap. **Methods:** We included 1299 patients with available HER2 status on both primary tumors and recurrent/metastatic lesions at Fudan University Shanghai Cancer Center and West China Hospital. **Results:** A total of 370 (28.5%) patients experienced HER2 status conversion throughout disease recurrence. 144 (31.7%) HER2-0 tumors converted to HER2-low. Inter-metastases heterogeneity of HER2 status was also observed. Compared to HER2-low tumors, HER2-0 tumors showed a higher TP53 mutation rate in the ER-positive subgroup, and a lower PIK3CA mutation rate in the ER-negative subgroup. Patients with tumors converting from HER2-0 to HER2-low had a longer overall survival (HR = 0.59, adjusted P = 0.033) than those with consistent HER2-0 status in the ER-negative subgroup. By combining four risk factors (ER status, Ki67 index, biopsy site, and disease-free interval), we established the first prediction tool to estimate the probability of HER2 status conversion from HER2-0 to HER2-low/positive. **Conclusions:** HER2 status was unstable during the disease course. Our prediction tool could help to screen out patients with a high probability of HER2 status conversion. Our results support that HER2-0 and HER2-low recurrent/metastatic tumors have different genomic features and prognoses. Research Sponsor: FUSCC.

1022 **Poster Discussion Session**

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

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Background: Optimizing sequential use of Antibody Drug Conjugates (ADCs) is an area of unmet need and of rising clinical importance. With the recent approvals of sacituzumab govitecan (SG) for HR+/HER2- and triple negative metastatic breast cancer (MBC) as well as trastuzumab deruxtecan (T-DXd) for HER2-low MBC, many patients are now candidates for multiple ADCs. However, given potential cross-resistance based on antibody target vs payload (Coates et al, Cancer Discov. 2021), optimal sequencing remains uncertain. We evaluated the safety and efficacy of ADC after ADC for patients with HER2 negative MBC. **Methods:** We included all patients at an academic institution treated with more than one ADC for MBC. Each line of ADC beyond the first was evaluated for presence of the same "antibody target" or "payload" compared to prior ADC. Clinicopathological information was gathered by chart review. We defined "cross-resistance" as progressive disease (PD) at time of first restaging on second ADC. Progression-free survival (PFS) was evaluated as time from start of treatment to disease progression or death from any cause. All PFS estimation was done using the KM method. All pairwise comparisons across ADC were done using a Wilcoxon Rank Sum test to allow for divergences from normality in progression times. Significance was declared as a type I error less than 0.05. **Results:** A total of 193 patients with MBC were treated with ADCs between August 2014-February 2023. Among these,32 patients were identified as having received more than one ADC (HR+/HER2- = 13, TNBC = 19, HER2 low = 22). Median age at time of second ADC was 57.1 years (range 31.3-88.6) and patients had received a median of 4 lines (range 2-12) of prior treatment before initiation of second ADC. The median PFS on the first ADC used (ADC1) was significantly longer at 7.55 months (95% CI 3.22-10.25) compared to a median of 2.53 months on the second ADC (ADC2) (95% CI 1.38-4.14) (p=0.006). PFS for ADC2 with antibody target change was 3.25 months (95% CI 1.38 months, n/a) compared to 2.30 months with no target change (95% CI 1.38 months, n/a) (p=0.16). At time of first imaging, cross-resistance was present in 17 cases (53.1%), absent in 12 (37.5%), and not evaluable in 3 cases. When the second ADC contained the same antibody target as the first, cross-resistance was present in 9/13 cases (69.2%), compared to 8/16 cases (50.0%) when the second ADC targeted a different tumor antigen. Similarly, differences were noted based on payload switch vs not. **Conclusions:** This study highlights a subset that had cross-resistance to ADC after ADC, while others had durable responses on latter lines of therapy, particularly if a different antibody target was utilized. Further research is needed to validate these findings and discern mechanisms of clinical resistance to guide optimal sequencing of ADC-based treatment options. Research Sponsor: U.S. National Institutes of Health.

1023 **Poster Discussion Session**

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

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Background: Cytoplasmic cyclin E protein expression, serving as a surrogate for the low molecular weight cyclin E isoform (LMW-E), is a biomarker associated with aggressive breast cancer and predicts resistance to aromatase inhibitors in luminal breast cancer. We investigated the prognostic and predictive value of cytoplasmic and nuclear isoforms of cyclin E in HR+/HER2- metastatic breast cancer (MBC) patients receiving palbociclib CDK4/6 inhibitor and endocrine therapy (PALBO+ET) versus capecitabine (CAPE) in the GEICAM/2013-02 PEARL trial (NCT02028507). **Methods:** Expression of Cytoplasmic and Nuclear isoforms of cyclin E were assessed by immunohistochemistry (IHC). An H-score based on the proportion and intensity of stained cells was explored using median value to categorize in Low / High expression the Nuclear and Cytoplasmic scores (N and C, respectively). In addition, N and C were independently assigned according to staining intensity (1 = no staining, 2 = weak, 3 = intermediate and 4 = strong staining) and then, combined in 4 phenotypes (Ph): Ph1 (N-/C-); Ph2 (N+/C-); Ph3 (N+/C+); and Ph4 (N-/C+), where negative=1-2, and positive=3-4. Cox regression models' analysis were assessed to predict outcome and benefit to treatment, in terms of PFS and OS. Multivariate models were adjusted for confounders: age, site of disease, sites of metastasis, prior chemotherapy for MBC and treatment. Interaction analysis with treatment arm were performed. **Results:** Cyclin E protein was obtained from 344 tumors, with 73% being primary tumors and 27% metastatic. High expression of the Nuclear isoform was independently associated with significantly worse OS (median OS [mOS]=34.23 months [m] for low expression vs 25.72m for high expression; adjusted HR=1.48; p-value=0.016). Phenotype analysis supported this finding, with Ph3 (N+/C+) and Ph4 (N-/C+) demonstrating the worst (mOS=19.55m) and best (mOS=37.19m) outcomes, respectively (using Ph1 as reference, Ph3 HR=2.92; p-value=0.0013). The interaction between the treatment arm and Cytoplasmic cyclin E expression was significant (p=0.0052). Patients with high expression of the Cytoplasmic isoform had significantly better PFS with CAPE (mPFS=14.8m) than with PALBO + ET (mPFS=5.73m) (HR=1.9, p-value=0.0418). Ph4 (N-/C+) had also significantly better PFS for CAPE (mPFS=22.67m) than for PALBO + ET (mPFS=8.51m) (HR=2.94; p-value=0.036). **Conclusions:** This study confirms Cyclin E as a poor prognostic marker associated with worse overall survival in luminal MBC patients. Low molecular weight Cyclin E, detected as Cytoplasmic Cyclin E, identifies luminal MBC that benefit more from CAPE than from PALBO + ET. The low molecular weight Cyclin E isoform appears to be a promising predictive biomarker for the benefit of CAPE and resistance to PALBO + ET treatments in this population. Clinical trial information: NCT02028507. Research Sponsor: AstraZeneca, Pfizer; SEOM.

Early prediction of endocrine responsiveness in ER+/HER2 negative MBC: Pilot study with 18F-fluoroestradiol (18F-FES) CT/PET.

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Background: Estrogen receptors (ER) are considered predictive biomarkers to identify ER+ MBC patients who would likely benefit from endocrine therapies (ET). However, 30 to 40% of ER+ MBC patients fail to achieve a durable response. 18F-FES PET/CT has been shown to represent a valuable and accurate diagnostic tool to determine ER status at the level of metastatic sites and can be proposed as a valid alternative to biopsy of metastatic lesions. In this trial, we evaluated 18F-FES PET/CT as a predictive tool for endocrine responsiveness in ER+ MBC. **Methods:** ET-FES is an international, multicenter, academic clinical trial, conducted within the JTC-2011 ERA-NET TRANSCAN programme. Patients with ER+/HER2- MBC and first evidence of relapse were eligible for the study. All patients underwent a baseline 18F-FES PET/CT in addition to conventional staging procedures. Tumors were classified as endocrine sensitive if overall Standardized Uptake Value (SUV) ≥ 2; SUVmax was measured in the 3 largest lesions to quantify ER expression and a cutoff value of 2 was used to dichotomize results (endocrine sensitive vs resistant). In the ET-FES trial, patients with SUV ≥ 2 received single agent ET until PD; patients with SUV < 2 were randomized to receive single agent ET or chemotherapy (CT). The predictive role of 18F-FES PET/CT results was assessed for PFS and OS by univariate and multivariate analyses. **Results:** Overall, 147 patients (142 for ITT analysis) were enrolled from 04/2015 to 12/2020; 113 presented with 18F-FES SUV ≥ 2 and received ET; 29 pts, with SUV $<$ 2 were randomly assigned to ET or first line chemotherapy (CT), following local clinical practice. After a median follow up of 4.6 years, 51 deaths had occurred (54.2%). Median PFS was 18,0 months (95%CI 11,2- 22,9) in the overall population and in 18F-FES SUV ≥ 2 versus 12,4 months (95%CI 3,1 – NR) in patients with SUV <2 treated with ET and 23.0 months (95%CI 7,7 – 30,0) if treated with CT. Median OS was not reached in the overall patient population and in patients with SUV ≥ 2, treated with single agent ET. Median OS was 28.1 months (95%CI 14,2 – NR) in patients with SUV <2 treated with ET versus 52,8 months (95%CI 16,1 – NR) if treated with CT. The Kaplan–Meier estimate of OS at 48 months was 64.4% (SE +/-5%) in all patients and 66% in 18F-FES SUV ≥ 2; at 60 months was 54.4% (SE +/-6%) and 57% (SE +/-5%), respectively. Among the 113 pts with SUV ≥ 2 treated with ET, the Kaplan–Meier estimate of OS at 60 months was 73.0% if treated with aromatase inhibitors versus 35% in case of fulvestrant or tamoxifen ($p< 0.0005$). **Conclusions:** ET-FES is the first prospective trial to assess the efficacy of ET alone in patients selected for endocrine responsiveness on the basis of whole body molecular ER imaging by 18F-FES PET/CT. These results suggest that the efficacy of ET may be maximized by using the appropriate assessment of endocrine responsiveness at the different metastatic sites. Clinical trial information: EUDRACT 2013-000-287-29. Research Sponsor: ERANET TRANSCAN JTC - AIRC (Italian Foundation for Cancer Research).

Prostate-specific membrane antigen (PSMA) expression in patients with metastatic triple negative breast cancer: Initial results of the PRISMA study.

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Background: Radioligand therapy (RLT) targeting prostate-specific membrane antigen (PSMA) prolongs survival of patients (pts) with prostate cancer. Preliminary immunohistochemistry (IHC)-based studies suggest that PSMA is highly expressed in triple negative breast cancer (TNBC). The PRISMA study aims to assess PSMA expression in pts with metastatic TNBC (mTNBC) via positron-emission tomography/computed tomography (PET/CT) to evaluate the feasibility of PSMA-targeted RLT for TNBC. **Methods:** PRISMA is a prospective, single-center study that enrolled pts with progressive mTNBC and measurable disease on ^{18}F-FDG PET/CT to undergo ^{68}Ga-PSMA-11 PET/CT. TNBC definition (ASCO/CAP) was based on the IHC of the primary breast cancer (BC) or metastasis. Target lesions (TL) were defined as metastatic lesions $\geq$1.5 cm with significant uptake in ^{18}FDG-PET/CT. The same TL regions were propagated to the ^{68}Ga-PSMA-PET/CT. ^{68}Ga-PSMA-11 maximum standard uptake value (SUV_{max}) was measured for each TL. PSMA patterns A and B were defined according to presence of a majority (pattern A) or a minority (pattern B) of positive TL on ^{68}Ga-PSMA (ie. uptake greater than that of normal liver parenchyma). Mann-Whitney U test was used to assess differences in median SUV_{max} ($mSUV_{max}$) between subgroups. **Results:** Ten pts with progressive mTNBC were enrolled. One pt was excluded due to lack of TL on ^{18}FDG-PET/CT. Median age was 48 years (range 36-68), median number of TL per patient was 8 (5-18). Five pts had a TNBC IHC since the initial BC diagnosis, while 4 had a switch to TNBC (4 with initial estrogen receptor [ER]-positive and 1 with HER2-positive BC). All evaluable pts had inter- and intra-organ heterogeneity in PSMA uptake in TL and 2 pts had some mismatch with FDG-positive and PSMA-negative TL. $mSUV_{max}$ was 2.99 (range 1.7-6.3) in the overall population and was higher in pts with pattern A (5.1 vs 2.6 in patterns A and B, respectively, p = 0.03). mSUVmax was numerically higher in younger pts (5.0 vs 2.6 in pts $<$50y and $\geq$50y, p = 0.28), PD-L1-positive (5.0 vs 2.7 in PD-L1-positive and -negative, p = 0.14), de novo metastatic disease (5.0 vs 2.9 in de novo and recurrent BC, p = 0.38) and those with ER-negative primary breast tumor (3.4 vs 3.0 in ER-negative and ER-positive primary BC, p = 0.9). **Conclusions:** A significant PSMA uptake was observed in a proportion of pts with mTNBC. Inclusion of additional pts and translational analyses will allow the identification of PSMA expression determinants. PSMA-targeted RLT may be considered as an innovative therapeutic strategy to be explored in selected pts with mTNBC. Research Sponsor: Association Jules Bordet.

Pts ID	Stage at diagnosis	Treatment lines	PD-L1	PSMA pattern	mSUVmax (range)
1	IV	1	Pos	A	5.0 (1.7-16.0)
2	I	2	Neg	B	2.7 (1.8-5.3)
3	II	3	Neg	B	1.7 (0.7-3.9)
4	II	2	-	B	2.2 (2.0-5.0)
5	IV	5	Pos	A	6.3 (1.9-9.6)
7	III	1	Neg	A	3.0 (1.2-7.2)
8	IV	1	Pos	B	2.6 (1.5-4.7)
9	III	4	Pos	A	5.2 (2.5-7.6)
10	II	3	Pos	B	4.1 (1.0-7.6)

1027 **Poster Session**

Clinical features, genomic landscapes, and survival outcomes of HER2-low breast cancer.

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Background: Novel human epidermal growth factor receptor 2 (HER2)-directed antibody–drug conjugates prompt the identification of the HER2-low subtype. To investigate whether HER2-low breast cancer can be defined as a distinct biological subtype, our study conducted a comprehensive analysis on the clinical and molecular features among patients with different HER2 statuses. **Methods:** Clinical and genomic data of 579 metastatic breast cancer patients were reviewed from our next-generation sequencing (NGS) database. Genomic data of breast tumor samples was generated by targeted NGS using a cancer-related gene panel. The cohort included 220 HER2-zero, 194 HER2-low and 165 HER2-positive patients according to the HER2 status from the most recent pathological results. **Results:** First, the clinicopathological characteristics of HER2-low patients were associated with hormone receptor (HR) status. Less lymph node invasion and higher bone metastasis in HER2-low patients were probably because of the higher percentage of HR-positive tumors in HER2-low patients than HER2-zero and HER2-positive patients (63.19%, 42.02% and 28.00%, respectively, $p<0.0001$). Second, HER2 status shifting from primary to recurrent breast cancer was common, with 38.1% and 48.4% of HER2-zero primary tumors converting to HER2-low tumors when they metastasized in the whole population and the HR-positive subgroup, respectively. Third, HER2-low patients had more brain and lung metastases and cases of de novo stage IV breast cancer than HER2-zero patients in the HR-positive subgroup. Fourth, germline *BRCA2* mutations were observed only in HER2-low patients (11/139, 7.91%) and HER2-low tumors had more somatic *PIK3CA* mutations than HER2-zero tumors in the HR-negative subgroup. Fifth, HER2-low patients had a longer median overall survival (mOS) and median disease-free survival (mDFS) than HER2-zero patients (mOS:49.1 vs. 30.3 months, log rank P = 0.0005; mDFS: 28.17 vs. 20.27 months, log rank P =0.036), but difference was not evident when paired by HR status. Finally, three molecular subtypes based on genomic alterations in HER2-low breast cancer were identified, and Cluster 2, which enriched in *TP53* mutations, was significantly associated with worse outcomes, which provided novel insights into heterogeneity in HER2-low breast cancer. **Conclusions:** The clinical and molecular significance of HER2-low status was influenced by HR expression, and HER2-low tumors had distinct features in subtype analyses based on HR status. Our elaboration of molecular subtypes in HER2-low tumors encourages clinicians to consider the heterogeneity in HER2-low breast cancer. Research Sponsor: National Natural Science Foundation of China (ID: 81903084).

1028 **Poster Session**

Concordance between liquid and tissue biopsy in participants with newly diagnosed recurrent breast cancer.

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Background: Tissue biopsy is recommended to confirm breast cancer (BC) recurrence. Liquid biopsy [including circulating tumour cells (CTCs) and circulating tumour DNA (ctDNA)] is a non-invasive approach for detecting cancer that may provide information to identify treatment choices and replace invasive biopsies. This ongoing study aims to assess the concordance between tissue and liquid biopsy testing in subjects presenting with suspicion of distant recurrence from BC. **Methods:** Patients with suspected metastatic BC were enrolled; tumour characteristics and treatment were recorded. Blood samples were collected within 30 days before tissue biopsy, or within 7-28 days after tissue biopsy and before any systemic or radiation treatment. Samples were shipped to EPIC Sciences and processed within 96 hours; after plasma isolation, nucleated cells were plated; slides and plasma were banked. CTCs were identified using Epic Sciences digital imaging and machine learning algorithms. Single-cell isolation for genomic ctDNA analysis was performed. Cell free DNA was analyzed using a validated NGS panel to detect ctDNA alterations. The presence of metastases was classified as suspicious, highly suspicious, definitely metastatic BC or other by the treating oncologist based on the patient's clinical presentation and biopsy pathology results. Epic Sciences classified samples into similar categories based on CTC and ctDNA assay results. These classifications were performed independently. Sensitivity of the Epic Sciences methodology to detect metastatic BC (as determined by the treating oncologist), and its false positive rate were calculated. **Results:** 100 patients were enrolled from June 2020 to October 2022; shipping delays precluded EPIC assays in six patients; 94 patients were analyzed. Of 83 cases deemed suspicious, highly suspicious, or definitely metastatic BC by the treating oncologist, 61 were also deemed so by Epic Sciences (sensitivity of 73.5%, 95% confidence interval, CI 63.1% - 81.9%). Of 66 cases assigned as suspicious, highly suspicious, or definitely metastatic BC by the Epic Sciences, 4 had new primary cancers (3 lung cancer, 1 hepatocarcinoma), for a false positive rate of 6.1% (95% CI 1.9% - 15.0%). One additional case was classified as un-specified adenocarcinoma (possibly breast) by the treating oncologist; resolution awaits further follow-up. **Conclusions:** Preliminary results show that 73.5% of distant BC recurrences were correctly identified by liquid biopsy. A small number of false positive results occurred in patients with other new primary cancers. Additional analyses with CTC characterization are ongoing. Research Sponsor: Epic Sciences; London Health Science Foundation; Grants.

		Epic Sciences		
		Suspicious, highly suspicious or definitely metastatic BC	Other*	Total
Treating Oncologist	Suspicious, highly suspicious or definitely metastatic BC	61	22	83
	Other*	5	6	11
	Total	66	28	94

*Other cancer diagnosis, other benign condition and non-diagnostic.

1029 **Poster Session**

Effect of homologous recombination deficient (HRD) breast cancers on a distinct immune marker phenotype by comprehensive genomic and immune profiling (CGIP).

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Background: Preclinical evidence suggests that breast cancer with features of genomic instability may upregulate the host antitumor immune response by producing neoantigens through DNA damage and increasing interferon production through the stimulator of interferon genes (STING) pathway. In this study, we evaluated the association between features of genomic instability and immune response in a real-world breast cancer population. **Methods:** We analyzed retrospective comprehensive genomic and immune profiling (CGIP) results from 529 breast tumors tested in the real-world clinical setting. We defined the HRD phenotype as tumor with any single nucleotide variants (SNV), indels, copy number variations (CNV) or fusions in the following genes: ARID1A, ATM, ATRX, BAP1, BARD1, BLM, BRCA1/2, BRIP1, CHEK1/2, FANCA, MRE11A, NBN, PALB2, RAD50 and RAD51. Otherwise, they were considered HR-proficient (HRP). PD-L1 expression (CPS positive $\geq$10) and TMB (high $\geq$10 Mut/Mb) were determined using IHC and DNA sequencing, respectively. mRNA expression signatures of tumor inflammation (TIGS, strong/moderate/weak), cell proliferation (CP, high/moderate/poor) and cancer testis antigen burden (CTAB, high/low) were determined by RNA-sequencing from a 395-gene panel. We used over-representation and proportion analysis using chi-squared test to determine association of HRD to immune correlates. **Results:** Among 529 cases, the median patient age was 63.2 years (25.5-93.5). The majority of patients were female (519, 98%), and the most common tumor histology was invasive ductal carcinoma (287, 54%). A total of 405 (77%) and 124 (23%) of patients had HRD and HRP phenotypes, respectively. A greater proportion of HRD tumors (16%) had higher TMB compared to HRP (5.6%, p=0.003). HRP tumors showed a relatively low CP index, whereas HRD tumors were associated with a moderate CP index score (p = 0.007). HRD phenotype was associated with a significantly higher proportion of weakly inflamed tumors, as represented by lower TIGS scores (p=0.007). No significant difference in PD-L1 or CTAB was found between HRD and HRP phenotypes. **Conclusions:** Breast tumors with mutations in the HR genes demonstrated greater TMB and moderate cellular proliferation index of both tumor and immune cells, which suggest susceptibility to immune checkpoint inhibitors. Interestingly, this cohort lacked elevated markers of immune infiltration (TIGS), indicating a mechanism of potential tumor immune evasion. These results suggest that CGIP may allow for more informed treatment decisions in HRD breast cancers. Furthermore, assessment of HR status and immunotherapy susceptibility may support clinical trial selections for therapies targeting the complex interplay of genomic and immune components of breast cancer (e.g., a combination of PARP inhibitor and immunotherapy). Research Sponsor: Labcorp.

1030 **Poster Session**

Comparison of immune microenvironment between primary and metastatic breast tumors.

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Background: Immune evasion is one of the mechanisms by which cancer cells gain the ability to metastasize from the primary tumor to distant sites. In triple-negative breast cancer (TNBC), metastatic tumors are shown to be more immunologically silent than primary tumors. As a result, there are varying degrees of responses to immunotherapy between early-stage and metastatic tumors. Positive clinical responses to immune checkpoint inhibitors (ICIs) are seen in patients with early-stage TNBC regardless of PD-L1 expression. In this study, we investigated the differences in the immune signatures of primary and metastatic breast cancer in a real-world patient population. **Methods:** We analyzed retrospective comprehensive genomic and immune profiling (CGIP) results from 529 breast tumors tested in the real-world clinical setting. Tumor specimens were classified as primary breast (PB), any lymph nodes (LN; regional and non-regional) or metastatic visceral (MV) sites. LN samples were chosen as positive controls due to expected elevated inflammatory signaling. PD-L1 (CPS positive $\geq$10) and TMB (high $\geq$10 Mut/Mb) were determined using IHC and DNA sequencing, respectively. mRNA expression signatures of tumor inflammation (TIGS, strong/moderate/weak) and expression of LAG3, TIGIT and TIM3 were determined by RNA-sequencing from a 395-gene panel. LAG3, TIGIT and TIM3 were selected due to emerging clinical trials in solid tumors. We used over-representation and proportion analysis using chi-squared test to determine the association of specimen sites to various genomic and immune correlates. **Results:** Among 529 cases, the median patient age was 63.2 years (25.5-93.5). The majority of patients were female (519, 98%), and the most common tumor histology was invasive ductal carcinoma (287, 54%). A total of 224 (42%), 72 (14%), and 232 (44%) of patients had specimens from PB, LN, MV, respectively, while 1 (0.19%) patient had an unknown source. Samples of PB harbored greater degree of immune infiltration, demonstrating higher TIGS score than MV ($p=0.014$). Primary lesions also demonstrated a greater proportion of PD-L1 positive than metastatic lesions (44% vs 21%, $p < 0.001$) and higher expressions of immune checkpoints such as TIGIT ($p<0.001$), LAG3 ($p=0.037$) and TIM3 ($p<0.001$). **Conclusions:** We found that non-lymph node breast cancer metastases harbor a less active immune response than primary breast lesions, showing a lower degree of immune cell infiltration and decreased expression of immune checkpoint markers. These findings support the notion that the immune microenvironment of breast cancer metastases is immunosuppressive and may exhibit a tempered response to ICIs. Therefore, combination treatments of ICIs with chemotherapy, targeted therapies or cancer vaccines may be promising therapeutic approaches to enhance the immune responses and potentially overcome resistance to ICIs in metastatic breast cancer. Research Sponsor: Labcorp.

1031 **Poster Session**

Metastatic patterns and outcomes by HER2 and hormone receptor (HR) status in patients (pts) with metastatic breast cancer (mBC).

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Background: HER2-low status in mBC is predictive of benefit to trastuzumab deruxutan, but whether it is biologically distinct from HER2-neg disease is unclear. To better understand the prognostic significance of HER2-low status, we assessed patterns of metastases and real world overall survival (rwOS) by HER2 and HR status. **Methods:** Pts with mBC diagnosis from 1/1/2011 to 5/31/2022 were selected from the nationwide deidentified Flatiron Health electronic health record (EHR)-derived database. HER2 and HR status was derived from human abstraction (IHC 0-1+/2+/3+, FISH pos/neg, ER/PR) and machine learning-extraction (to classify IHC 0/1+). HER2 and HR tests prior and up to 60 days after metastatic diagnosis date (met Dx date) were included, results closest to met Dx date were used. Sites of metastasis (SOM) were grouped into mutually exclusive groups: brain, non-visceral (bone, skin, lymph node) and visceral (liver, lung, etc). Metastatic patterns stratified by HR/HER2 status were compared using chi-square tests. The association between HER2 status and rwOS, stratified by HR status, was evaluated using Cox models adjusted for age, race/ethnicity, practice, SOM, SES, and stage. rwOS stratified by HR/HER2 status and SOM were estimated via KM analysis. **Results:** Among 22,932 pts with mBC, HER2-low prevalence was 49%. HER2-low mBC was more likely to be HR+ than HER2-neg or HER2+ (84%, vs 70% and 65%; $p<0.01$). Pts with HER2-low and HER2-neg mBC had similar SOM overall, distinct from HER2+. For example, among HR+ pts, HER2-low and HER2-neg pts were less likely than HER2+ pts to have brain (4% and 4% vs 10%; $p<0.01$) or visceral metastases (51%, 50% vs 58%; $p<0.01$) but more likely to have non-visceral metastases (45% and 46% vs 32%; $p<0.01$). Compared to HER2-low pts, HER2-neg pts had similar rwOS if HR+ (hazard ratio 1.02, 95% CI 0.98-1.08) and slightly worse if HR-neg (hazard ratio 1.18, 95% CI 1.03-1.21). rwOS varied by HR/HER2 status and SOM. **Conclusions:** Our findings indicate that HER2-low mBC has biologic similarities to HER2-neg mBC. While slight differences were observed between HER2-neg and HER2-low pts in the HR-neg subgroup, overall rwOS differences were associated more strongly with HER2+ status, HR+ status, and metastatic pattern, indicating that HER2-low status may be more informative as a predictive rather than a prognostic biomarker. Research Sponsor: Flatiron Health.

rwOS in months, median (95% CI), stratified by HR/HER2 status and SOM.

	HR+/HER2-low N = 9,376	HR+/HER2-neg N = 5,094	HR+/HER2+ N = 2,847	HR-neg/HER2-low N = 1,873	HR-neg/HER2-neg N = 2,153	HR-neg/HER2+ N = 1,570
Brain	17.8 (14.2 - 20.2)	15.9 (13.0 -24.0)	28.4 (24.9 - 34.2)	8.3 (7.1 - 10.7)	8.3 (6.4 - 9.8)	17.2 (13.4 -26.5)
Visceral	34.6 (33.3 - 36.5)	33.6 (31.9 -36.3)	46.1 (42.0 - 50.2)	12.8 (12.2 - 14.1)	11.5 (10.6 - 12.8)	37.2 (33.6 - 41.4)
Non-visceral	47.3 (45.7 - 49.7)	47.2 (43.7 - 49.2)	61.0 (56.0 - 66.2)	21.0 (18.3 - 24.0)	19.6 (18.1 - 23.3)	54.9 (49.0 - 72.9)

Gene expression profiling of paired primary breast cancers and brain metastases to identify brain metastases-specific biological changes.

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Background: Despite the clinical impact of breast cancer (BC) brain metastases (BM), their biological complexity still remains poorly understood. We here evaluate the genomic profile of paired primary and metastatic samples to characterize biological changes acquired by BC during metastatization to the brain. **Methods:** The expression of 758 BC–related genes was evaluated using the BC360 Panel (nCounter platform) in matched primary BC and their associated BM. Intrinsic molecular subtyping was determined using the PAM50 subtype predictor (Parker et al. JCO 2009). Hormone receptor (HR) and HER2 status were evaluated on the BCBM. A False Discovery Rate (FDR) corrected paired two-class SAM was used to identify changes in single genes expression between paired BC and BMs samples. **Results:** Twenty-one matched primary BC and BMs samples were analyzed. BC subtype evaluated on the BMs was distributed as follows: 24% (N=5) HR-/HER2-, 24% (N=5) HR+/HER2- and 52% (N=11) HER2+. A considerable shift in PAM50 subtype was observed between primary BC and paired BM. While subtype concordance was high for HER2-enriched (HER2-E) tumors (100%), all Luminal A (LumA) primary BCs switched to either HER2-E (75%) or Luminal B (LumB, 25%) on the BM sample, as did 45% of Basal-like BCs (Basal to HER2-E). A clinical switch from HER2- primary BC to HER2+ BM (defined by IHC and ISH) was observed in only one pair (5%). Consistently, HER2-E ($p<0.001$) and LumB (p=0.001) PAM50 signatures were significantly more expressed, while the LumA ($p<0.001$) and Normal-like (p=0.001) signatures were significantly less expressed in BMs as compared to paired primary BCs (FDR-corrected Wilcoxon paired signed rank test). No significant change was observed in the expression of the Basal-like signature (p=0.562). Among the 758 evaluated genes, 60 and 318 genes, respectively, were significantly up- and downregulated in BMs as compared to primary BC (FDR<5%). Upregulated genes were enriched, among others, in genes involved in survival and migration (e.g. FGFR4), cell proliferation (e.g. CCNB1, CDK1) and HER2-amplicon (e.g. ERBB2, GRB7). Downregulated genes were enriched in genes involved in immune response (e.g. CD8A, CCL5, PDCD1LG2, TNF), angiogenesis (e.g. PDGFRB) and response to hormonal stimuli (e.g. ESR1, BCL2). **Conclusions:** Gene-expression profiling of matched primary BCs and BMs shows recurrent gene expression modifications in metastatic samples which might have potential therapeutic implications (e.g. acquisition of HER2-E subtyping and increase in ERBB2 mRNA levels). Research Sponsor: University of Padova - STARS Grant; AIRC.

	Brain Metastasis			
Primary Breast cancer	**Basal-like**	**HER2-enriched**	**Luminal A**	**Luminal B**
Basal-like	6 (55%)	5 (45%)	0	0
HER2-enriched	0	6 (100%)	0	0
Luminal A	0	3 (75%)	0	1 (25%)
Luminal B	0	0	0	0

1033 **Poster Session**

UGT1A1 *28/*28 genotype and risk of toxicity and disease progression in breast cancer patients treated with sacituzumab govitecan-hziy.

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Background: In metastatic and locally recurrent breast cancer the antibody drug conjugate, sacituzumab govitecan-hziy (SG), is approved as a second-line therapy in triple negative disease and a third-line therapy and beyond for ER+, endocrine resistant disease. UGT1A1 metabolizes the SN-38 payload of SG, and polymorphisms of the gene can lead to decreased enzyme activity and increased toxicity. We sought to determine if patients who were homozygous for the UGT1A1*28 allele polymorphism (*28/*28) experienced increased toxicity and a lower rate of disease progression when treated with SG. **Methods:** To evaluate the association of the *28/*28 genotype with the competing endpoints of Discontinuations for Disease Progression, Toxicity, and Futility, this pilot study undertook a single-center, retrospective chart review of breast cancer patients who received SG at City of Hope. Eligible subjects included breast cancer patients who received at least one dose of SG, had a known UGT1A1 status, and were followed for toxicity and disease progression. Data collection and analysis included reasons for discontinuing SG, onset of adverse effects, UGT1A1 status, age, gender, race and ethnicity, prior lines of therapy, and tumor receptor status. **Results:** Between July 2020 and September 2022, 67 women and 1 man underwent UGT1A1 testing prior to initiation of SG; the median age was 57.8 years, 75.0% had triple negative disease, and SG was given as a median third line of therapy. Seventeen (25%) patients were homozygous for *28 and 24 (35.3%) were heterozygous. Notably relating race and genotype, all 7 self-reported Black subjects were either carriers or homozygous for *28; there were no Black wildtype subjects. Most subjects were followed until Discontinuation for Disease Progression (55.9%), Toxicity (8.8%), or Futility (5.9%). Alternatively, 4.4% of subjects were lost to follow-up and 1 subject halted treatment due to cancer remission. The remaining 23.5% of subjects still took SG by the close of study in November 2022. On competing risk analysis comparing the wildtype group, *28/*28's association with increased Discontinuation for Toxicity, was confirmed with a Hazards Ratio of 5.52 (95% confidence interval [CI] 1.15-26.49, p = 0.03). In contrast, Discontinuation for Disease Progression was unassociated to *28/*28 status in comparison to the wildtype group with a Hazards Ratio of 0.80 (95% CI 0.39-1.65, p = 0.54). **Conclusions:** Despite the relatively small sample size, 25% of patients had the *28/*28 genotype. We confirmed that *28/*28 is associated with a higher risk for discontinuation of SG for toxicity without an association to disease progression based on mutation status. Early UGT1A1 testing as standard practice may identify patients at risk for excess toxicity, who may undergo early dose reductions to prevent discontinuation of this important advanced breast cancer treatment. Research Sponsor: City of Hope Comprehensive Cancer Center.

1034 **Poster Session**

Negative estrogen receptor expression assessed by 18F-FES PET in metastatic breast cancer with ER-positive primary tumor.

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Background: The 18F-fluoroestradiol positron emission tomography/computed tomography (18F-FES PET/CT) technique provides a convenient method to evaluate the overall estrogen receptor (ER) expression in metastatic breast cancer (MBC) patients. There are long debates on the characteristics and treatment strategy of patients with positive primary ER lesion but negative ER expression in metastatic disease. 18F-FES PET offers an opportunity to answer this question. **Methods:** This study enrolled MBC patients with ER-positive primary tumor who received 18F-FES PET/CT in our center. Descriptive statistics were used in clinicopathologic characteristics and compared with Chi square test or t test. Progression-free survival (PFS) was estimated by Kaplan-Meier method and compared by log-rank test. **Results:** 16.46% (52/314) patients with an ER-positive primary tumor had negative ER expression assessed by 18F-FES for MBC prior to receiving first-line systemic therapy. The rate of ER-negativity tested by 18F-FES was negatively co-related with levels of ER expression in early stage, with a positive to negative conversion in 2 of 3 (46.3%) ER-low (ie, ER 1%-9%) tumors, 7 of 10 (70.0%) ER-moderate (ie, ER 10%-49%) tumors, 16 of 114 (14.0%) ER-high (ie, ER 50%-95%) tumors, and 1 of 8 (12.5%) ER-very high (ie, ER $>$ 95%) tumors ($p < 0.001$). Chemotherapy (83.33%, 40/48) was the most common treatment strategy afterward, among which capecitabine monotherapy (64.29%, 27/42) was a dominant alternative. PFS was significantly prolonged with capecitabine alone versus other chemotherapy (median PFS: 13.14 vs 6.21 months, $p = 0.035$). **Conclusions:** 18F-FES could identify negative conversion of ER in MBC which occurred frequently. Patients with lower ER expression in the primary lesion were more likely to have negative ER expression in the metastasis. In real-world clinical practice, chemotherapy was the primary choice by most physicians and capecitabine monotherapy had shown good efficacy. Research Sponsor: None.

1035 **Poster Session**

Comprehensive characterization of androgen receptor expression in breast cancer.

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Background: The androgen receptor (*AR*) is a hormone-regulated transcription factor that plays an important role in breast cancer (BC) pathogenesis. While estrogen receptor inhibitors are well-studied in BC, the role of AR on prognosis and therapy is less well-known. Here we aim to characterize the clinicopathologic and molecular features of *AR* expression in BC. **Methods:** 27,169 BC samples were tested by NGS (592, NextSeq; WES, NovaSeq), WTS (NovaSeq) (Caris Life Sciences, Phoenix, AZ). Microsatellite-instability (MSI) was tested by IHC and NGS. Tumor mutational burden (TMB) totaled somatic mutations per tumor (high≥10 mt/MB). Tumors with *AR*-high(H) and *AR*-low(L) expression were classified by top and bottom quartile, respectively. Real world overall survival (OS) and treatment-associated survival was obtained from insurance claims and calculated from tissue collection or treatment start to last contact using Kaplan-Meier estimates. Statistical significance was determined by chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons ($q<0.05$). **Results:** Median *AR* expression was higher in lobular compared to ductal carcinoma (2.2-fold) and in $HR^+/HER2^-$ compared to TNBC (13.9-fold). Compared to *AR*-L, *AR*-H BC had higher frequency of *PIK3CA* (50.6% vs 12.7%), *CDH1* (20% vs 2.2%), *ESR1* (12.8% vs 1.4%), *MAP3K1* (9.4% vs 1.4%), *GATA3* (11.2% vs 2.7%), *AKT1* (5.7% vs 1.4%), *NF1* (8.6% vs 3.6%), *ARID1A* (6.9 vs 3.6), *SPEN* (2.8% vs 1.5%), and *PTEN* (7.9% vs 6.2%) mutations and TMB high (9.5% vs 7.7%), but lower frequency of dMMR/MSI-H (0.6% vs 1.7%) and PD-L1 (18.7% vs 45.3%) positivity (all $p<0.05$). *AR*-H tumors also showed enrichment of the *IL2-STAT5* pathway (NES: 1.33, FDR: 0.24). Further, *AR*-H BC had higher expression of immune checkpoint genes (*CD274*, *PDCD1LG2, LAG3, HAVCR2, FOXP3*, FC: 1.1-1.4, all $p<0.05$) and T cell inflamed scores (32.5% vs 26.2%, $p<0.05$). *AR*-H BC had increased immune cell infiltration of B cells (6% vs 4%), M2 Mφ (5% vs 2%), and NK cells (3% vs 2%), but decreased infiltration of M1 Mφ (2% vs 3%) (all $p<0.05$). *AR*-H BC had upregulation of M2 Mφ related genes (*ARG1, IL10, CCL17, CXCR1*, FC: 1.2-1.8, all $p<0.05$) and downregulation of M1 Mφ related genes (*CCL2, CCL5, CXCL9, CXCL10*, FC: 1-1.5, all $p<0.05$). *AR*-H BC was associated with improved OS compared to *AR*-L BC (mOS: 1843 vs 1096 days; HR 0.6, 95% CI 0.5-0.7, $p<0.00001$), and with doxorubicin (2294 vs 2054 days; HR 0.7, 95% CI 0.5-0.9, $p<0.001$) , paclitaxel (2239 vs 1967 days; HR 0.7, 95% CI 0.5-0.9, $p<0.001$) and trastuzumab (inf vs 2351 days; HR 0.6, 95% CI 0.4-0.9, $p<0.01$) treatment. **Conclusions:** Our data suggest a strong association between *AR* expression and increased mutations in several cancer related genes, immune checkpoint markers, the *IL2-STAT5* pathway, differential immune cell infiltration, and improved overall survival. Research Sponsor: None.

Metastatic breast cancer (MBC) with ultra-high tumor mutational burden (UHTMB): A comprehensive genomic profiling (CGP) study.

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Background: Pts with MBC whose tumors feature high TMB (≥ 10 mutations/Mb) are eligible for on label immune checkpoint inhibitor (ICI) treatment. This study evaluated the genomic landscape of MBC with "Ultra high" TMB, defined at > 20 mutations/Mb. **Methods:** 2049 MBC underwent hybrid capture-based CGP to evaluate all classes of genomic alterations (GA), TMB, microsatellite instability (MSI) and trinucleotide mutational signatures. HER2 IHC results were available in a subset of pts. PD-L1 expression on immunocytes was determined by IHC (Ventana SP142). **Results:** 45/2049 (2.2%) of MBC were UHTMB. 45 (100%) pts had metastatic disease. 38 (84%) had documented Stage IV disease and 7 documented axillary LN metastases at the time of sequencing. Local breast tumor was used for CGP in 19 (42.2%) MBC and metastatic site biopsy was used in 26 (57.8%). When compared with 2004 non-UHTMB pts with UHTMB were older (mean 64.6 yrs vs 58.2 yrs p < .0001), more often had lobular histology (40.0% vs 14.5% p < .0001) and ER+ disease (86.6% vs 70.0%). Of the 35 UHTMB cases with HER2 IHC data available, 11 (31.4%%) were HER2 IHC negative (0+), 21 (60.0%) were HER2-low status (9 1+ and 12 2+/ISH negative) and 3 (8.6%) were HER2 IHC positive (3+). 1/3 HER2 IHC2+ cases and 2/45 (4.4%) of all UHTMB cases were positive for HER2 copy number gain on CGP. UHTMB cases had more driver GA/tumor (mean 9.8 vs 5.7 p < .0001) and were less often TNBC (13.3% vs 27.0% p = .041) compared to non-UHTMB high cancers. Mutation signature analysis revealed APOBEC was predominant in UHTMB samples (82.5%); MMR signature was also observed in 10% of cases. MSI high status was significantly more frequent in UHTMB high cases (11.6% vs 0.4% p < .0001). GA more frequently identified in UHTMB cases included *CDH1* (45.5% vs 14.3% p < .0001), *PIK3CA* (81.8% vs 37.9% p < .0001), *CDKN2A* (11.4% vs 3.2% p = .017), *ARID1A* (25.0% vs 5.0% p < .0001) and *NF1* (20.5% vs 5.9% p = .0014). PD-L1 (*CD274*) gene amplification (2.3% vs 1.3%) or protein expression by the Ventana SP142 assay (57.14% vs 51.10%) were not significantly different among groups. **Conclusions:** UHTMB MBC is a rare, yet clinically important subset of clinically advanced breast cancer driven by APOBEC mutagenesis, with high incidence of ER+ lobular histology and frequent alterations in *CDH1* and *PIK3CA*. In addition to potential benefit from ICI based treatment, UHTMB MBC present with a high frequency of HER2-low status which may impact therapy decisions for this rare disease. Research Sponsor: Foundation Medicine.

	Cases with 10-20 Mut/Mb (120)	Cases with TMB < 20 Mut/Mb (2004)	Cases with TMB >20 Mut/Mb (45)	P Value (TMB < 20 vs >20)
Mean Age	60.3	58.2	64.6	0.000
ER+ Status by IHC	69.10%	68.22%	86.60%	0.013
HER2+ Amplification by CGP	14.17%	8.87%	6.81%	NS
Frequency of ILC Status	31.77%	14.50%	40.00%	< .0001
TNBC Status	20.83%	27.05%	13.30%	0.041
CDH1	27.10%	14.32%	45.50%	< .0001
PIK3CA	55.10%	37.86%	81.80%	< .0001
MSI High Frequency	1.81%	0.40%	11.60%	< .0001
Mean TMB	12.500	3.5	32.4	< .0001

1037 **Poster Session**

Association of C-MYC, MYC target gene, and unfolded protein response (UPR) expression with clinical benefit from the oral aurora kinase A (AURKA) inhibitor, alisertib (A), in combination with paclitaxel (P) compared with P alone in patients (Pts) with HER2-negative metastatic breast cancer (MBC).

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Background: AURKA is a key regulator of the mitotic spindle, G2/M transition and epithelial-mesenchymal transition. AURKA is amplified and/or overexpressed in breast cancer and is associated with therapy resistance and worse survival. A randomized phase II trial in hormone receptor (HR)-positive, HER2-negative and triple negative (TN) MBC pts showed that addition of A to weekly P significantly improved progression-free survival (PFS) compared with P alone (O'Shaughnessy J et al. *JAMA Network Open*, 2021). Pts' primary or metastatic disease tissues were analyzed for biomarkers associated with clinical benefit from A. **Methods:** Retrospective analysis of tumor whole exome and whole transcriptome sequencing of formalin-fixed paraffin embedded pre-treatment tissues from 96 pts (77 HR+, 19 TN) was performed. Clinical benefit from A+P or P was defined as having PFS of at least 6 mos and lack of benefit as PFS less than 6 mos. Enrichment for cancer gene mutations was assessed using Fisher's exact test. Transcriptome data were evaluated for differential expression with DeSeq2 and gene set enrichment analysis (GSEA) and compared to cancer hallmark gene sets. Molecular features were compared between A+P responders and non-responders, P responders and non-responders, and A+P and P responders. P-values <0.05 were considered significant. **Results:** *PIK3CA*, *TP53*, and *CDH1* were altered in 41%, 39%, and 13% of tumors, respectively, and these and other known cancer genes were not associated with A+P benefit. Alterations in *AKT1*, *PIK3CA*, *ERBB2*, *CDH1*, *TP53*, and *KMT2C*/*KMT2D*, as well as amplifications of *CCND1*, *MYB*, and *MDM2*, did not preclude benefit from A+P. RNA expression of AURKA, or its upstream regulator, FOXM1, was not significantly different based on treatment group or benefit from A+P or P. Increased C-MYC RNA expression ($p=0.008$), and enrichment for MYC targets and UPR by GSEA were enriched in pts with lack of benefit from P compared to those with benefit from P ($p<0.05$), but not in pts with lack of benefit from A+P. Wnt/Beta-catenin signaling was enriched in pts with lack of benefit from P compared to those with benefit from P ($p=0.03$), and with lack of benefit from A+P compared to those with benefit from A+P ($p=0.086$). Benefit from A+P was associated with enrichment for MYC targets and UPR compared with benefit from P ($p=0.024$), suggesting activity of A+P, but not P, with high MYC activation and UPR. **Conclusions:** A added to P improved PFS in HR+ HER2- and TN MBC pts compared with P alone. Pts whose breast cancers had increased C-MYC expression, high MYC activation and increased UPR on RNA expression derived greater clinical benefit from A+P than from P alone. Clinical trial information: NCT02187991. Research Sponsor: Takeda Pharmaceuticals.

1038 **Poster Session**

Multi-factor dynamic analysis of ctDNA and CTC to aid the diagnostic prognosis of patients with metastatic breast cancer (MBC).

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Background: The monitoring of circulating tumor DNA (ctDNA) and circulating tumor cell (CTC) in patients with MBC predicts treatment resistance and prognosis. We previously reported that *ESR1* alterations in ctDNA were associated with tumor tissue characteristics and CTCs which may predict metastasis and worse prognosis in MBC (2019 ASCO#1036, 2022 ASCO#1057). Furthermore, ctDNA can be used to evaluate tumor heterogeneity in MBC (2020 ASCO #1028). Here, we report a multi-factor analysis in ctDNA and CTC which may help to elucidate disease prognosis in MBC. **Methods:** This study included 391 MBC patients who received systemic treatment before 2022 under an IRB-approved clinical trial at NU Lurie Cancer Center. Whole blood samples (7.5ml/each) were collected from all patients at three time points including before treatment, three months, and six months after treatment for CTC enumeration using the CELLTRACKS system (Menarini). The corresponding ctDNA was analyzed by Guardant360 NGS evaluating 74-gene mutations. The maximum follow-up period was 380 months from first diagnosis. Causal Inference with Ensembel Learning was used for statistical analyses. **Results:** Of the 391 patients ctDNA analysis, TP53 mutations were found in 160 patients ($TP53^{Mut}$, 40.92%), CDH1 mutations were found in 21 patients ($CDH1^{Mut}$, 5.37%), Myc mutations were found in 53 patients (Myc^{Mut}, 13.55%), and BRAF mutations were found in 35 patients ($BRAF^{Mut}$, 8.95%) inclusive of all timepoints. The corresponding ctDNA mutations were not detected in 231 patients for TP53 ($TP53^{WT}$, 59.08%), in 370 patients for CDH1 ($CDH1^{WT}$, 94.63%), in 338 patients for Myc (Myc^{WT}, 86.45%), or in 356 patients for BRAF ($BRAF^{WT}$, 91.05%). There was shorter median overall survival (mOS) in the ctDNA mutated groups compared to the non-mutated groups: 88 months $TP53^{Mut}$ vs 184 months $TP53^{WT}$, HR 1.91, $P = 0.0002$; 133 months $CDH1^{WT}$ vs 81 months $CDH1^{Mut}$, HR 2.03, $P = 0.02$; 76 months Myc^{Mut} vs 179 months Myc^{WT}, HR 3.24, $P < 0.0001$, and 77 months $BRAF^{Mut}$ vs 146 months $BRAF^{WT}$ HR 2.45, $P = 0.007$. Furthermore, ≥ 5 CTCs were found in 32.42% patients. These patient had a shorter mOS compared to patients had no CTC detected at any time point (70.1 months vs 131 months; $P < 0.001$; HR 2.97). CTC-clusters were 50 times more likely to predict metastasis than single CTCs. We also found that greater than 5 CTC-clusters, clusters with 1-5, and no CTC-clusters were found in 12.55%, 11.25%, and 76.19% patients, respectively. Larger CTC-clusters had shorter mOS at 63 months, 121 months, and 163 months, respectively ($P < 0.0001$). **Conclusions:** In this study, we identified multiple liquid biopsy factors including ctDNA and CTC-clusters at various time points, and found that these are associated with prognosis. The synergy of multiple ctDNA mutations and CTC-clusters during treatment may expand the predictive role of liquid biopsy for the monitoring of disease progression in patients MBC. Research Sponsor: This study was supported in part by grants from the Lynn Sage Breast Cancer Research OncoSET Program, Robert H Lurie Cancer Center, Northwestern University.

1039 **Poster Session**

Genomic characterization of the GATA3 mutational landscape in breast cancer.

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Background: GATA3 expression is broadly used as a biomarker for diagnosing cancer of breast origin and its expression is strongly associated with estrogen receptor (ER)-positive luminal phenotype. Although *GATA3* mutations are observed in 12-18% of breast cancers (BC), they are poorly characterized. Recently, the pharmacological inhibition of MDM2 has been shown to significantly impair tumor growth in *GATA3*-deficient models in vitro, in vivo, and patient-derived xenograft harboring *GATA3* somatic mutations. Therefore, given the potential targetability of *GATA3*-mutated BC cells, it is important to better understand and characterize the mutational landscape of *GATA3* to help guide future prospective clinical studies. **Methods:** We accessed a cohort of BC samples profiled genomically and transcriptomically from two open-source datasets: TCGA (n=961) and METABRIC (n=1866). We used the chi-squared test to analyze the frequency of *GATA3* mutations across PAM50 subtypes (Basal, HER2, Luminal A, Luminal B, Normal-like) and histological BC subtypes (invasive ductal carcinoma [IDC] and invasive lobular carcinoma [ILC]). Mutations affecting other genes in the *GATA3*-mutated samples and the *GATA3* wild-type (WT) samples were compared using the chi-squared test. We analyzed the mutational landscape of the *GATA3* gene and correlated different sites of mutations with GATA3 expression, MDM2 amplification, other co-occurring mutations, and clinical behavior. GATA3 expression levels were compared using the Mann-Whitney test. **Results:** Of the analyzed 2,827 BC samples, *GATA3* mutations were unevenly distributed in the five PAM50 subtypes, as Luminal A and B subtypes had the highest frequency (16% and 17%, respectively) and the basal subtype had no observed *GATA3* mutations ($p < 0.0001$). Further analysis showed that *GATA3* mutations were more common in luminal IDC than ILC (17% vs 8.7%; $p < 0.0001$). While mutations in *CBFB*, *AKT1*, *TBX3* and *ARID1A* were more frequently co-occurring with *GATA3* mutations, mutations in *TP53*, *CDH1* and *PIK3CA* were mutually exclusive with *GATA3* mutations (adjusted $p < 0.0001$ for all genes). Analysis of the *GATA3* mutational landscape identified two types of mutations in *GATA3*: a group of truncating mutations occurring at the end of the *GATA3* gene (after the 307 position including the splice site at 308) and a group occurring before the 307 position. The first group was associated with increased GATA3 expression, *MDM2* amplification, and was mutually exclusive with *TP53* mutations. The second group had little to no effect on GATA3 expression and behaved similarly to GATA3 WT. **Conclusions:** A subtype of *GATA3* mutations are mutually exclusive with TP53 mutations and are associated with increased *MDM2* amplification, making them an ideal target for clinical trials involving MDM2 inhibitors. Research Sponsor: None.

Preclinical and early clinical data of ZN-1041, a best-in-class BBB penetrable HER2 inhibitor to treat breast cancer with CNS metastases.

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Background: HER2+ breast cancer brain metastases (BCBM) is an aggressive malignancy with high prevalence and limited treatment options. ZN-1041 is a best-in-class HER2 inhibitor designed to be delivered across the blood-brain barrier (BBB) with high selectivity and broader safety margin to treat HER2+ BCBM. **Methods:** Brain penetration of ZN-1041 and other approved HER2 tyrosine kinase inhibitors (TKI) were evaluated. Anti-tumor activity of ZN-1041 alone or in combination were evaluated in xenograft models. ZN-A-1041-101 (NCT04487236) is an on-going phase 1, multicenter, open-label study. The study comprises first-in-human dose escalation of ZN-1041 monotherapy (phase 1a) in HER2+ solid tumor patients (pts) with or without BM, dose escalation (phase 1b) and expansion (phase 1c) of ZN-1041 in combination with capecitabine and trastuzumab in pts with HER2+ BCBM (including active BM). The primary objective was safety and tolerability. The secondary objective includes pharmacokinetics and anti-tumor response including ORR per RECIST 1.1 and intracranial ORR (iORR) per RANO-BM. **Results:** Unlike currently approved HER2 TKIs which are strong human efflux transporter P-gp and BCRP substrates, ZN-1041 is not a substrate of either and has high BBB permeability, therefore predicted to have good BBB penetration. ZN-1041 alone demonstrated dose-dependent and significant anti-tumor activity when compared to tucatinib in BM model. ZN-1041 could synergize with capecitabine and trastuzumab to demonstrate significantly improved intracranial efficacy in BM models, while maintaining good tolerability. In total, 21 HER2+ mBC pts were enrolled to complete phase 1a and 1b. No dose-limiting toxicities or treatment-related SAE were observed across all dose levels. PK exposure was increased with dose escalation and $K_{puu,CSF}$ of ZN-1041 was 4.9. In ZN-1041 monotherapy, the overall ORR and iORR were 50% in TKI naïve, unequivocal HER2+ pts. The longest treatment duration was 15 months. As of data cutoff (Dec 02, 2022), totally 35 TKI naïve, HER2+ BCBM pts with median 2L treatments were enrolled for phase 1c and all pts were well tolerated to date. Adverse reactions of grade 3 or higher (≥5%) were hepatic function impairment (8.7%), headache (8.7%), hyperbilirubinemia (5.7%), ALT increased (5.7%), AST increased (5.7%), GGT increased (5.7%) and WBC decreased (5.7%). Among 19 BCBM pts with at least twice tumor assessment, the overall ORR was 78.9% (95% CI: 54.4–93.9) and iORR was 73.7% (95% CI: 48.8–90.9), DCR was 100%. In addition, 6 pts completed first tumor assessment and 5 achieved PR and 1 had SD per RECISIT 1.1. **Conclusions:** Encouraging efficacy and tolerability was observed for ZN-1041 monotherapy or combined with capecitabine and trastuzumab in TKI naïve, HER2+ BCBM patients. A Phase 2 pivotal trial for HER2+ BCBM with ZN-1041, capecitabine and trastuzumab combination therapy is planned. Clinical trial information: NCT04487236. Research Sponsor: Suzhou Zanrong Pharma Limited.

1041 **Poster Session**

Preclinical and early clinical data of ZN-1041 in combination with trastuzumab deruxtecan to treat breast cancer with or without CNS metastases.

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Background: While treatment options for advanced HER2+ breast cancer have improved, HER2+ breast cancer brain metastases (BCBM) remain a clinical challenge warranting the development of additional, brain permeable HER2-targeted therapies. ZN-1041 is a brain permeable, selective HER2-targeted oral tyrosine kinase inhibitor. Preclinical studies have demonstrated efficacy and safety of ZN-1041 warranting clinical development alone and in combination with approved monoclonal antibodies or antibody drug conjugates for patients (pts) with HER2+ BCBM. **Methods:** Anti-tumor activity of ZN-1041 alone or in combination with trastuzumab emtansine (TDM1), trastuzumab deruxtecan (TDXd), or trastuzumab (H) plus pertuzumab (P) was evaluated in BT474 BM orthotopic xenograft models. ZN-A-1041-101-US (NCT05593094) is an on-going phase 1, multicenter, open-label study. The study comprises dose escalation of ZN-1041 monotherapy (Phase 1a) in pts with HER2+ solid tumors with or without BM, dose escalation (Phase 1b) and expansion (phase 1c) of ZN-1041 in combination with TDM1 (Arm 1), TDXd (Arm 2), or HP as maintenance therapy (Arm 3) in pts with HER2+ mBC with or without BM. The primary objectives were safety, tolerability and recommended phase 2 dose. The secondary objective includes pharmacokinetics (PK) and preliminary efficacy per RECIST 1.1. **Results:** Preclinically, ZN-1041 alone or combined with TDM1, TDXd or HP demonstrated significant improvement in intracranial tumor growth inhibition compared to TDM1, TDXd, or HP alone. As of data cutoff, Phase 1a (n = 7 pts) and Arm 2 of Phase 1b (n = 3 pts) were completed. Among 10 pts enrolled, 8 pts had received prior HER2 TKI. In Phase 1a, ZN-1041 was well tolerated with no dose-limiting toxicities (DLTs) or drug discontinuation due to toxicity up to a dose of 800 mg BID. Adverse reactions were mainly grade 1. The most common treatment related adverse reactions (TRAEs$\geq$15%) were grade 1 nausea (43%) and vomiting (29%), with no $\geq$ grade 2 diarrhea reported. PK exposure was increased with dose escalation. In Phase 1a, one pt with mBC (without BM) achieved a confirmed partial response (PR) at 400 mg BID dose for $>$ 15 months; one with gastric cancer achieved stable disease at the first dose level of 50mg BID for nearly 1 year. In Phase 1b, pts who had previously progressed on TDXd and/or TKI were enrolled and received ZN-1041 at a dose of 800 mg BID in combination with TDXd. Combination therapy was well tolerated with no DLTs reported. One pt with BCBM who was previously on tucatinib and TDXd had a confirmed PR. **Conclusions:** Safety and tolerability was observed for ZN-1041 with maximum tolerated dose 800 mg BID as monotherapy and combined with TDXd in pts with advanced HER2+ malignancies. Encouraging efficacy was observed in treatment-refractory settings. Additional safety and efficacy data of ZN-1041 in combination with TDM1, TDXd or HP are warranted. Clinical trial information: NCT05593094. Research Sponsor: Suzhou Zanrong Pharma Limited.

Anti-HER2 antibody inetetamab plus camrelizumab and utidelone for pretreated HER2-positive metastatic breast cancer: Final results from the phase 2 ICU trial.

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Background: We previously reported (Yan, ASCO 2022) promising efficacy and acceptable safety of anti-HER2 antibody inetetamab in combination with camrelizumab and utidelone regimen in preliminary 20 HER2-positive metastatic breast cancer (MBC) patients who progressed after at least two lines of HER2-directed therapies with trastuzumab and TKIs. Inetetamab is a novel anti-HER2 antibody. Camrelizumab is an anti-programmed death receptor 1 [PD-1] antibody. Utidelone, a genetically engineered epothilone analogue, has shown promising efficacy in heavily pretreated MBC. Here we report the final ICU study results. **Methods:** In the ICU study (NCT04681287), patients received intravenous camrelizumab (200 mg once every 3 weeks), inetetamab (initial dose of 8 mg/kg, then 6 mg/kg, once every 3 weeks), and utidelone (30 mg/m2, days 1-5, every 3 weeks) until disease progression or intolerable toxicity. The primary endpoint was 3-month progression-free survival (PFS) rate according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Secondary endpoints included objective response rate (ORR), PFS and safety. Simon's two-stage design was adopted for this study. All AEs were graded according to the grading criteria in the Common Terminology Criteria for the Evaluation of Adverse Events, 5th edition. **Results:** From Apr 23 2021 to Sept 1 2022, a total of 46 HER2-positive MBC patients were enrolled with median age of 52 (range 43-57). As of Jan 18, 2023, the median follow-up was 11.37 months. There were 12 patients (26.09%) with ER+/PR+, 7 patients (15.22%) with ER+/PR-, one patient (2.17%) with ER-/PR+, 26 patients (56.52%) with ER-/PR-. The median number of previous systemic therapies for advanced disease was three. Previous HER2-targeted therapies included trastuzumab (46 [100%]), TKIs (46 [100%], of which pyrotinib 39 [84.78%] and lapatinib 12 [26.09%]), pertuzumab (13 [28.26%]), and margetuximab (3 [6.52%]), T-DM1 or other HER2-ADC (7 [15.22%]). The 3-month PFS rate in 46 patients was 71.84%. The confirmed ORR was 28% (13/46), include one (2.17%) patient achieved complete response. The median PFS was 5.59 months. The most common treatment-related adverse events (TRAEs) were peripheral neuropathy (40 [86.96%]), capillary proliferation (27 [58.7%]), and alopecia (17 [36.96%]). Grade ≥3 TRAEs included rash (3 [6.52%]), peripheral neuropathy (1 [2.17%]) and AST increase (1 [2.17%]). Moreover, there were no grade 4 or above TRAEs. No related treatment discontinuation or deaths occurred. **Conclusions:** Final efficacy and safety results were consistent with previous ICU study preliminary analyses. The ICU study showed a favorable benefit-risk profile and is an important option for Chinese patients with HER2-positive MBC after at least two lines of HER2-directed therapies with trastuzumab and TKIs. Clinical trial information: NCT04681287. Research Sponsor: China Scientific Research Fund for HER2 Target from China Anti-Cancer Association (No.CORT-239-M14).

Cardiac function of long-responders to dual anti-HER2 antibodies amongst patients with HER2 positive advanced breast cancer.

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Background: Dual anti-HER2 antibodies pertuzumab (P) and trastuzumab (T) in combination with taxane (D), followed by PT maintenance, is the standard first line treatment for HER2 positive advanced breast cancer (HER2+ ABC). Treatment associated cardiotoxicity necessitates regular cardiac function surveillance, which is a burden particularly for treatment long-responders. Data for cardiac safety of prolonged P+T exposure is scarce. We investigate the real-world impact on cardiac function in long-responders to treatment with dual anti-HER2 antibodies. **Methods:** We identified consecutive patients with HER2+ ABC who received the CLEOPATRA regimen (PT-D) between Jan 2014 and Dec 2020 from an institutional cancer registry. All patients had pre-treatment multiple-gated acquisition (MUGA) scan or echocardiogram, and subsequently at 3-monthly intervals until end of treatment to monitor left ventricular ejection fraction (LVEF). Patients on treatment for ≥36 months were considered long-responders. The Wilcoxon signed-rank test was used to assess any significant difference in LVEF at various landmark time-points in comparison to their pretreatment baseline. **Results:** 101 women with HER2+ ABC were eligible for analysis. Median age at treatment was 62 (IQR, 56.0-69.0). The median duration of treatment was 17.3 months (IQR, 9.0-31.3). 22.8% of patients were long-responders, who received a median of 67 cycles of treatment (IQR, 58-88). Compared to baseline, median LVEF was significantly decreased at 6m (median, 66% vs 69%, p=0.02), however there were no significant differences for any of the subsequent time-points up to 84 m. All of the larger LVEF drop (≥10% from baseline) occurred by the first 24 months, representing 4.7% of the overall measurements. Risk factors present for patients experienced treatment suspension (n=3) included previous exposures to anthracycline and left sided radiotherapy. **Conclusions:** In patients with HER2+ ABC who were long-responders to first-line PT-D, prolonged exposure to dual anti-HER2 antibodies was not associated with significant cardiotoxicity. It is safe to de-escalate the cardiac surveillance for this population. Research Sponsor: None.

Time-points (months)	Number of patients	Baseline LVEF (%) (median, IQR)	Subsequent LVEF (%) (median, IQR)	Wilcoxon signed-rank test
0	101	69 (64.0-72.5)	-	-
6	90	69 (64.8-72.3)	66 (63.0-72.0)	p=0.02
12	64	69 (63.5-72.0)	69 (63.0-73.0)	p=0.27
24	48	69 (65.0-72.8)	69 (63.0-73.0)	p=0.76
36	23	71 (63.5-74.5)	68 (63.0-72.0)	p=0.11
48	13	72 (63.5-74.5)	66 (64.0-72.0)	p=0.08
60	8	72 (63.0-74.0)	69 (63.5-71.5)	p=0.17
72	3	74 (66.0-76.0)	71 (64.0-75.0)	p=0.10
84	3	74 (66.0-76.0)	70 (58.0-73.0)	p=0.10

Zanidatamab (zani), a HER2-targeted bispecific antibody, in combination with docetaxel as first-line therapy (1L) for patients (pts) with advanced HER2-positive breast cancer (BC): Updated results from a phase 1b/2 study.

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Background: Despite HER2-targeted agents improving outcomes in HER2-positive (+) BC, some pts develop resistance, relapse, or do not respond to current 1L therapies. Zani, also known as ZW25, is a novel HER2-targeted bispecific antibody that binds to two distinct extracellular domains of HER2. Preliminary results from this phase 1b/2 trial (NCT04276493) showed that zani plus docetaxel had a manageable safety profile and demonstrated promising antitumor activity in pts with advanced HER2+ BC; here we present the updated data following enrollment completion. **Methods:** Cohort 1 of this open-label study is evaluating zani in combination with docetaxel as a 1L therapy in adult females with advanced HER2+ BC who may have received prior neoadjuvant/adjuvant therapy. Cohort 1a pts received zani 30 mg/kg intravenously (IV), Cohort 1b pts received zani 1800 mg IV, both with docetaxel 75 mg/m^2 IV every 3 weeks. The primary endpoints were safety and investigator (INV)-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints included INV-assessed duration of response (DoR) and disease control rate (DCR). **Results:** As of Nov 22, 2022, 37 pts (median age 55.0 years [range: 33-80]) were assigned to Cohort 1a (n=10) or 1b (n=27). Median study follow-up was 15.5 months (range: 1.1-29.3); patients received a median of 13 treatment cycles (range 1-37) and 18 (48.6%) pts remained on treatment. Of the 33 efficacy evaluable (EE) pts, confirmed ORR was 90.9% (95% confidence interval [CI]: 75.7, 98.1). Efficacy data are summarized in Table. In total, 36 (97.3%) pts experienced ≥1 treatment-related adverse event (TRAE); 25 (67.6%) pts experienced ≥grade 3 TRAEs. The most common ≥grade 3 TRAEs were decreased neutrophil count, experienced by 18 (48.6%) pts, and decreased white blood cell count, experienced by 7 (18.9%) pts. Serious TRAEs occurred in 6 (16.2%) pts; no TRAEs led to death. **Conclusions:** Zani combined with docetaxel demonstrated promising antitumor activity as 1L therapy for advanced HER2+ BC, with a manageable safety profile. Clinical trial information: NCT04276493. Research Sponsor: BeiGene, Ltd.; This study was sponsored by BeiGene, Ltd. Medical writing support for the development of this abstract, under the direction of the authors, was provided by Emily Finn, MSc, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd.

Summary of efficacy results (EE analysis set*).

	Cohort 1a (n=8)	Cohort 1b (n=25)	Total (n=33)
Confirmed best overall response, n (%)			
Complete response	1 (12.5)	1 (4.0)	2 (6.1)
Partial response	7 (87.5)	21 (84.0)	28 (84.8)
Stable disease	0 (0.0)	2 (8.0)	2 (6.1)
Progressive disease	0 (0.0)	1 (4.0)	1 (3.0)
Confirmed ORR, n (%)	8 (100)	22 (88.0)	30 (90.9)
95% CI	63.1, 100	68.8, 97.5	75.7, 98.1
Confirmed DCR, n (%)	8 (100)	24 (96.0)	32 (97.0)
95% CI	63.1, 100	79.6, 99.9	84.2, 99.9
Median DoR, months	12.4	NE	NE
(95% CI)	5.5, NE	12.1, NE	12.1, NE
Confirmed DoR, range†	3.5†-23.5†	4.3†-16.5†	3.5†-23.5†

*Four pts without any postbaseline tumor assessments were excluded from the EE analysis set.
Data cut off: November 22, 2022.
†Censored.

1045 **Poster Session**

Updated results from a phase 2 study on dalpiciclib and pyrotinib, a dual-oral chemotherapy-free regimen in HER2-positive advanced breast cancer (DAP-HER-01).

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Background: Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have shown synergistic effect with anti-HER2 therapy on hormone receptor (HR)-positive and HER2-positive breast cancer from preclinical models and several clinical studies, while data of this combination in HR-negative and HER2-positive diseases are limited so far. DAP-HER-01 (NCT04293276) was aimed at evaluate the efficacy and safety of the novel dual-oral, chemotherapy-free regimen of CDK4/6 inhibitor dalpiciclib and pan-HER tyrosine kinase inhibitor pyrotinib in HER2-positive advanced breast cancer (ABC) regardless of HR status, and reported to meet the primary endpoints previously (overall ORR 70%), in which HR-negative patients achieved a higher ORR (81.8%, vs 55.6% in HR-positive patients; Min Yan, et al. ESMO 2021, Poster 276P). Here we reported the updated results of this trial. **Methods:** DAP-HER-01 was a single-arm, phase 2 study conducted in HER2-positive ABC patients with no more than one prior systemic treatment at advanced setting. Enrolled patients received dalpiciclib and pyrotinib until progression, unaccepted toxicity, or no further benefit. The primary endpoint was ORR as per RECIST 1.1, and secondary endpoints included progression-free survival (PFS), overall survival and safety. **Results:** Between April 9, 2020, and May 19, 2021, 41 patients were enrolled and received study treatment, and 40 of them were assessable for efficacy. With a median follow-up of 19.2 months, the median progression-free survival (PFS) was 11.0 months (95% CI 7.3-19.3). Considering HR status, the PFS in HR-negative patients was not matured (estimated median: 16.6 months; 95% CI: 7.3- NA), but still showed a tendency to be longer than that in HR-positive patients (median: 9.1 months; 95% CI: 5.4-11.0). Patients with brain metastases at baseline could also benefit from this treatment (median PFS: 11.0; 95% CI: 5.4-NA). Consistent with the safety data reported before, the most common grade 3 or 4 treatment-related adverse events were leukopenia (68.3%), neutropenia (65.9%) and diarrhea (19.5%). Most adverse events were tolerable, and no study-related death reported. **Conclusions:** Combined with previous reports, our findings suggest dalpiciclib combined with pyrotinib achieved promising efficacy and manageable toxicity in the treatment of HER2-positive ABC, including patients with HR-negative disease or brain metastases. This combination could be considered as a completely oral, chemo-free regimen for patients with HER2-positive ABC and is worthy of further study. Clinical trial information: NCT04293276. Research Sponsor: XINRUI Project of Cancer Supportive Care and Treatment Research.

PLEASURABLE: Results and biomarkers analysis from the phase II study of dalpiciclib combined with pyrotinib and endocrine therapy (ET) in women with dual-receptor positive (ER+/HER2+) metastatic breast cancer (MBC).

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Background: In the front-line setting, our previous work demonstrated an impressive median progression-free survival (PFS) of 11.3 months with 66.7% response rate, and concluded a recommended phase 2 dose of pyrotinib 320mg/d, dalpiciclib (SHR6390, a novel CDK4/6i) 125mg/d, and letrozole 2.5mg/d for HR+/HER2+ MBC patients (pts) (Xichun Hu, FRONT ONCOL 2022). Results and biomarkers analysis from phase II dose expansion study are presented. **Methods:** ER+/HER2+ MBC Pts eligible for first- or second-line treatment were enrolled to receive dalpiciclib combined with pyrotinib and ET (letrozole or fulvestrant determined by physician's choice). The primary endpoint was objective response rate (ORR). For biomarkers analysis, ^{68}Ga-HER2 affibody, pre-treatment tissue-derived DNA and circulating tumor DNA (ctDNA) were assessed by PET/CT, and next-generation sequencing (NGS), respectively. **Results:** As of January 19, 2023, 48 pts were enrolled. 17 pts (35.4%) were treatment naïve, and 31 pts (64.6%) had received prior trastuzumab. The ORR was 68.1% (32/47) and disease control rate was 100% (47/47). In trastuzumab-naïve and trastuzumab-pretreated patients, ORR was 81.3% (13/16) and 61.3% (19/31), respectively. PFS and OS data were not mature by cut-off date. No new safety signals were observed. The most frequent treatment-related adverse events were neutropenia (95.8%; G3:60.4%, G4:6.3%), leukopenia (91.7%; G3:45.8%), diarrhea (87.5%; G3:2.1%), anemia (79.2%; G3:4.2%), oral mucositis (68.8%, G3:2.1%) and platelet count decreased (41.7%; G3:2.1%, G4:2.1%). The heterogeneity of ^{68}Ga-HER2 affibody uptake was observed among patients, both at baseline (N=16 , median SUV $_{max}$ 7.5, range, 2.3-34.9) and after 2 cycles of therapy (N=12 , median SUV $_{max}$ 4.0, range, 0-14.9). All patients with a decline in ^{68}Ga-HER2 affibody uptake (N=8) achieved partial response, while the uptake in non-responders was elevated (N=2). NGS was conducted to detect somatic and germline mutations in baseline tissue (n=10) and ctDNA (n=10) samples. Two patients with *BRCA* mutation (one had somatic *BRCA1/2* mutation and another with germline *BRCA2* mutation) had no tumor response. **Conclusions:** The chemotherapy-sparing regimens showed significant anti-tumor activity for ER+/HER2+ MBC pts in the front-line setting. The ^{68}Ga-HER2 affibody PET/CT may be a potential predictive biomarker of therapy response. Additional analysis including correlation of biomarkers with long-term outcomes is underway. Clinical trial information: NCT03772353. Research Sponsor: None.

Real-world treatment patterns in patients with HER2+ unresectable or metastatic breast cancer: Interim results from HER2 REAL Asia cohort.

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Background: HER2 REAL (NCT04857619) is the first multi-country, retrospective study exploring the treatment practices and outcomes in patients (pts) with HER2+ locally advanced, unresectable (u)/metastatic (m) breast cancer (BC) from routine clinical care in the APAC and LATAM. **Methods:** Adult HER2+ u/mBC pts diagnosed since reimbursement or wider access of trastuzumab emtansine (T-DM1) or 01 Jan 2017, whichever was earlier with ≥12 months (mo) of follow-up data from index date (u/mBC diagnosis) and treated with ≥1-line of therapy (LOT) were enrolled per medical chart review from 6 countries. Here we present interim descriptive analyses (cut-off 30 June 2022) on demographics, clinical characteristics, and treatment patterns. **Results:** Of the 763 enrolled pts, 370 with median (range) age of 55 (20–81) yrs from Hong Kong, Korea, Singapore, and Taiwan were eligible for interim analyses; 368 (99.5%) were female with 210 (57.1%) postmenopausal. A total of 210 (57.1%) pts with reported data had a median time of 2 (0–18) yrs from initial BC diagnosis to u/mBC relapse. At index date, majority had ductal carcinoma (227/254 [89.4%]), visceral (255/355 [71.8%]), and non-visceral (258/355 [72.3%]) metastases; 80/355 (22.5%) had CNS metastases. Family history of BC was reported by 45/370 (12.2%) pts completing the questionnaire; 209/370 (56.5%) had hormone receptor-positive BC. Treatments reported in the first to fifth line were quite variable. HER2-directed therapy was received by 323/367 (88.0%) in LOT1 (mainly trastuzumab [TRA] and pertuzumab [PTZ]-based) and 298/343 (86.9%) in LOT2 (mainly T-DM1). Median duration of LOT1 and LOT2 were 7.8 (0–130) and 5.0 (0–100) mo, respectively, that decreased to 2.3 (0–30) mo in LOT5. The prime reason for treatment discontinuation was disease progression (LOT1: 294 [80.1%]; LOT2: 273 [79.6%]; LOT3: 187 [68.5%]). Serious adverse effects from treatments were rare (LOT1: 7 [1.9%]; LOT2: 10 [2.9%]; LOT3: 5 [1.8%]). **Conclusions:** The interim analyses show heterogeneous treatment patterns in real-world among pts with HER2+ u/mBC progressing on HER2-directed therapies possibly due to access disparity in these 4 Asian countries. Clinical trial information: NCT04857619. Research Sponsor: AstraZeneca.

Real-world treatment patterns.

LOT[a], n (%)	Median duration of LOT (range), mo	TRA + PTZ + CT	T-DM1	TRA + CT	Lapatinib + CT	CT alone	HT alone	Anti-HER2[b] + HT	Anti-HER2[b] + CT + HT
LOT1 (N=367)	7.9 (0–130) (n=361)	163 (44.4)	17 (4.6)	51 (13.9)	-	54 (14.7)	16 (4.4)	-	63 (17.2)
LOT2 (N=343)	5.0 (0–100) (n=314)	22 (6.4)	155 (45.2)	24 (7.0)	30 (8.7)	45 (13.1)	-	19 (5.5)	21 (6.1)
LOT3 (N=273)	4.2 (0–57) (n=221)	13 (4.8)	40 (14.7)	42 (15.4)	35 (12.8)	89 (32.6)	16 (5.9)	18 (6.6)	-
LOT4 (N=167)	2.7 (0–33) (n=145)	8 (4.8)	-	29 (17.4)	29 (17.4)	85 (50.9)	11 (7.8)	-	-
LOT5 (N=114)	2.3 (0–30) (n=99)	10 (8.8)	7 (6.1)	17 (14.9)	14 (12.3)	55 (48.3)	7 (6.1)	-	-

[a]Reported in ≥4.0% pts. [b]Mainly includes TRA, PTZ, and Lapatinib. Abbreviations: CT, chemotherapy; HT, hormone therapy.

1048 **Poster Session**

Pyrotinib plus capecitabine for patients with HER2-positive metastatic breast cancer and brain metastases: 3-year follow-up results from the phase 2 PERMEATE trial.

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Background: HER2-positive metastatic breast cancer has a high risk of brain metastases, leading to poor survival. Our phase 2 PERMEATE trial (NCT03691051) has shown the promising efficacy of pyrotinib (an irreversible pan-HER receptor tyrosine kinase inhibitor) plus capecitabine in patients with HER2-positive metastatic breast cancer and brain metastases, with an intracranial objective response rate of 74.6% (44/59) and 42.1% (8/19) in patients with radiotherapy-naïve (cohort A) and radiotherapy-treated (cohort B) brain metastases, respectively. Here we updated 3-year follow-up results from this trial. **Methods:** Patients received 21-day cycles of pyrotinib (400 mg orally once daily) and capecitabine (1000 mg/m^2 orally twice daily on days 1-14) until disease progression or intolerable toxicity. Patients with progression isolated to the brain lesions would be withdrawn from the study, but could resume on the study treatment after local surgery or radiotherapy until the second progression at any site or death, at the discretion of the investigator. Intracranial and extracranial responses were assessed according to the Response Evaluation Criteria In Solid Tumors, version 1.1. Progression-free survival (PFS; time from the initiation of the study treatment to progression at any site or any-cause death), overall survival (OS), and second PFS (PFS2; time from progression isolated to the brain lesions to the second progression at any site) were reported. **Results:** By the data cutoff date on February 8, 2023, the median follow-up duration was 40.5 months (95% CI: 39.0-43.0). Cohort A showed a median PFS of 10.7 months (95% CI: 7.6-14.9) and a median OS of 35.9 months (95% CI: 25.1-not reached). The 1-year and 3-year OS rates were 84.6% (95% CI: 76.0-94.4) and 49.8% (95% CI: 38.0-64.6), respectively. Fifteen patients with progression isolated to the brain lesions in cohort A resumed on the study treatment after local treatment, with a median PFS2 of 10.4 months (95% CI: 6.5-19.7). Cohort B showed a median PFS of 5.6 months (95% CI: 5.4-11.9) and a median OS of 31.4 months (95% CI: 22.0-not reached). The 1-year and 3-year OS rates were 78.9% (95% CI: 64.0-99.6) and 29.1% (95% CI: 13.0-60.4), respectively. **Conclusions:** These findings suggest the long-term survival benefit provided by pyrotinib plus capecitabine in patients with HER2-positive metastatic breast cancer and brain metastases, especially in the radiotherapy-naive cohort. Clinical trial information: NCT03691051. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

1049 **Poster Session**

Artificial intelligence–powered tumor-infiltrating lymphocytes analyzer to reveal distinct immune landscapes in breast cancer by molecular subtype and HER2 score.

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Background: Tumor-infiltrating lymphocytes (TIL) reflect an ongoing anti-tumor immune response in the tumor microenvironment (TME) and have been studied as a predictive as well as prognostic biomarker in breast cancer (BC). The immune profile differs depending on BC molecular subtypes, with triple-negative BC (TNBC) and HER2-positive BC more frequently infiltrated by higher numbers of TIL than hormone receptor (HR)-positive tumors. In this study, we analyze TIL and immune phenotype by molecular subtype in BC and explore differences based on HER2 scores using an AI-powered TIL analyzer. **Methods:** A total of 1,973 cases of BC with molecular subtype, HER2 immunohistochemistry (IHC) or in situ hybridization (ISH) results, and TIL analysis from H&E slides from TCGA (n=1021), Samsung Medical Center (SMC, n=663), and KyungHee Medical Center (KHMC, n=289) were included in the analysis. The density of TIL were spatially analyzed from H&E WSI, and the immune phenotype (IP) was analyzed for each 1 mm2-sized patch. Tumor microenvironment (TME) was categorized into three types: inflamed (TIL distributed intratumorally), Immune-excluded (TIL excluded, out of cancer stroma), immune-desert (scant TIL in TME), and the score for each IP was calculated as the percentage of the total patches in WSI. **Results:** TNBC showed the highest TIL density in both cancer epithelium (214.5 ± 299.7/mm2) and stroma (1133.3 ± 1245.9/mm2), and a high percentage of inflamed IP (35.7%), IS (28.4 ± 28.1) than other subtypes (inflamed IP: 17.5%, IS 16.2±20.2, both $p<0.001$). HER2-positive BCs showed higher sTIL density (904.0 ± 901.7/mm2) compared to HR- positive BC (616.7 ± 794.1/mm2) but were associated with a higher percentage of immune-excluded IP (71.2%) and IES (57.6 ± 24.6). HR-positive BC had a high percentage of immune-desert IP (30.4%). In both HR-positive and negative BCs, higher IES was observed as the HER2 score increased. HER2-positive BC significantly showed a higher proportion of cancer stroma in the cancer region from WSI (Stromal ratio, 0.682 ± 0.149 vs. 0.578 ± 0.176, $p<0.001$). **Conclusions:** Different TIL densities and IP were seen in BC for each molecular subtype, pointing to a distinct immune landscape. HER2 score was associated with immune-excluded IP despite having higher TIL density, which should be considered for immunotherapy in BC. Research Sponsor: None.

1050 **Poster Session**

Secondary primary malignancy risk by ER, PR, and HER-2 status in post-menopausal women with breast cancer: A population-based analysis.

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Background: Breast cancer is the most commonly diagnosed cancer and second leading cause of death due to cancer in women in the United States. We aimed to determine site specific incidence of SPMs in post-menopausal women with primary BC using data from the US Surveillance, Epidemiology, and End Results (SEER-17) cancer registries. **Methods:** We retrospectively analyzed post-menopausal women aged 45 or older with a first primary breast cancer diagnosis between 2000 and 2019, excluding those aged 45 or younger or with non-breast cancers as their first malignancy. We defined SPMs as second malignancies occurring at least 6 months after the initial breast cancer diagnosis and calculated standardized incidence ratios (SIRs) and absolute excess risk (AER) using SEER*Stat. Statistical significance was determined using p-values <0.05 and a 95% CI assuming a Poisson distribution of SPM incidence. **Results:** Among 774,965 post-menopausal women $\geq$45 years old with primary breast cancer, 10.8% developed SPMs, with significantly increased risk compared to the general population (SIR=1.14, 95% CI=1.13-1.15, $p<0.05$), particularly for solid tumors (SIR=1.16, 95% CI=1.15-1.16, $p<0.05$) and certain malignancies including salivary gland (SIR=1.77), thyroid (SIR=1.56), endocrine system (SIR=1.56), and hematological malignancies such as ALL, ANLL, and AML (SIR$>$1.70). Women aged 45-59 and Black women had the highest risk for all malignancies. PR receptor-positive women had higher risk for thyroid SPMs, while PR-negative women had higher risk for SPMs in female genitalia, bones and joints, and hematological malignancies. HER-positive and triple-positive (HER ER PR) women had higher risk for thyroid and hematological SPMs, while triple-negative women had higher risk for ALL, ANLL, and AML. **Conclusions:** This study found that 11% of post-menopausal women with primary BC develop SPMs, with thyroid cancer being the most common. Black and older women (45-59 years) had a higher risk of developing SPMs. Research Sponsor: None.

	ER(-)				PR(-)				HER2(-)			
Site of SPM	N	SIR	95%CI	AER	N	SIR	95% CI	AER	N	SIR	95% CI	AER
All Sites	13,305	1.25#	1.23-1.27	30.5	21,753	1.18#	1.17-1.2	23.4	18,716	1.10#	1.09-1.12	12.9
All Solid Tumors	11,863	1.27#	1.25-1.29	29.13	19,263	1.20#	1.18-1.22	22.43	16,451	1.11#	1.09-1.12	11.82
All Lymphatic and Hematopoietic Diseases	46	2.08#	1.52-2.77	0.28	1,586	1.03	0.98-1.08	0.34	1,589	1.13#	1.07-1.18	1.32
Thyroid	348	1.41#	1.27-1.57	1.18	587	1.47#	1.35-1.59	1.31	789	1.93#	1.8-2.07	2.81
Other Female Genital Organs	89	2.31#	1.85-2.84	0.58	140	2.11#	1.78-2.49	0.52	120	1.52#	1.26-1.82	0.3
Bones and Joints	21	2.10#	1.3-3.21	0.13	27	1.58#	1.04-2.29	0.07	23	1.39	0.88-2.09	0.05
Salivary Glands	46	2.08#	1.52-2.77	0.28	68	1.78#	1.38-2.25	0.21	57	1.58#	1.2-2.05	0.16
Female Genital System (uterus, ovary, vagina)	1,446	1.19#	1.13-1.25	2.66	2,194	1.07#	1.03-1.12	1.05	1,916	0.99	0.95-1.04	-0.1

1051 **Poster Session**

Real-world patient characteristics and treatment patterns associated with tucatinib therapy in patients with HER2+ metastatic breast cancer.

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Background: Tucatinib (TUC) is an oral HER2-targeted therapy approved by the FDA in Apr 2020 for use in combination with trastuzumab and capecitabine (TRA+CAP) for patients with previously treated HER2+ metastatic breast cancer (MBC). In the randomized HER2CLIMB trial, median (95% CI) overall survival (mOS) and progression-free survival (PFS) for patients receiving TUC with TRA+CAP were 21.9 (18.3, 31.0) and 7.8 (7.5, 9.6) months, respectively. Median duration of therapy was 7.3 months. HER2CLIMB used a standard of care comparator arm and included patients with active and stable brain metastasis (BM). HER2CLIMB was conducted prior to approval of fam-trastuzumab deruxtecan (T-DXd) so did not assess the impact of TUC-based therapy following T-DXd. Objective: Describe patient characteristics, treatment patterns, and clinical outcomes for TUC-based treatment in the real-world setting. **Methods:** This retrospective study included patients in the Komodo Health dataset (aggregating data from patient administrative health claims in the United States) diagnosed with MBC between Jan 1, 2017 and Sep 3, 2022 and initiating TUC post- approval in Apr 2020. Patient characteristics were described in the baseline period (≤6 months from TUC initiation). Key outcomes were time to next treatment (TTNT; as a proxy for PFS), time to discontinuation (TTD), and persistence (proportion continuing treatment at each timepoint) in all TUC-treated patients, and in patients receiving TUC immediately following T-DXd. **Results:** Of 16,990 patients identified with HER2+ MBC, 528 received TUC-based treatment. Of these, 57 (11%), 164 (31%), 154 (29%), and 153 (29%) received TUC in first-line (1L), second-line (2L), third-line (3L), and fourth-line or later (4L+), respectively. Median follow-up from TUC initiation was 9 months. Overall, 400 patients (76%) had BM prior to initiating TUC (43 [75%], 138 [84%], 111 [72%], and 108 [71%] in 1L, 2L, 3L, and 4L+, respectively). Median (95% CI) TTNT was 10.7 (9.4, 13.1) months overall and 11.5 (9.6, 14.4) in patients receiving TUC in 2L or 3L. Median (95% CI) TTD was 8.5 (7.2, 9.3) months overall, and 9.1 (7.7, 9.9) in patients receiving TUC in 2L or 3L. TUC persistence in the overall cohort was 46% (91/200) at 12 months and 35% (40/115) at 18 months. Sixty-one patients (12%) received TUC immediately following T-DXd (median 4L; 12 in 2L/3L, 49 in 4L+); of whom 36 (59%) had BM prior to initiating TUC. TTNT and TTD for patients treated with TUC following T-DXd were 7.5 (5, 13.3) and 7.3 (3.2, 9.5) months, respectively. **Conclusions:** In the real-world setting, a higher proportion of patients receiving TUC had BM compared with the HER2CLIMB patient population. TUC-based treatment in the real world is used in multiple lines of therapy and is associated with a similar TTNT and TTD to PFS observed in HER2CLIMB, inclusive of a cohort of patients who received TUC following T-DXd therapy. Research Sponsor: Seagen Inc; Merck.

HER2 persistence after treatment with T-DXd in breast and gastrointestinal cancers.

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Background: T-DXd is a HER2-targeted antibody drug conjugate approved for treatment of advanced HER2-positive breast and gastroesophageal cancers and HER2-low breast cancers. The prevalence of HER2 loss after exposure to T-DXd is unknown and has implications for treatment strategies in refractory patients. **Methods:** We investigated clinically reported HER2 immunohistochemistry (IHC) scoring on post-treatment tissue biopsies from patients who received at least 2 cycles of T-DXd as of 2/2023. IHC was performed using mAB clone 4B5 (Ventana) and scored by ASCO/CAP guidelines on a scale of 0 to 3+. MSK-IMPACT next generation sequencing (NGS) was performed on paired pre- and post-treatment samples when available. Statistics are descriptive. **Results:** A total of 62 patients with breast, gastroesophageal, or colon cancer had available post-treatment biopsies. The majority (n = 51) had breast cancer, including 32 with HER2-positive and 19 with HER2-low disease. Median time on therapy was 30 weeks in HER2-positive and 21 weeks in HER2-low breast cancer. All 32 patients with HER2-positive breast cancer had detectable HER2 expression by IHC on post-treatment biopsies (median IHC score 2+; range 1+ to 3+). Of those with HER2-low breast cancer, 12 (63.1%) patients had detectible IHC after treatment. Of the 7 with IHC scores of zero, 3 also had scores of zero on the most proximal pre-treatment biopsies. Seven patients with gastroesophageal and 3 with colorectal cancer were included, with a median time on therapy of 12 and 9 weeks respectively, of which 1 (9%) exhibited HER2-loss after treatment. Among all patients with HER2-positive cancers, the rate of complete HER2-loss by IHC after exposure to T-DXd was 2.3%. Thirty-two patients had paired genomic analysis, including 25 breast and 7 gastrointestinal cancers. No change was observed in the fraction of genome altered (p = 0.0736, q = .327) or tumor mutational burden (p = 0.139, q = .487) with T-DXd exposure. Changes in *ERBB2* copy number did not show clear directionality, with 15 patients (46.7%) exhibiting *ERBB2* amplification pre-treatment and 12 (37.5%) post-treatment, the sum of 3 temporal gains and 6 losses of *ERBB2* amplification across the threshold of 1.8. **Conclusions:** HER2 remained detectable by IHC in the majority of patients treated with T-DXd in this cohort, especially those with HER2-positive cancers. These findings suggest that resistance to T-DXd may occur via target-independent factors, and that HER2 could still be exploited therapeutically in these populations. Further prospective studies using quantitative assays are needed to confirm these hypotheses. Research Sponsor: U.S. National Institutes of Health.

Tumor Type	N	Median Time on Tx (Wks)	Median HER2 IHC Post-Tx	IHC 0 Post-Tx N (%)
HER2-Positive Breast Cancer	32	30	2+ (1-3)	0 (0)
Her2-Low Breast Cancer	19	21	1+ (0-2)	7 (36)*
Gastroesophageal Cancer	7	12	3+ (0-3)	1 (14.2)
Colorectal Cancer	4	9	2+ (2-3)	0 (0)
Total	62	23.5	2+ (0-3)	8 (12.9)

*3 of these 7 patients had IHC scores of 0 pre-treatment.

1053 **Poster Session**

Validation of a single-cell sequencing assay for the detection of circulating tumor cells in metastatic breast cancer.

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Background: Blood Biopsy and the evaluation of Circulating Tumor Cells (CTC) has provided valuable clinical information for patients with metastatic breast cancer, specifically where a tissue biopsy is not feasible. A critical problem in the field is that most assays cannot distinguish true CTCs from other types of rare cells. By combining established protein biomarkers associated with circulating epithelial cells with single-cell whole-genome sequencing to assess copy number variations (CNVs, a signature for genomic instability - GI), we differentiate rare cells from true CTCs. Additionally, we can determine the presence or absence of regions that contain gene amplifications (e.g., ERBB2/HER2). Here we report the validation of a clinical blood biopsy CTC assay that can enumerate CTCs, determine if those CTCs have GI and if selected CTCs are expressing HER2 or ER antigens. **Methods:** Relevant cell line controls of epithelial origin and known expression levels of ER or HER2 were spiked into healthy donor whole blood at varying concentrations. The nucleated cells were deposited on microscope glass slides at high density. Immunofluorescence staining of slides was performed to identify the presence and localization of nuclei (via DAPI), pan-CK, HER2, ER, CD45 and CD31. Nucleated cells were classified as CTC candidates if they were pan-cytokeratin$^{(+)}$ and CD45/CD31$^{(-)}$, and were further characterized for expression of ER and HER2 protein. Defined CTC candidates were imaged and located by specific coordinates allowing single-CTC isolation for whole genome amplification. Single-cell sequencing data was then analyzed with the Epic CTC DNA copy number analysis pipeline to detect GI and amplification at the ERBB2 locus. **Results:** The limit of detection for CTCs was determined to be 1 CTC in 6 million white blood cells with a linear range of 1- 300 CTC per slide. The sensitivity and specificity for HER2 detection was determined to be 94% and 97%, respectively. ER assay sensitivity and specificity were 91% and 100%, respectively. Overall accuracy was 100% for HER2 and 94% for ER detection. Overall precision across all relevant variables produced %CVs $<$10% for HER2 and ER. A genome possessed GI if more than 12 large-scale transitions (LSTs) were detected. For detection of 2-fold amplification at the ERBB2 locus, gene amplification was detected with 85% sensitivity and 94% specificity. Tested healthy donor blood samples were absent of detected CTCs and lacked LST/GI or ERBB2 amplification in all (46) isolated WBCs. **Conclusions:** These results reflect the validation of a novel clinical assay combining CTC detection with single-cell GI and amplification of the ERBB2 locus. This assay better discriminates CTC detection with the addition of an assessment of GI. Additionally, along with protein expression measures of ER and HER2, it provides the ability to assess if HER2 expression is driven by ERBB2 amplification. Research Sponsor: Epic Sciences.

1054 **Poster Session**

First-in-human phase 1 dose escalation study of the KAT6 inhibitor PF-07248144 in patients with advanced solid tumors.

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Background: KAT6A and KAT6B regulate gene transcription via acetylation of histone H3K23 and their dysregulation drives lineage-specific gene expression in cancer. We report dose escalation data from the first-in-human phase 1 (Part 1A and 1B; NCT04606446) study of the KAT6-selective inhibitor PF-07248144. **Methods:** Part 1A (monotherapy dose escalation) enrolled patients (pts) with advanced/metastatic ER+/HER2− breast cancer (mBC), CRPC, or NSCLC, resistant/intolerant to standard therapy. Part 1B (PF-07248144 + fulvestrant combination dose escalation) enrolled pts with advanced/metastatic ER+/HER2- mBC with disease progression after ≥1 line of CDK4/6 inhibitor and endocrine therapy (ET). PF-07248144 (1-15 mg in Part 1A) was administered orally once per day (QD) in 28-day cycles following Bayesian design with overdose control. Study objectives: primary - assess PF-07248144 safety and tolerability, including dose limiting toxicities (DLT); secondary - evaluate PF-07248144 pharmacokinetics (PK); and exploratory - evaluate pharmacodynamics (PD; peripheral blood mononuclear cells [PBMC] and tumor H3K23Ac inhibition) and antitumor activity (using RECIST 1.1 by investigator assessment). **Results:** At data cut off (30 Sep 2022), 29 pts were enrolled: 25 in Part 1A (12 mBC, 11 CRPC, 2 NSCLC) and 4 in Part 1B (mBC). Part 1A evaluated 5 dose levels (1-15 mg QD) and Part 1B evaluated 5 mg PF-07248144 QD + 500 mg fulvestrant. Median age across Part 1A and 1B was 67 yrs (range 48-90). A total of 83% (Part 1A) and 75% (Part 1B) of pts with mBC had received > 3 prior lines of systemic anticancer therapy. Three DLTs (Grade 3 [G3] neutropenia) were observed: 2 in Part 1A (8 mg and 2 mg QD) and 1 in Part 1B (5 mg QD). A maximum tolerated dose was not identified; 5 mg QD was identified as the recommended dose for expansion for both monotherapy and fulvestrant combination. Across Parts 1A and 1B, treatment-related AEs (TRAEs; any grade) in ≥20% pts were dysgeusia (72%), anemia (52%), neutropenia (48%), thrombocytopenia (31%), diarrhea (31%), white blood cells (WBC) decreased (28%), fatigue (24%), and aspartate aminotransferase increased (21%); the majority of TRAEs were G1-2. TRAEs ≥G3 seen in > 1 pt were neutropenia (6/29; 21%), anemia (5/29; 17%), and WBC decreased (2/29; 7%). PF-07248144 PK was linear between 1 and 15 mg. H3K23Ac inhibition (≥70%) in PBMCs was achieved at steady state at doses of ≥1 mg. Tumor H3K23Ac levels were reduced by > 50% in 4 paired tumor biopsies at exposures associated with preclinical anti-tumor activity. Confirmed and durable partial responses were observed in 1/8 (Part 1A) and 2/4 (Part 1B) response-evaluable pts with ER+/HER2- mBC who progressed on prior ET+CDK4/6 inhibitor treatment. **Conclusions:** PF-07248144 was well tolerated and associated with strong KAT6 inhibition in PBMCs and tumors and confirmed partial responses in pts with heavily treated ER+/HER2- mBC during dose escalation. Clinical trial information: NCT04606446. Research Sponsor: Pfizer.

Impact of race and age on intrinsic subtype distribution and treatment decisions in metastatic breast cancer: Preliminary analysis of HARMONY (LCCC1829).

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Background: Gene expression profiling (GEP) is used to classify breast cancer (BC) into four intrinsic subtypes: Luminal A (LumA), Luminal B (LumB), HER2-Enriched, and Basal-like. Non-LumA subtypes are associated with poorer outcomes. Studies in early BC show that hormone receptor-positive (HR+)/HER2-negative (HER2-) tumors have a higher frequency of non-LumA subtypes in Black and younger (<50) women. Similarly, triple negative BC, which carries the poorest prognosis and is mostly Basal-like, are overrepresented in Black and younger women. These variations in intrinsic subtype contribute to outcomes disparities. The extent to which these racial and age differences in subtypes and mortality occur in metastatic breast cancer (MBC) is unknown. **Methods:** HARMONY (NCT03769415) is a prospective clinical trial in patients with newly diagnosed MBC. Bulk tumor GEP (PAM50 intrinsic subtyping) is performed on primary and metastatic tumors. A primary objective is to determine the extent and treatment implications of molecular discordance (defined *a priori* as treatment differences by intrinsic subtype compared to clinical subtype); other endpoints to be reported later include GEP comparisons between primary and metastatic samples. Here we examine differences in a) intrinsic subtype and b) treatment patterns in MBC by race and age. **Results:** At the time of analysis, the study had accrued 220 participants. Mean age was 58, 24% were Black women. Sixty-five percent had HR+/HER2- MBC, 14% HER2-positive, and 21% triple negative. Unlike in early BC, LumB exceeded LumA (LumA 27%, LumB 35%, HER2-Enriched 12%, Basal-like 25%). Similar to early BC, subtype varied by race and age with more non-LumA subtypes in young and Black women. Discordance between intrinsic and clinical subtype was seen in 24% of Black, 20% of White women, in 29% of younger and 18% of older women. Treatment patterns also differed by race and age, where a higher percentage of younger Black women received first-line chemotherapy compared to younger White women overall (45% vs. 10%, p=0.0025), and in HR+/HER2- disease (33% vs 8.7%, p=>0.05). No difference was seen in older women (24% vs 17%, p=0.44). Median progression free survival was worst in younger Black women compared to all other participants (5.4 vs 19.5 months, p=0.027), which may be driven by clinical subtype. **Conclusions:** Intrinsic subtype of tumors in a metastatic population has a different distribution by race and age than early BC, with more poor-prognosis non-LumA subtypes, and approximately 1 in 5 have discordance between clinical and molecular subtype, which may be therapeutically relevant. Clinical trial information: NCT03769415. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

	Total population			
	≤ 50 (59)	> 50 (136)	Black (46)	White (140)
Luminal A	10.2%***	34.6%***	15.2%	28.6%
Luminal B	40.7%	33.1%	39.1%	35%
HER2-Enriched	20.3%*	8.8*	15.2%	12.1%
Basal-like	28.8%	23.5%	30.4%	24.3%

*** p-value <0.001, * p-value <0.05.

Comparative overall survival of patients in trials of CKD4/6 inhibitors in combination with endocrine therapy in advanced breast cancer.

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Background: CDK4/6i and endocrine therapy (ET) are an international gold standard therapy in estrogen receptor (ER) positive and HER2-negative advanced breast cancer (aBC). Individual trials of abemaciclib, palbociclib and ribociclib show similar impact on progression-free survival yet differing statistical significance for OS. A robust comparative evaluation of the efficacy, safety, and tolerability of the three drugs is warranted. **Methods:** We searched PubMed, ASCO, ESMO and SABCS proceedings to identify phase 3 randomized clinical trials reporting OS of CDK4/6i in combination with ET in ER-positive aBC in first or second line. A network meta-analysis using WinBUGS was performed to evaluate comparative efficacy, based on the ET partner, in the absence of direct comparisons. Trial level data on common and serious adverse events (AE) were extracted for each drug. The odds ratio (OR) for each AE was calculated comparing each CDK4/6i to the respective endocrine therapy backbone (aromatase inhibitor (AI) or fulvestrant) alone. **Results:** Seven studies comprising 4087 patients met the inclusion criteria. Median follow up was 70.2 months. Four studies paired a CDK4/6i with an AI or tamoxifen, 3 studies were paired with fulvestrant. There were no statistically significant differences in OS between any of the CDK4/6i with any ET backbone. Compared to palbociclib, ribociclib and abemaciclib showed significantly lower grade 1-2 fatigue/asthenia (ribociclib OR 0.69 [95% CI 0.58, 0.83]; abemaciclib OR 0.6 [95% CI 0.49, 0.74]) and abemaciclib showed significantly lower grade 1-2 alopecia (abemaciclib 0.76 [95% CI 0.6, 0.97]). Compared to palbociclib, ribociclib and abemaciclib showed significantly higher GI toxicity (ribociclib any grade vomiting OR 1.71 [95% CI 1.36, 2.15]; abemaciclib any grade vomiting OR 2.1 [95% CI 1.61, 2.62], any grade diarrhea 13.2 [95% CI 10.31, 16.78]). Treatment discontinuation was highest with abemaciclib. **Conclusions:** In this network meta-analysis, there was no statistically significant difference in OS between CDK4/6i despite differences in individual trials. Real-world data analyses may help to identify if a there is a meaningful inter-drug difference in efficacy. Significant differences between CDK4/6i are observed for safety and tolerability outcomes. Research Sponsor: None.

Differences in OS between the CDK4/6i with any ET or AI backbone.

AI backbone.

Control Experimental	Palbociclib	Ribociclib	Abemaciclib
Palbociclib	-	0.79 (0.56, 1.14), p = 0.21	0.79 (0.52, 1.19), p = 0.26
Ribociclib	1.26 (0.88, 1.80), p = 0.21	-	0.99 (0.74, 1.33), p = 0.96
Abemaciclib	1.27 (0.84, 1.92), p = 0.26	1.01 (0.70, 1.46), p = 0.96	-
Fulvestrant backbone			
Palbociclib	-	0.90 (0.60, 1.33), p = 0.59	0.93 (0.62, 1.40), p = 0.73
Ribociclib	1.12 (0.75, 1.66), p = 0.59	-	1.04 (0.71, 1.52), p = 0.85
Abemaciclib	1.08 (0.72, 1.61), p = 0.73	0.96 (0.66, 1.42), p = 0.85	-

HR (95% CI), p value.

1057 **Poster Session**

Lasofoxifene (LAS) plus abemaciclib (Abema) for treating *ESR1*-mutated ER+/HER2- metastatic breast cancer (mBC) after progression on prior therapies: ELAINE 2 study update.

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Background: Endocrine therapy (ET), particularly aromatase inhibitors (AIs), for estrogen receptor (ER)-positive breast cancer can lead to acquired *ESR1* mutations (*mESR1*) driving endocrine resistance and tumor progression. Treatments for mBC with *mESR1* are limited, especially after progression on ET/cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i) combinations. In ELAINE 2, LAS, a next-generation ET (breast ER antagonist) plus Abema had a median progression-free survival (PFS) of ~13 mos, objective response rate (ORR) of 33%, and 24-wk clinical benefit rate (CBR) of 62% with a favorable safety profile in patients with resistant *mESR1* mBC (Damodaran S, et al. *J Clin Oncol*. 2022; 40:16 suppl 1022). Here, we report ELAINE 2 data with longer patient follow up (Jan 31, 2023). **Methods:** In this open-label, phase 2, single-arm study, 29 women with *mESR1*, ER+/HER2- mBC that progressed on prior ET took oral LAS 5 mg/day and Abema 150 mg BID until disease progression/toxicity. The primary endpoint was safety/tolerability; secondary included PFS, CBR, and ORR. Data were summarized descriptively with no formal hypothesis testing. **Results:** Patients (median age 60 yrs) had received a median of 2 prior therapy lines for mBC; all but one had prior CDK4/6i exposure and 14 (48%) had prior chemotherapy for mBC. LAS/Abema was well tolerated with primarily grade 1/2 treatment-emergent adverse events (most commonly diarrhea, nausea, fatigue, and vomiting). One treatment withdrawal occurred due to grade 2 diarrhea. No deaths occurred. LAS dose was not reduced; Abema dose was reduced to 100 mg BID in 6 (21%) patients. Median PFS was 56.0 wks (~13 mos) and CBR 65.5% (95% CI, 47.3–80.1). Median overall survival was not estimable. In 18 patients with measurable lesions, ORR was 55.6% (95% CI, 33.7–75.4), with median time to response of 5.7 mos and median duration of response of 6.4 mos. Seventy-six percent, 56%, and 39% of patients were progression free at 6, 12, and 18 mos, respectively. Three (10%) patients had scan-identified venous thromboembolic events, with one symptomatic pulmonary embolism and one symptomatic deep vein thrombosis. In 26 patients with evaluable baseline and wk 4 ctDNA, *ESR1* mutant allele fraction decreased from baseline to wk 4 in 81% of patients and was not detected in 54%. **Conclusions:** With longer ELAINE 2 follow up, LAS/Abema continues to be well tolerated with clinically meaningful efficacy in women with *mESR1*, ER+/HER2- mBC that had progressed on ET and CDK4/6is. Decreases in *mESR1* ctDNA suggest effective target engagement of LAS. The PFS (median ~13 mos) and ORR (56%) with LAS/Abema are promising and a confirmatory phase 3 study (ELAINE 3) will begin in 2023. If ELAINE 2 results are confirmed, the combination of LAS and Abema would address a critical unmet need, providing a practice changing option for treating *mESR1* breast cancer. Clinical trial information: NCT04432454. Research Sponsor: Sermonix Pharmaceuticals.

1058 **Poster Session**

Prognostic factors in hormone receptor positive oligometastatic breast cancer.

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Background: Some recommend curative treatment for oligometastatic breast cancer (OMBC). To date, no randomized clinical trial has demonstrated the benefits of such a strategy. We present the largest retrospective series of patients treated consecutively for ER and/or PR positive (HR+) OMBC in a single institution. The objective was to describe the clinical and biological characteristics and prognostic factors of HR+ OMBC. **Methods:** We retrospectively reviewed all patients treated consecutively from 2014 to 2018 at our institution for synchronous or metachronous metastatic breast cancer (MBC). HR+ OMBC was defined as MBC with up to five metastases at diagnosis, positive hormone receptor status, and no other inclusion criteria. Clinical and biological characteristics, treatment modalities - intent-to-cure vs palliative - and outcomes were recorded. Progression-free survival (PFS) and overall survival (OS) were calculated. Log rank test and Cox regression models were used for survival analyses including time-dependent variable. **Results:** Of 998 patients treated for MBC within our institution between 2014 and 2018, 11.3% (N=113/998) met inclusion criteria. 62.5% of them had SBR grade I/II HR+ OMBC and 80.5% had HR+/HER2- OMBC. 89.3% patients had only one organ involved. None had more than two; 89.3% patients had 1-3 metastases at diagnosis. Among these 113 patients, 63.7% had bone metastases, 54.9% had bone only metastases, 19.5% had visceral metastases, 17.7% had lymph node metastases, 7.1% had brain metastases, and 3.5% had other metastases. Forty-one patients (36.3%) were treated in a curative intent with systemic treatment plus ablative focal treatment of primary tumor – or local relapse – and all distant metastases. Median follow up was 67.2 months (95%CI= [63.1-75.4]). For the entire series, five-year PFS and OS were respectively 35.2% (95%CI= [25.6-44.6]) and 67.0% (95%CI= [56.7-75.3]) respectively. In univariable analysis, liver metastases was associated with worse OS (HR=3.13, 95%CI=[1.43-6.87], p=0.003). In multivariable analysis, HER2 positive status (HR=0.43, 95%CI= [0.21-0.90], p=0.024), bone only metastases (HR=0.46, 95%CI= [0.27-0.78], p=0.004), and intent-to-cure treatment (HR=0.53, 95%CI= [0.30-0.93], p=0.027) were significantly associated with longer PFS. In multivariate analysis, only intent-to-cure strategy was associated with better OS (HR=0.24, 95%CI= [0.09-0.60], p=0.002). **Conclusions:** This is the largest retrospective series of patients treated consecutively for HR+ OMBC to date. 71.5 % of OMBC and 11.3 % of all MBC are HR+ OMBC. Most had only one invaded organ and 1-3 metastases. Among our cohort, intent-to-cure treatment improve drastically HR+ OMBC PFS and OS. A multimodal intent-to-cure strategy should be routinely discussed for patients with HR+ metastatic breast cancer with one to five metastases at diagnosis. Research Sponsor: None.

Circulating tumor cells (CTCs) dynamics after CDK4/6i for hormone-receptor positive (HR+) metastatic breast cancer (MBC): A biomarker analysis of the PACE randomized phase II study.

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Background: PACE is a multicenter randomized phase II trial investigating palbociclib (P) in combination with fulvestrant (F) after progression on any CDK4/6 inhibitor (CDK4/6i), with or without the PD-L1 inhibitor avelumab (A), in HR+/HER2- MBC. CTCs are rare cells in the blood stream whose detection is associated with worse outcome and treatment resistance. **Methods:** Eligible patients (pts) had HR+/HER2- MBC with prior progression after ≥ 6 months (mo) of AI and CDK4/6i for MBC, or during/within 12 mo in the adjuvant setting, with ≤ 1 prior chemotherapy for MBC. Pts were randomized 1:2:1 to F, F+P, or F+P+A. CTC detection and enumeration were performed utilizing CellSearch (Menarini Silicon Biosystems) at baseline (BL), at time of first tumor assessment (TTA1), and at progression. Results were dichotomized using the standard CTC threshold (≥ 5 CTCs/7.5 ml) into a novel prognostic classification: StageIV$_{indolent}$ and StageIV$_{aggressive}$ (Cristofanilli et al 2019). Concurrent ctDNA Sequencing was performed using Guardant360 (Guardant Health). **Results:** Of the 220 randomized pts, 203 (92%) had sample available for BL CTC enumeration, 155 had detectable CTCs (70.5%), and 99 (48.8%) were StageIV$_{aggressive}$. *De novo* disease at initial diagnosis was associated with StageIV$_{aggressive}$ (47.5% vs 30.8% StageIV$_{indolent}$), and distribution of visceral versus non-visceral disease was similar across the two CTCs groups. StageIV$_{aggressive}$ represented 38.3%, 54.8%, and 46.2% of the F, F+P and F+P+A treatment groups, respectively. BL CTCs were prognostic in the overall cohort; median PFS was 5.7mo vs 3.5mo for StageIV$_{indolent}$ vs StageIV$_{aggressive}$ (HR: 1.69, 90%CI 1.27,2.24, P<0.001). Median PFS for the F, F+P and F+P+A arms was 1.9mo, 4.6mo and 5.4mo in StageIV$_{aggressive}$ compared to 8.2mo, 5.3mo and 8.3mo in StageIV$_{indolent}$. Among patients in the StageIV$_{aggressive}$ subgroup, the F+P and F+P+A arms demonstrated improved outcomes compared to F alone. (F+P vs F HR 0.43, 90% CI 0.25-0.71, and F+P+A vs F HR 0.26, 90% CI 0.14-0.49). No benefit of F+P or F+P+A over F was observed in the StageIV$_{indolent}$ subgroup (F+P vs F HR 1.45, 90% CI 0.87 - 2.40 and F+P+A vs F HR 1.06, 90% CI 0.61 - 1.84, each p(interaction)<0.01). Changes in StageIV CTC characterization (indolent vs aggressive) between BL and TTA1 among the subset of 175/203 pts with both timepoints available are reported. **Conclusions:** Baseline CTC enumeration is prognostic in patients receiving F with or without CDK4/6i. The StageIV$_{aggressive}$ subgroup may derive preferential benefit with combinations of F+P or F+P+A over F alone. Findings should be confirmed in other studies. ctDNA analyses are ongoing. Clinical trial information: NCT03147287. Research Sponsor: Pfizer.

CTC at BL	CTC at TTA1	
	StageIV$_{indolent}$	StageIV$_{aggressive}$
StageIV$_{indolent}$ (n=94)	72 (76.6%)	22 (23.4%)
StageIV$_{aggressive}$ (n=81)	31(38.3%)	50 (61.7%)
Overall (n=175)	103 (58.9%)	72 (41.1%)

ctDNA mutational profiles in luminal breast cancer with early vs late distant relapse: Geicam/2014-03.

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Background: Patients with hormone receptor-positive early breast cancer (BC) can develop resistance to endocrine therapies (ET) and face a continuous risk of relapse, which can occur anywhere from a few months (m) to several decades after surgery. The causes of early vs late relapses are not well understood. Our research examines the presence of oncogenic drivers in circulating tumor DNA (ctDNA) at the time of relapse in patients with luminal BC who have either an early or late distant recurrence. **Methods:** We identified pts included in the GEICAM/2014-03 study (NCT02819882) with: 1) HR-positive BC, 2) metastatic relapse either <36m (early relapse, [early-R]) or >120m (late relapse, [late-R]) from diagnosis, and 3) ctDNA obtained before first line treatment for advanced disease. The AVENIO ctDNA assay was used for identifying genomic aberrations in 77 cancer-related genes. **Results:** Eighty-four pts, 36 in early-R and 48 in late-R groups, were selected. Median time to relapse was 24.97m in early-R vs 151.84m in late-R. Median time from last dose of adjuvant ET to relapse was 0.03m for early-R vs 74.06m for late-R. Median PFS to first line treatment was 7.62m in early-R and 35.15m in late-R. With a median follow-up of 32.08m, median OS after diagnosis of metastatic disease was 27.74m for early-R and not reached for late-R. ctDNA analysis detected at least 1 mutation (mut) in 71/84 (85%) pts (89% in early-R vs 81% in late-R). Early-R pts were enriched in mut in *TP53* (44% vs 19%), *ESR1* (11% vs 4%), MAPK_ERK pathway (14% vs 6%), and *ERBB2* copy number alterations (CNA) (25% vs 2%). PI3K/AKT pathway alterations had similar frequency in both recurrence groups (38% vs 42%) and they were not associated with OS. Seven *ESR1* mut were detected in 6 pts. In the early-R group there were 5 *ESR1* mut (71% of total *ESR*1 mut), median mutant allele frequency (mMAF): 0.64%; while in the late-R, 2 *ESR1* mut (29%), mMAF: 0.4%. *ESR1* mut were associated with worse OS (median OS 48.48m vs 12.84m wild-type vs mutant; p=0.0025). There were 10 pts with E*RBB2* CNA at metastatic relapse; 9 (25%) in the early-R and 1 pts (2%) in the late-R. Seven pts (70%) had HER2-positive. Pts with ctDNA *ERBB2* CNA had worse OS (median OS 48.48m vs 20.52m wild-type vs mutant; p-adj=0.025). **Conclusions:** In luminal breast cancer (BC), early and late distant relapse differ at both the clinical and genomic levels. Early relapse is a highly aggressive form of the disease and is enriched in *TP53* mutations and actionable genetic alterations, such as mutations in the *ESR1* and CNA in ERBB2, as detected by ctDNA analysis at the time of metastatic relapse diagnosis. Clinical trial information: NCT02819882. Research Sponsor: AstraZeneca in alliance with Daiichi Sankyo Spain, Roche, Celgene, Pfizer and SEAGEN; AMACMEC Association.

Mutations identified in ESR1.

ID	Recurrence Group	Adyuvant ET	Mutation	MAF (%)
1	late-R	Tamoxifen	p.Y537S	0.20
2	late-R	AI (Letrozol)	p.Y537N	0.60
3	early-R	AI (Anastrozol)	p.E380Q	0.14
4	early-R	Tamoxifen	p.E380Q	0.17
5	early-R	AI (Letrozol)	p.E380Q	0.89
5	early-R	AI (Letrozol)	p.Y537C	0.64
6	early-R	AI (Exemestane)	p.S463P	1.89

1061 **Poster Session**

Interim analyses (IA) of the giredestrant (G), G + abemaciclib (A), and G + ribociclib (R) arms in MORPHEUS Breast Cancer (BC): A phase I/II study of G treatment (tx) combinations in patients (pts) with estrogen receptor-positive, HER2-negative locally advanced/metastatic BC (ER+, HER2– LA/mBC).

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Background: Limitations of current approved endocrine therapies (ETs), a mainstay tx for ER+ BC, include incomplete ER signaling inhibition. Novel ETs, such as selective estrogen receptor antagonists and degraders (SERDs), may help overcome this. G, a potent, nonsteroidal, oral (PO) SERD, is well tolerated and has shown robust ER occupancy and encouraging antitumor activity as monotherapy and in combination with the cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) palbociclib (P). MORPHEUS BC (NCT04802759) is evaluating the safety and efficacy of G tx combinations in ER+, HER2– LA/mBC. We present results from the 16-week IA of G and G + CDK4/6i (A or R). **Methods:** Eligible pts had disease progression on 1–2 lines of ET (including a CDK4/6i) for LA/mBC. Pts were randomized 1:6 (planned n = 15 per arm) to receive G (30 mg PO QD; control arm), G + A (150 mg PO BID), or sequentially, G + R (600 mg PO QD) until disease progression/unacceptable toxicity. The study was not designed to make explicit power and type I error considerations for a hypothesis test. Primary endpoints were safety and objective response rate; other endpoints included progression-free survival, overall survival, clinical benefit rate, disease control rate (DCR), duration of response, and pharmacokinetics. Genetic alterations were defined using baseline circulating tumor DNA. **Results:** As of Feb 4, 2022, 15 pts were enrolled in the G + A arm; 73% received one prior line of tx in the LA/mBC setting; 27% received prior fulvestrant; 73% had liver metastases at baseline (BL). As of Sept 22, 2022, 11 and 16 (of whom 14 were evaluable) pts were enrolled in the G and G + R arms, respectively; 64%/86% received one prior line of tx in the LA/mBC setting; 73%/36% received prior fulvestrant; 73%/57% had liver metastases at BL. Three pts had a partial response (PR; G + A, n = 1; G + R, n = 2); 19 had stable disease (G, n = 5; G + A, n = 7; G + R, n = 7). DCRs were 36% (G), 40% (G + A), and 50% (G + R). Safety is shown. **Conclusions:** G combined with a CDK4/6i (A or R) was well tolerated, with no unexpected safety signals. Three PRs were seen in this heavily pretreated population of pts with disease progression post-CDK4/6i tx. This study provides the first data supporting the combinability of G with the CDK4/6is A and R, in addition to P as seen in prior studies. G can therefore be combined with all three approved CDK4/6is. Clinical trial information: NCT04802759. Research Sponsor: F. Hoffmann-La Roche Ltd.

	G	G + A	G + R
Tx-related adverse events (TRAEs)	46%	80%	100%
Grade 3–4	0	40%	43%
AEs/TRAEs leading to tx discontinuation	0	0	7%
AEs leading to dose modification/interruption	18%	60%	64%
Fatal AEs	0	0	0
Most common TRAEs (≥ 20% of pts)	Fatigue	Diarrhea, nausea, abdominal pain, fatigue, neutropenia, vomiting, decreased appetite	Nausea, fatigue, neutropenia, asthenia, QT interval prolongation

Endocrine therapy resistance (ETR) in hormone receptor-positive, HER2-negative metastatic breast cancer (HR+, HER2– mBC): Prevalence, biomarker characteristics, and outcomes.

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Background: ETR to prior adjuvant ET poses challenges to first-line treatment (1L tx) of HR+, HER2– mBC. Understanding patient (pt)/disease heterogeneity is crucial for developing new txs that target specific ETR mechanisms to improve pt outcomes. We investigate ETR, including prevalence, genomic profiles, and survival outcomes in pts with HR+, HER2– mBC treated in the 1L setting. **Methods:** This retrospective two-cohort study of pts initiating 1L systemic tx for mBC (diagnosed after Jan 1, 2015) used data from the Flatiron Health (FH) electronic health record-derived de-identified database (FH cohort), and FH-Foundation Medicine, Inc. (FMI) clinico-genomic database (CGDB cohort; solid biopsy FMI test required). The de-identified data originated from ~280 US cancer clinics (~800 sites of care). Pts with ETR to prior adjuvant ET were defined per ESMO guidelines (table footnote); primary ETR (1ETR) was divided into pts relapsing within 1 year (yr) or 1–2 yrs of adjuvant ET. Genomic profiles were assessed in the CGDB cohort. In both cohorts, real-world (rw) progression-free survival (PFS) and overall survival (OS) were estimated in pts who received 1L tx with fulvestrant (F) + CDK4/6 inhibitor (CDK4/6i). **Results:** In the FH cohort (N = 4052), 16.1% of pts had 1ETR (ET <1 yr: 7.9%) and 33.9% had secondary ETR (2ETR). In the CGDB cohort (N = 696), *ESR1* mutations *(ESR1*m) were present in 10.8% of 158 pts with 1ETR (ET <1 yr: 4.2%; 1–2 yrs: 16.1%) and 19.9% of 317 pts with 2ETR. In pts who received 1L F + CDK4/6i, shorter median (m) rwPFS (statistically significant) and OS (not significant) were seen in pts with 1ETR vs. 2ETR, but outcomes were not affected by the presence of *ESR1*m in pts with 2ETR. **Conclusions:** Overall, half of pts with 1L HR+, HER2– mBC have ETR to prior adjuvant ET. Pts with ETR have tumors with heterogeneous genomic profiles and varied survival outcomes. *ESR1*m are infrequent in pts with 1ETR and <1 yr of adjuvant ET but are more common in 2ETR. In pts treated with 1L F + CDK4/6i, PFS and OS were worse with 1ETR than 2ETR. This study highlights the importance of further understanding the heterogeneity in molecular profiles and outcomes within ETR. Research Sponsor: F. Hoffmann-La Roche Ltd.

Survival outcomes in pts with ETR and 1L F + CDK4/6i tx	Pts, n	Events, n	mPFS, mo (95% CI)	Pts, n	Events, n	mOS, mo (95% CI)
FH cohort						
1ETR*	171	124	7.7 (6.2, 9.0)	171	99	20.6 (16.7, 31.2)
1ETR (ET 0–1 yrs)	69	54	7.3 (5.0, 10.3)	69	45	17.0 (13.6, 35.0)
1ETR (ET 1–2 yrs)	102	70	7.7 (6.4, 11.0)	102	54	24.3 (17.6, 33.5)
2ETR† (ET 2+ yrs)	490	325	11.7 (9.8, 13.5)	490	246	32.3 (30.0, 39.1)
CGDB cohort, 2ETR only‡						
***ESR1*m**	22	14	10.6 (5.0, NE)	33	15	30.5 (19.9, 46.5)
***ESR1* wildtype**	55	35	10.0 (4.7, 16.1)	72	30	22.4 (16.7, NE)

* Relapsing during <2 yrs of adjuvant ET.
† Relapsing during ≥ 2 yrs of adjuvant ET or ≤ 1 yr from last ET.
‡ Risk set adjustment applied in survival analyses to account for delayed entry of pts in the cohort post-index date.

1063 **Poster Session**

Outcomes with first-line (1L) ribociclib (RIB) + endocrine therapy (ET) vs physician's choice combination chemotherapy (combo CT) by age in pre/perimenopausal patients (pts) with aggressive HR+/HER2− advanced breast cancer (ABC): A subgroup analysis of the RIGHT Choice trial.

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Background: The progression-free survival (PFS; primary endpoint) results from the Phase II RIGHT Choice trial demonstrated a statistically significant median PFS (mPFS) benefit of ≈1 y with RIB + ET over combo CT (mPFS, 24.0 vs 12.3 mo; hazard ratio [HR], 0.54; 95% CI, 0.36-0.79; $P = .0007$) in pts with aggressive HR+/HER2− ABC. Younger pts with aggressive ABC have a worse prognosis, which impacts treatment (tx) decisions. Hence, a subgroup analysis of key efficacy endpoints from RIGHT Choice by age (< 40 vs ≥ 40 y) was undertaken. **Methods:** Pre/perimenopausal pts (aged 18-59 y) with HR+/HER2− ABC and no prior systemic therapy for ABC were randomized 1:1 to either RIB with letrozole/anastrozole + goserelin or investigator's choice of combo CT (docetaxel + capecitabine, paclitaxel + gemcitabine, or capecitabine + vinorelbine). Pts in the trial had ABC not amenable to curative therapy and for which combo CT was clinically indicated by physician's judgment (ie, symptomatic visceral metastases, rapid progression of disease or impending visceral compromise, or markedly symptomatic non-visceral disease). **Results:** In total, 70 pts were aged < 40 y and 152 were aged ≥ 40 y. In the combo CT arm, pts aged < 40 y fared worse and had a shorter mPFS, shorter median time to tx failure (mTTF), and higher 3-month tx failure rate (TFR) than pts aged ≥ 40 y. Pts aged < 40 y showed a significant PFS benefit with RIB + ET vs combo CT (mPFS, not reached [NR] vs 10.2 mo; HR, 0.38). This PFS benefit with RIB + ET over combo CT was also observed in pts aged ≥ 40 y (21.2 vs 16.0 mo; HR, 0.71). Regardless of age, the mTTF was longer and the 3-month TFR was lower in the RIB + ET arm than the combo CT arm. The median time to response (mTTR), overall response rate (ORR), and clinical benefit rate (CBR) were similar between the two tx arms in both age groups. **Conclusions:** This analysis demonstrated a clinically meaningful PFS benefit and improved secondary outcomes with 1L RIB + ET over combo CT along with similar treatment responses in both tx arms in pts aged < 40 y as well as in those ≥ 40 y with aggressive HR+/HER2− ABC. This analysis supports RIB + ET as a preferred tx option in this pt population, including younger pts aged < 40 y. Clinical trial information: NCT03839823. Research Sponsor: Novartis Pharmaceuticals Corporation.

Age	Arm	n	mPFS (95% CI), mo	HR (95% CI)	mTTF (95% CI), mo	HR (95% CI)	mTTR* (95% CI), mo	ORR,* %	CBR,* %	3-mo TFR (95% CI), %
< 40 y	RIB + ET	32	NR (10.2-NR)	0.38 (0.18-0.79)	NR (10.2-NR)	0.30 (0.15-0.58)	4.7 (2.8-15.9)	65.6	75.0	9.4 (2.0-25.0)
	CT	38	10.2 (6.7-11.2)		7.0 (5.3-10.2)		2.7 (1.4-4.9)	57.9	65.8	26.3 (13.4-43.1)
≥ 40 y	RIB + ET	80	21.2 (17.1-29.3)	0.71 (0.44-1.15)	18.5 (12.7-24.0)	0.58 (0.38-0.88)	6.3 (4.4-12.9)	65.0	82.5	12.5 (6.2-21.8)
	CT	72	16.0 (8.8-21.7)		11.0 (7.8-15.5)		4.5 (2.8-8.4)	61.1	76.4	19.4 (11.1-30.5)

* Unconfirmed.

Efficacy and safety of tenalisib, a PI3K δ/γ and SIK3 inhibitor, in patients with locally advanced or metastatic breast cancer: Updated results from an on-going phase II study.

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Background: Several studies have shown that the upregulation of the PI3K–AKT–mTOR pathway interacts with the Estrogen Receptor pathway and confers endocrine resistance. Elevated Salt Inducible Kinase-3 (SIK3) expression, which often is overexpressed breast cancer, is shown to contribute to tumorigenesis. Tenalisib (RP6530), a highly selective, PI3Kδ/γ and SIK3 inhibitor, has shown promising efficacy in T-cell lymphoma with a distinct safety profile. Tenalisib's major metabolite, IN0385 is a SIK3 inhibitor. Breast cancer cell line studies have demonstrated that tenalisib potentiated the activity of paclitaxel and doxorubicin. The aim of this phase II study was to investigate the efficacy and safety of single-agent tenalisib in patients (pts) with HR+ HER2- locally advanced or metastatic Breast cancer. **Methods:** This randomized, open-label study was designed to evaluate two doses (800 mg BID and 1200 mg BID) of Tenalisib in MBC pts (including TNBC) whose disease had progressed following at least one line of therapy. Tenalisib was administered orally daily for every 28 days cycles until the disease progression. The study would enroll forty pts (20 at each dosage level), with the primary outcome being the proportion of patients who did not have disease progression at the end of six months. Other outcomes were investigator-assessed ORR, PFS, DCR (DCR=CR+PR+SD) and Clinical Benefit Rate (CBR= CR+PR+SD≥24 weeks) as per RECIST v1.1 criteria. **Results:** The trial enrolled 40 pts. Pts had a median of 3 (range 1-7) prior therapies of which, 87% pts had prior endocrine therapy, which included 40% pts treated with an aromatase inhibitor and 30% of pts treated with fulvestrant as their last therapy respectively. Prior chemotherapy in any setting included taxane (60%), and anthracycline (47.5%). The median age was 63.8(31-71) years, 77.5% pts had visceral disease, and 95.0% had 2 or more metastatic lesions. As of 06-Feb-2023, of the 40 pts, 5 pts (12.5%) showed PR and 22 (55%) had SD. The CBR was 57.5% while the DCR was 67.5%. The median duration of response in PR pts and median duration of clinical benefit were 9.36 and 7.46 months respectively. The progression free survival (PFS) was 5.6 months (range: 0.93 to 15.26+ months). Drug related AEs were manageable. The most common AEs (≥10%) of any grade were transaminitis, GGT elevation, and rash. Grade 3/ 4 events were limited to GGT elevation (12.5%), and transaminitis (12.5%). Discontinuations due to related AEs were infrequent (<5%) and limited to two events (one event each of rash and GGT elevation). **Conclusions:** Based on the data from the ongoing study, tenalisib shows encouraging efficacy as a single agent in pts with relapsed/refractory HR+ HER2- difficult to treat MBC patients. Updated efficacy and tolerability data will be provided at the time of presentation. Clinical trial information: NCT05021900. Research Sponsor: Rhizen Pharmaceuticals AG.

Efficacy analysis of CDK4/6 inhibitors (CDKi) + endocrine therapy (ET) treatment in hormone receptor-positive/HER2-negative (HR+/HER2-) advanced breast cancer (aBC): Biomarker analysis including chemoendocrine score (CES) by CDKi type in SOLTI-1801_CDK-PREDICT study.

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Background: CDKi + ET improved progression-free survival (PFS) and ribociclib also overall survival (OS) in HR+/HER2- aBC first-line setting. Intrinsic subtypes (IS) are prognostic and predict benefit from CDKi + ET (Finn. SABCS 2017, Prat. JCO 2021, Tolosa. SABCS 2022). We previously reported a PAM50-based CES in HR+/HER2-negative early BC (Prat et al. CCR 2016). Here, we evaluated the association of CES with PFS following CDKi therapy in aBC. **Methods:** CDK-PREDICT prospectively evaluated 113 HR+/HER2- aBC patients (pts) treated in the first-line setting with CDKi + ET. RNA from FFPE metastatic tumors was analyzed at the nCounter (Nanostring Technologies) using a 72 custom gene panel including the PAM50 genes. CES was evaluated as a continuous variable, and categorically (CES-E[endocrine-sensitive], CES-I[intermediate] and CES-C[chemo-sensitive]) using the previously reported cut-offs. Multivariable analyses were used to test CES association with PFS. **Results:** The median follow-up for PFS was 18.5 m. PAM50 IS and CES distribution are shown**.** No statistically significant difference in mPFS by CDKi. CES (as a continuous variable or as group categories) was found significantly associated with mPFS. mPFS for CES-E pts was NR (95% CI: 26.0 - NR), 20.7m for CES-I (95% CI: 14.2 – 31.7m; HR= 1.98, $p<0.05$) and 11.7m for CES-C (CI 95%: 7.0 - 18.8; HR= 3.72, $p<0.05$). CES-C was associated with lower PFS compared to CES-I (aHR= 0.55, p=0.10) and CES-E (aHR= 0.29, $p<0.05$) independent of CDKi, ET, intrinsic subtype (Luminal versus not), endocrine sensitivity, onset metastatic and visceral disease. CES-C was significantly associated with higher expression of, MIA and lower expression of CCND1, CCNE1, FOXA1, MLPH and UBE2T compared with CES-E ($p< 0.05$). In CES-E pts mPFS for palbociclib was NR (IC95:22.9-NR) compare with 43.8 m for ribociclib (IC95: 12.0-NR); aHR=1.17 p=0.546), in CES-I pts mPFS for palbociclib was 18.9 m (IC95: 5.8-27.3) compare with 31.7 m for ribociclib (IC95: 12.2-NR); aHR=0.50 p=0.294), and in CES-C pts mPFS for palbociclib was 11.6 m (CI95: 2.7-15-7) compare with 10.0 m for ribociclib (CI95: 2.1-NR; aHR=0.48 p=0.102). Abemaciclib not reported due to low numbers (n=16). **Conclusions:** We confirmed independent prognostic value of CES in first-line setting, suggesting a not statistically significant benefit with ribociclib vs palbociclib in CES-I. Research Sponsor: This project has received a research grant from "Instituto de Salud Carlos III (ISCIII), Ministerio de Economía y Competitividad" (Spain) awarded within the National Research Program with reference PI 18/01408, co-funded with European Union ERDF funds.

Patient characteristics n (%)	Total (113)	Palbociclib (61)	Ribociclib (36)	Abemaciclib (16)
Intrinsic Subtypes:				
Luminal	101 (89)	56 (92)	35 (97)	10 (63)
Non-Luminal	12 (11)	5 (8)	1 (3)	6 (37)
Chemoendocrine score:				
CES-E	54 (48)	36 (59)	13 (36)	5 (31)
CES-I	37 (33)	17 (28)	13 (36)	7 (44)
CES-C	22 (19)	8 (13)	10 (28)	4 (25)

Clinical activity of camizestrant, a next-generation SERD, versus fulvestrant in patients with a detectable *ESR1* mutation: Exploratory analysis of the SERENA-2 phase 2 trial.

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Background: Camizestrant, a next-generation oral selective estrogen receptor antagonist and degrader (ngSERD), was compared at two dose levels to fulvestrant 500 mg (F) in post-menopausal women with advanced ER+, HER2→ breast cancer with disease recurrence or progression after ≤1 endocrine therapy in the advanced setting in the Phase 2 randomized SERENA-2 study (NCT04214288). Camizestrant demonstrated statistically significant and clinically meaningful benefit vs F in progression-free survival (PFS) in the overall study population (Oliveira M et al. SABCS 2022 Annual Meeting. Abstract GS3-02.). **Methods:** Baseline circulating tumour DNA was collected at screening and/or Cycle 1 Day 1 and analysed by next-generation sequencing. A post hoc exploratory analysis compared investigator assessed PFS with camizestrant (data from 75 and 150 mg combined) vs F in patients with detectable baseline *ESR1* (the gene that encodes ERα) hotspot mutations (*ESR1*m). Patients were divided into subgroups based on whether 1 or >1 *ESR1*m variants were detected, the specific *ESR1*m, and whether mutations were detected in *BRCA1/2* or the MAPK pathway. The most prevalent mutations are presented. A Cox proportional hazards model was used to compare PFS. **Results:** 48/147 (32.7%) patients treated with camizestrant and 35/73 (47.9%) treated with F had a detectable *ESR1*m in at least 1 baseline sample. *ESR1*m were detected in 6/9 (67%) patients with a *BRCA*1/2 mutation and 5/26 (19%) with a MAPK pathway alteration; however, the numbers were too small to analyse efficacy in these subgroups. **Conclusions:** Camizestrant showed improved outcome vs F in patients with a detectable *ESR1*m at baseline and in the subgroups tested. The greatest median PFS improvement was seen in patients where a single *ESR1*m variant was detected, suggesting that early intervention upon detection of an *ESR1*m may provide the maximum patient benefit for camizestrant, a hypothesis that is being tested in the SERENA-6 clinical trial (NCT04964934). Clinical trial information: NCT04214288. Research Sponsor: Astra Zeneca.

	Camizestrant n (%)	Camizestrant median PFS, months (90% CI)	F n (%)	F median PFS, months (90% CI)	Camizestrant vs F PFS HR (90% CI)
***ESR1*m detected**	48/147 (33)	8.0 (4.5–12.0)	35/73 (48)	2.2 (1.9–3.8)	0.44 (0.28–0.68)[a]
1 *ESR1*m variant detected[b]	21 (44)	12.9 (4.5–14.7)	17 (49)	2.2 (1.9–9.3)	0.52 (0.28–0.97)[c]
>1 *ESR1*m variant detected[b]	27 (56)	4.7 (2–11.1)	18 (51)	2.3 (1.9–3.8)	0.45 (0.25–0.81)[c]
D538G detected[b]	28 (58)	4.5 (2–9.1)	23 (66)	2.2 (1.9–3.8)	0.61 (0.36–1.03)[c]
Y537C/D/N/S detected[b]	33 (69)	9.1 (3.9–12.7)	23 (66)	2.3 (1.9–5.6)	0.46 (0.28–0.76)[c]

[a] Stratified Cox proportional hazards model used, adjusting for prior CDK4/6i and lung/liver metastases. [b] % calculated based on the number of patients with *ESR1*m detected (camizestrant n=48; F n=35). [c] Unadjusted HR presented due to smaller number of events in subcategories.

Capivasertib (C) and fulvestrant (F) for patients (pts) with aromatase inhibitor (AI)-resistant HR+/HER2– advanced breast cancer (ABC): Characterization and management of common adverse events (AEs) from the phase 3 CAPItello-291 trial.

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Background: In the CAPItello-291 trial in eligible pts with AI-resistant HR+/HER2– ABC, the addition of C (a potent, selective pan-AKT inhibitor) to F significantly improved PFS (primary endpoint) compared with placebo (P) in the overall (HR 0.60; 95% CI 0.51–0.71; p<0.001) and AKT pathway-altered population (HR 0.50; 95% CI 0.38–0.65; p<0.001). We report a detailed analysis of AEs. **Methods:** Pts were randomized 1:1 to receive F (500 mg IM on days 1 and 15 of cycle 1, and day 1 of each subsequent 28-day cycle) with either P or C (400 mg BID; 4 days on, 3 days off). Pts with HbA1c <8.0% and diabetes not requiring insulin were eligible. Incidence, management, and time to onset were summarized for common AEs (>10% any grade and >2.0% grade ≥3; CTCAE v5.0). **Results:** Overall, 708 pts were randomized to C+F (n=355) vs P+F (n=353); safety population C+F (n=355) vs P+F (n=350). Baseline risk factors potentially associated with hyperglycemia were a history of diabetes in 34 pts (10%) in the C+F arm vs 20 pts (6%) in the P+F arm (baseline median [range] HbA1c 5.4% [4.0–8.3] vs 5.4% [3.9–7.7]), median weight 65.0 kg (34–150) vs 66.5 kg (37–147) and 54% vs 53% of pts overweight/obese in the C+F vs P+F arms, respectively. Common AEs were diarrhea, rash, and hyperglycemia; maximum AE grade was mostly 1/2 and led to low rates of discontinuation. In the C+F arm, medications for the management of AEs were used in 151/257 pts (59%) with diarrhea (mostly loperamide; n=135), 109/135 pts (81%) with rash (mostly antihistamines; n=75/topical corticosteroids; n=64), and 28/60 pts (47%) with hyperglycemia (mostly metformin; n=18). **Conclusions:** Diarrhea, rash, and hyperglycemia, the most commonly reported AEs associated with AKT pathway inhibition, occur early in treatment with C+F, are generally low grade and manageable, and are associated with low rates of dose modifications/discontinuations. Clinical trial information: NCT04305496. Research Sponsor: AstraZeneca.

		Diarrhea[a]		Rash[a]		Hyperglycemia[a]	
		C+F	P+F	C+F	P+F	C+F	P+F
Any grade; n (%)		257 (72.4)	71 (20.3)	135 (38.0)	25 (7.1)	60 (16.9)	14 (4.0)
Maximum grade; n (%)	1	164 (46.2)	61 (17.4)	57 (16.1)	19 (5.4)	26 (7.3)	8 (2.3)
	2	60 (16.9)	9 (2.6)	35 (9.9)	5 (1.4)	26 (7.3)	5 (1.4)
	3	33 (9.3)	1 (0.3)	43 (12.1)	1 (0.3)	7 (2.0)[b]	1 (0.3)
Median (interquartile range) time to onset, days		8.0 (2.0–22.0)	22.0 (10.0–57.0)	12.0 (10.0–15.0)	48.0 (22.0–108)	15.0 (1.0–51.0)	47.5 (28.0–120.0)
AE leading to dose change; n (%)	Reduction	28 (7.9)	0	16 (4.5)	0	2 (0.6)	0
	Interruption	35 (9.9)	3 (0.9)	42 (11.8)	0	9 (2.5)	3 (0.9)
	Discontinuation	7 (2.0)	0	16 (4.5)	0	1 (0.3)	1 (0.3)

[a]Group terms (preferred terms): diarrhea (diarrhea, frequent bowel movements, gastrointestinal hypermotility); rash (rash, rash macular, maculopapular rash, rash papular, rash pruritic) and hyperglycemia (blood glucose increased, hyperglycemia). [b]One additional pt (0.3%) had grade 4 hyperglycemia.

LBA1068 **Poster Session**

Palbociclib (P) plus tamoxifen (TAM) ± goserelin in women with hormone receptor-positive (HR+)/HER2-negative (HER2−) advanced breast cancer (ABC): Primary results of NCCH1607/PATHWAY, an Asian international double-blind randomized phase 3 trial.

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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, 2023, issue of the *Journal of Clinical Oncology*.

1069 **Poster Session**

Exploratory biomarker analysis of acelERA breast cancer (BC): Phase II study of giredestrant vs. physician's choice of endocrine therapy (PCET) for previously treated, estrogen receptor-positive, HER2-negative advanced BC (ER+, HER2– aBC).

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Background: ET is the mainstay treatment of ER+ aBC. Giredestrant is a highly potent, nonsteroidal, oral selective ER antagonist and degrader (PO SERD) that achieves robust ER occupancy. acelERA BC (NCT04576455) is a Phase II, randomized, open-label study that evaluated giredestrant vs. PCET in the second- or third-line ER+, HER2– aBC setting. The study did not reach statistical significance for the primary endpoint of investigator-assessed progression-free survival, although giredestrant demonstrated a more pronounced effect in patients (pts) with *ESR1*-mutated (*ESR1*m) tumors. We present an exploratory biomarker analysis. **Methods:** Pts (N = 303) were post- or pre-/perimenopausal women, and men, with ER+, HER2– aBC who had received 1–2 prior lines of systemic therapy for aBC. Randomization was 1:1 to giredestrant (30 mg PO daily) or PCET (fulvestrant/aromatase inhibitor). Baseline plasma circulating tumor (ct)DNA (n = 232) was evaluated with the FoundationOne Liquid CDx (n = 229) or PredicineCARE (n = 3) assays; *ESR1* and other gene mutations in ctDNA were defined as variants with known or likely impact on protein function. Gene expression and PAM50 molecular subtype were assessed by RNAseq from tumor tissue (n = 184) which, based on collection date relative to aBC, was defined as representing early BC (eBC, n = 67), first line (1L, n = 64), or post-1L (n = 46). ER pathway activity was quantified by expression of a predefined set of 38 ER-induced or -repressed genes. **Results:** The majority of tumors were of the Luminal A (51%) and Luminal B (43%) PAM50 subtypes. Post-1L *ESR1*m tumors (n = 17) were significantly enriched for Luminal B (64%) compared with eBC (39%), 1L (44%), and post-1L tumors with no *ESR1*m detected (*ESR1*nmd; n = 29; 45%) ($p < 0.001$). Post-1L *ESR1*nmd tumors, but not *ESR1*m tumors, had significantly lower ER pathway activity compared with eBC or 1L tumors (p = 0.0001, 0.001). Within the post-1L subgroup, those with *ESR1*m had a distinct ctDNA mutational profile with more *GATA3* (n = 29) and fewer *CHEK2* mutations (n = 0) than *ESR1*nmd (n = 3 and n = 11, respectively). Tumor ER pathway activity and *ESR1* expression in tumor tissue, as well as pre-treatment ctDNA composite tumor fraction and *ESR1* variant allele frequency, were significantly correlated with best overall response to single-agent ET (partial response vs. progressive disease; $p < 0.001$, p = 0.022, p = 0.001, and 0.045, respectively). **Conclusions:** These data show that tumor response to single-agent ET is correlated with baseline ctDNA features and with tumor ER pathway activity. Interestingly, ER pathway activity was significantly lower in late-line tumors, except in *ESR1*m tumors. Overall, these results support the continued investigation of improved and personalized treatment options for pts with ER+, HER2– aBC. Clinical trial information: NCT04576455. Research Sponsor: F. Hoffmann-La Roche Ltd.

1070 **Poster Session**

Oral elacestrant vs standard-of-care in estrogen receptor-positive, HER2-negative (ER+/HER2-) advanced or metastatic breast cancer (mBC) without detectable *ESR1* mutation (EMERALD): Subgroup analysis by prior duration of CDK4/6i plus endocrine therapy (ET).

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Background: The phase 3 EMERALD trial reported significantly prolonged progression-free survival (PFS) and a manageable safety profile with oral elacestrant (Ela) vs standard of care ET (SoC) in patients (pts) with ER+/HER2− mBC following progression on prior endocrine and CDK4/6i therapy. Duration of prior CDK4/6i was shown to be a potential predictor of efficacy in pts with *ESR1* mutations (*ESR1*m) receiving elacestrant. Median PFS (mPFS) for pts with *ESR1*m receiving <6 mos of prior CDK4/6i was 1.87 mos (Ela) vs 1.87 mos (SoC), compared with 4.14 mos (Ela) vs 1.87 mos (SoC) for pts receiving CDK4/6i ≥6 mos and 8.61 mos (Ela) vs 1.91 mos (SoC) for pts receiving ≥12 mos of prior CDK4/6i. Understanding the clinical activity of Elacestrant in *ESR1* non-detected (*ESR1*nd) ER+/HER2- mBC is still needed. Preclinical ER+ PDX models suggest that elacestrant is equally active in *ESR1* wild-type (*ESR1*wt) and *ESR1*m. In the PDX model ST3932 (*ESR1*wt), derived from a pt treated with palbociclib plus aromatase inhibitor (AI) that was resistant to palbociclib in vivo, elacestrant demonstrated statistically significant single-agent antitumor activity (Patel, 2019). **Methods:** Pts with ER+/HER2- advanced or mBC who previously had 1-2 lines of ET, mandatory CDK4/6i, and ≤1 chemotherapy were randomized, 1:1 to receive oral elacestrant or SoC (investigator's choice of AI or fulvestrant). An ad hoc subgroup analysis was performed on pts with *ESR1*nd by prior duration of CDK4/6i plus ET (<6 mos, ≥6 mos, ≥12 mos) in the advanced or metastatic setting. **Results:** Among the 478 pts enrolled, 250 (n=124, Ela; n=126, SoC) did not have a detectable *ESR1*m. Interestingly, in 41 pts with *ESR1*nd (n=20, Ela; n=21, SoC) that rapidly progressed on prior CDK4/6i plus ET (<6 mos), treatment with elacestrant was associated with prolonged mPFS vs SoC (5.32 mos vs 1.87 mos, respectively) (HR=0.518 [95% CI 0.216-1.165]), compared with a mPFS of 1.91 mos (Ela) vs 1.97 mos (SoC) for pts who were on CDK4/6i for ≥6 mos (HR=0.911 [95% CI 0.640-1.298]) and 2.33 mos (Ela) vs 2.04 mos (SoC) for pts who were on CDK4/6i for ≥12 mos (HR=0.886 [95% CI 0.586 - 1.337]). In these 41 pts, mean time to chemotherapy was 137.7 days for elacestrant vs 75.5 days for SoC. Safety results were consistent with previously reported data. Specific pt characteristic information will be provided in the presentation. **Conclusions:** In this post-hoc analysis, oral elacestrant delayed disease progression and time to subsequent chemotherapy in pts who did not have a detectable *ESR1*m and rapidly progressed within 6 months of CDK4/6i plus ET before study entry. Preclinical data support these findings. While caution needs to be exerted given small numbers, the results highlight the potential role of elacestrant in *ESR1*wt tumors, and more research is warranted. Clinical trial information: NCT03778931. Research Sponsor: Stemline Therapeutics, Inc.

Indirect treatment comparison of first-line CDK4/6-inhibitors in post-menopausal patients with HR+/HER2- metastatic breast cancer.

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Background: In phase III studies, the CDK4/6-inhibitors palbociclib, ribociclib, and abemaciclib all have demonstrated similar clinical efficacy in hormone receptor-positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer (MBC) with regards to the primary endpoint of progression-free survival (PFS). However, the lack of overall survival (OS) benefit in the PALOMA-2 study is inconsistent with the OS benefit seen with the other two CDK4/6-inhibitors. This study sought to elucidate indirect treatment survival outcomes between CDK4/6-inhibitors in this setting. **Methods:** Phase III randomized controlled trials comparing first-line aromatase inhibitor with or without a CDK4/6-inhibitor in post-menopausal patients with HR+/HER2- MBC. A graphical reconstructive algorithm was utilized to retrieve patient level time-to-event data from reported Kaplan-Meier OS and PFS curves. Survival analyses were conducted with Cox proportional hazards model with a shared-frailty term incorporated to account for inter-study differences. Two-stage indirect treatment comparison model was conducted as a sensitivity analysis. **Results:** Three randomized phase III trials – PALOMA-2, MONALEESA-2 and MONARCH-3 – comprising 1,827 patients were included. Indirect pairwise comparison of all CDK4/6-inhibitor showed no significant PFS differences across one-stage and two-stage models (all $p>0.05$). Likewise, indirect treatment comparison between ribociclib vs palbociclib (one-stage: HR=0.903, 95%-CI: 0.746-1.094, p=0.297), abemaciclib vs palbociclib (one-stage: HR=0.843, 95%-CI: 0.690-1.030, p=0.094) and abemaciclib vs ribociclib (one-stage: HR=0.933, 95%-CI: 0.753-1.157, p=0.528) failed to demonstrate a significant OS difference. **Conclusions:** Findings from this indirect treatment comparison suggest no significant PFS or OS differences between CDK4/6-inhibitor agents when combined with an aromatase inhibitor in post-menopausal patients with HR+/HER- MBC. Research Sponsor: None.

Indirect treatment comparison outcomes.

		One-Stage Model		Two-Stage Model	
	Comparison	**HR (95%-CI)**	**p-value**	**HR (95%-CI)**	**p-value**
Progression-free survival	abemaciclib vs ribociclib	0.722 (0.520 – 1.002)	0.051	0.921 (0.597 – 1.420)	0.710
	abemaciclib vs palbociclib	0.790 (0.583 – 1.071)	0.129	0.790 (0.514 – 1.216)	0.285
	ribociclib vs palbociclib	1.094 (0.825 – 1.451)	0.531	0.858 (0.594 – 1.239)	0.415
Overall Survival	abemaciclib vs ribociclib	0.933 (0.753 – 1.157)	0.528	0.993 (0.719 – 1.372)	0.966
	abemaciclib vs palbociclib	0.843 (0.690 – 1.030)	0.094	0.815 (0.585 – 1.135)	0.227
	ribociclib vs palbociclib	0.903 (0.746 – 1.094)	0.297	0.821 (0.614 – 1.098)	0.183

HR, hazard ratio; CI, confidence interval.

1072 **Poster Session**

A multicenter, single-arm, open-label trial of birociclib, a CDK4/6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer.

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Background: Birociclib is a new molecular entity and selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6. This phase II study (NCT04539496) was to evaluate the single-agent efficacy and safety of Birociclib in patients with refractory HR+/HER2- metastatic breast cancer (MBC). **Methods:** This phase II study is a multicenter, single-arm, open-label trial in patients with $HR^+/HER2^-$ MBC who had progressed after prior endocrine therapy and 1-2 prior chemotherapy regimens in the metastatic setting. Birociclib 480 mg was administered orally on a continuous schedule twice daily until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). The secondary endpoints included disease control rate (DCR), clinical benefit rate (CBR), duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety. **Results:** 131 patients were enrolled from 29 hospitals in China between 10/2020 and 8/2021, with a median duration of follow-up of 17.74 months. Among them, 84.7% patients had visceral disease, and 61.1% patients had ≥3 metastatic sites. In the metastatic setting, patients had received a median of 3 (range, 1-6) prior systemic therapies including a median of 1 (1-2) chemotherapy regimen and 2 (1-5) endocrine therapy regimens. The investigator-assessed confirmed ORR was 22.9% (95% CI: 16.0-31.1); DCR was 66.4% (95% CI: 57.6-74.4); CBR was 39.7% (95% CI: 31.3-48.6), among which 1 (0.8%) patient was with confirmed complete response (CR) and 29 (22.1%) patients were with confirmed partial response (PR). Median DoR was 13.1 months (95% CI: 9.4- 16.6). Median PFS was 7.4 months (95% CI: 5.5- 9.2). The OS rates at 12 months and 21 months were 81.8% and 64.6%, respectively. Birociclib demonstrated similar activity in subgroups with visceral disease and liver disease, ORR were 20.7% (95% CI: 13.6-29.5) and 18.5% (95% CI: 9.9-30.0), DCR were 64.9% (95% CI: 55.2-73.7) and 66.6% (95% CI: 51.7-76.9), CBR were 39.6% (95% CI: 30.5-49.4) and 35.4% (95% CI: 23.9-48.2), DoR were 14.8 months (95% CI: 7.6-NA) and 11.2 months (95% CI: 5.5-NA), PFS were 8.2 months (95% CI: 5.5-9.3) and 7.3 months (95% CI: 5.388-9.101), respectively. The most common treatment-emergent adverse events (TEAE) were diarrhea [93.1% (all grades); 18.3% (≥grade 3)], neutropenia [87.0% (all grades); 43.5% (≥grade 3)], and leukocytopenia [86.3% (all grades); 32.8% (≥grade 3)]. Most of AEs were grade 1 or grade 2 and could be alleviated or cured by symptomatic treatment. **Conclusions:** In patients who have limited treatment options with refractory HR+/HER2- metastatic breast cancer, continuous dosing of single-agent Birociclib exhibited promising and sustaining clinical activity with acceptable safety profile, thus it provided an alternative orally administered therapy option. Clinical trial information: NCT04539496. Research Sponsor: Xuanzhu Biopharmaceutical Co., Ltd.,Beijing, China.

1073 **Poster Session**

Clinical outcomes and correlation with longitudinal circulating tumor (ct)DNA dynamics of a phase I/II study of GSK525762 combined with fulvestrant in patients with hormone receptor-positive/HER2-negative (HR+/HER2−) advanced or metastatic breast cancer.

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Background: Endocrine therapy is the main treatment option for hormone receptor-positive and human epidermal growth factor receptor 2-negative (HR+/HER2−) metastatic breast cancer (mBC). However, many patients experience disease progression due to resistance to endocrine therapy. Molibresib (GSK525762) is a small-molecule inhibitor of bromodomain and extra-terminal (BET) family proteins (BRD2, BRD3, BRD4, and BRDT). Pre-clinical data suggested that the combination of molibresib with endocrine therapy might overcome endocrine resistance. This study aimed to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy (objective response rate [ORR]) of molibresib combined with fulvestrant in women with HR+/HER2− mBC. The association between early ctDNA dynamics and clinical outcomes was also assessed. **Methods:** In this phase I/II dose-escalation and expansion study, patients received oral molibresib 60 mg or 80 mg once daily in combination with intramuscular fulvestrant. Patients enrolled had relapsed/refractory, advanced/metastatic HR+/HER2− BC with disease progression on prior treatment with an aromatase inhibitor, with or without a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. Baseline and week 4 plasma samples were collected and tested using a 74-gene ctDNA panel. Molecular response (MR) was defined as at least 50% reduction of baseline ctDNA level calculated as the average allele frequency of detected single nucleotide variants or indels. **Results:** The study included 123 patients. The 3 most common molibresib-related adverse events (AEs) were nausea (52%), dysgeusia (49%), and fatigue (44%). At molibresib 60 mg, >90% patients experienced treatment-related AEs, with varying incidence of Grade ≥3 AEs (17%–71%) amongst subgroups. The ORR was 13% (95% confidence interval [CI], 8–20), not meeting the 25% threshold for proceeding to phase II. Among 82 patients with detected baseline circulating tumor DNA, a strong association was observed between baseline copy number amplification (CNA) presence and poor progression-free survival (PFS) with hazard ratio (HR) of 2.89 (95% CI, 1.73–4.83; $P < 0.0001$). MR was significantly correlated with better PFS (HR=0.38; 95% CI, 0.19–0.75; $P = 0.0037$), which was further improved when MR was refined as no baseline CNA (HR=0.22; 95% CI, 0.09–0.54; $P = 0.0003$). **Conclusions:** Molibresib in combination with fulvestrant did not demonstrate clinically meaningful activity in this study. Copy number adjusted ctDNA MR is a promising early marker for clinical benefit. Clinical trial information: NCT02964507. Research Sponsor: GlaxoSmithKline.

1074 **Poster Session**

ESR1 mutational landscape and impact of co-existing resistance variants on clinical outcomes in patients with metastatic breast cancer.

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Background: Mutations in estrogen receptor 1 (*ESR1*) confer resistance to aromatase inhibitors but may retain sensitivity to selective estrogen receptor degraders (SERD). Recently, elacestrant, an oral SERD, was approved for patients with HR+/HER2- $ESR1^{mut}$ metastatic breast cancer (MBC). In this study, we evaluated the genomic landscape of *ESR1* alterations from a genomic database and also evaluated the impact of resistance-associated alterations on clinical outcomes. **Methods:** A large de-identified database of mutations detected in plasma cell-free DNA (cfDNA) from patients with HR+/HER2- MBC was assessed for *ESR1* mutations and resistance-associated co-alterations. We used the Guardant 360 assay, a 70- to 74-gene targeted next generation sequencing panel and applied a breast cancer subtype classifier based on detected mutations (Bardia A, SABCS 2020). In addition, clinical outcomes were evaluated from a clinically annotated institutional dataset, linking genomic alterations with progression-free survival (PFS) and overall survival (OS) to single-agent SERD therapy for patients with MBC. **Results:** Among 11,456 patients with MBC and detectable cfDNA, 4,694 were classified as likely HR+/HER2-, of which 2,708 (58%) had *ESR1* missense mutations, the majority of which occurred in the ligand binding domain (n = 2,690, 99%). Among the latter, alterations included 204 unique mutations, of which 55 were variants of uncertain significance (VUS). Multiple *ESR1* mutations were detected in 979 (36%) patients. Among 567 patients classified as HR+/HER2- that underwent serial sampling, 136 (24%) had detectable *ESR1* missense mutations that were previously undetectable. Within the $ESR1^{mut}$ population, 1,990 (74%) had co-existing non-synonymous, non-VUS alterations at genes associated with SERD resistance: *PIK3CA* (n = 1,330; 49%), *ARID1A* (n = 314; 12%), *PTEN* (n = 201; 7%), *ERBB2* (n = 180; 7%), *AKT1* (n = 139; 5%), and *NF1* (n = 103; 4%); top amplifications were *FGFR1* (n = 522; 19%), *EGFR* (n = 277; 10%), and *MYC* (n = 177; 7%). Among a clinically annotated HR+/HER2- subgroup (n = 350), 51 patients received SERD monotherapy, either fulvestrant (n = 9) or oral SERD on clinical trial (n = 42); among 28 patients with cfDNA variants associated with SERD resistance, median PFS and OS were lower compared to the 23 patients without resistance mutations (PFS: 2.4 vs 11.3 mo; HR = 0.44; 95% CI, 0.23-0.81; p = 0.008; and OS: 21.1 vs 31.4 mo; HR 0.47; 95% CI, 0.22-0.98; p = 0.045). **Conclusions:** *ESR1* mutations that qualify patients to receive approved SERD therapy are detectable by plasma-based genotyping and can associate with various genomic co-alterations, including variants that may impact clinical outcomes. Further research is needed to confirm the impact of co-alterations in additional datasets and evaluate the role of SERD-based combination therapy to further improve clinical outcomes of patients with MBC.
Research Sponsor: None.

1075 **Poster Session**

Impact of pathogenic germline *BRCA1/2* and *PALB2* mutations and tumor aneuploidy in patients with HR+/HER2- metastatic breast cancer treated with CDK4/6 inhibitors.

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Background: CDK4/6 inhibitors lack established predictors of efficacy in $HR^+/HER2^-$ mBC. Pathogenic germline *BRCA2* variants, somatic homologous recombination deficiency (HRD) and APOBEC signatures conferred worse survival in small series. Broader tumor DNA panels enable the detection of these and other parameters such as aneuploidy and tumor mutational burden. **Methods:** Clinical and molecular data from a single institution cohort of CDK4/6i-treated $HR^+/HER2^-$ mBC pts were analyzed. ECOG PS was 0-1. Clinical variables were collected retrospectively. Primary endpoints were progression-free survival (PFS) and overall survival (OS). Tumor-only sequencing was performed on clinical samples with 161-gene OCAv3, 523-gene TSO500 or 555-gene lab-developed NGS panels. HRD was assessed with the Signature Multivariate Analysis (SigMA) tool using a likelihood-based measure to estimate single base substitution signature 3. Aneuploidy scores were defined as the fraction of covered arms harboring arm-level somatic copy number alterations as determined by ASCETS v.1.1. **Results:** 153 pts were available for analysis. Median age was 54 y (29–88). 74% were postmenopausal, 28% *de novo* metastatic and 67% had visceral disease. Palbociclib was used in 80%, ribociclib in 17% and abemaciclib in 3%, mostly as early lines (1L 65%, 2L 22%). Median follow up was 46 mo (7–84) and median time from sample collection to CDK4/6i was 0.6 y (-18.5–+2.6). 76% of samples have been sequenced. The median number of mutations (muts) was 3 (1–32), most commonly in *PIK3CA* (37%), *GATA3* (26%) and *TP53* (20%). *ESR1*, *KRAS* and *ARID1A,* but not *RB1* muts were numerically enriched in post–CDK4/6i mets (n=8). *TP53* (HR 1.85 CI 1.02–3.33) and *GATA3* (HR 0.48, CI 0.28–0.83) muts were associated with PFS. Germline (*g*) testing was available in 68 (44%) pts, with 21 pts carrying pathogenic variants including 11 *BRCA2*, 2 *BRCA1 and* 2 *PALB2*. Cox regression showed a strong negative impact of *gBRCA1/2-PALB2* on PFS (HR 4.0 CI 2.0–7.9) and OS (HR 3.5 CI 1.6–7.7) adjusted for age, visceral disease and prior chemo. In 1L, mPFS/OS was 9.9/28.1 mo for *gBRCA1/2-PALB2* carriers, 26.8/NR mo for non-carriers and 23.7/49.2 mo for untested (Cox HR PFS 5.1 CI 2.1-14.0; HR OS 4.0 CI 1.4-11.2). Pts with *gATM*/*CHEK2*/*BRIP1* had a 1L PFS/OS>15/45 mo. Among 36 pts assessed for HRD, 22 were HRDlow and 14 HRDhigh with no significant survival association. 3/4 known *gBRCA1/2* carriers were HRDhigh and 7/8 gWT HRDlow. In these pts, higher aneuploidy was associated with shorter PFS and OS (Cox HR PFS 2.0 CI 0.9-4.3, p=0.07; HR OS 2.6 CI 1.0-7.1; p=0.05). **Conclusions:** Pathogenic *gBRCA1/2-PALB2* and higher aneuploidy were associated with shorter survival. Profiling of aneuploidy, HRD, TMB and APOBEC in all pts is ongoing including 55 baseline ctDNA samples and 361 samples from the GENIE BPC cohort. Results will account for FDR, left truncation and optimal cutoffs. Research Sponsor: Government of Ontario through the OICR Adaptive Oncology (AO); Princess Margaret Cancer Foundation (PMCF) through the Cancer Genomics Program (CGP) at University Health Network (UHN).

1076 **Poster Session**

Comparing the prognostic and predictive utility of serum thymidine kinase 1 and CA 15-3 in patients with hormone receptor positive metastatic breast cancer starting first-line endocrine therapy in SWOG S0226.

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Background: Serum levels of thymidine kinase 1 activity (TKa), a fundamental enzyme in DNA synthesis and cellular proliferation, are prognostic of benefit from endocrine therapy (ET) in patients (pts) with hormone receptor positive (HR+) metastatic breast cancer (MBC) who participated in SWOG S0226, a prospective randomized trial comparing anastrozole vs. anastrozole and fulvestrant given in 4 week cycles. The assay for TKa (DiviTum TKa) was FDA approved in July 2022 for monitoring of post-menopausal HR+ MBC pts. The assay for circulating MUC1, CA 15-3, is routinely utilized in monitoring of pts with MBC. We compared the prognostic and predictive utilities of CA 15-3 and TKa in pts from S0226. **Methods:** TKa was measured in 1725 sera from 432 pts while CA 15-3 was measured in 1298 sera from 326 pts at baseline (BL), cycles 2, 3, 4 and 7. Prespecified cutoff levels of $\geq$ 250 DuA and $\geq$ 30 U/mL were considered high for TKa and CA 15-3 respectively. Progression-free survival (PFS) and overall survival (OS) were analyzed by Kaplan-Meier and Cox regression stratified by prior adjuvant tamoxifen use. To examine markers over time, a landmarked Cox regression analysis was done starting at initiation of Cycle 4. BL and recent (Cycle 3 if available, otherwise Cycle 2) markers were assessed for simultaneous prediction of subsequent PFS and OS. **Results:** BL TKa was elevated in 190/432 (44%) and CA 15-3 was elevated in 254/326 (78%). Agreement between assays was 53%. Pts with high versus low BL TKa had significantly worse PFS (median 11.6 vs. 17.2 months, HR = 1.68, 95% confidence interval (CI) 1.37-2.06) and OS (median 34 vs. 58 months, HR = 2.16, 95% CI 1.73-2.70) whereas pts with high versus normal BL CA 15-3 had no significant difference in PFS (median 13.6 vs. 16.1 months, HR = 1.23, 95% CI 0.93-1.62) but worse OS (median 45 vs. 66 months, HR = 1.82, 95% CI 1.30-2.53). A multivariable Cox model with both markers shows only TKa as being prognostic for PFS (TKa HR = 1.61, 95% CI 1.28-2.03; CA 15-3 HR = 1.21, 95% CI 0.91-1.59), but both prognostic for OS (TKa HR = 2.09, 95% CI 1.61-2.71; CA 15-3 HR = 1.70, 95% CI 1.22-2.38). In the landmarked multivariable analysis, positive TKa at BL was a strong predictor of PFS (HR = 1.65, 95% CI 1.28-2.14), but recent TKa was not (HR = 1.25, 95% CI 0.93-1.68). In contrast, positive CA15-3 at BL was not a predictor of PFS (HR = 0.73, 95% CI 0.46-1.17), but recent CA15-3 was (HR = 1.97, 95% CI 1.26-3.06). **Conclusions:** BL TKa is highly prognostic in pts with HR+ MBC initiating first-line systemic ET, with low BL TKa conferring superior prognosis. In contrast, CA 15-3 is only modestly prognostic at BL, but is prognostic after 3 cycles of treatment. These hypothesis-generating data suggest further study is needed to determine how these biomarkers should be employed in a complementary manner to monitor response to systemic therapy in HR+ MBC. Clinical trial information: NCT00075764. Research Sponsor: U.S. National Institutes of Health; AstraZeneca, Biovica.

1077 **Poster Session**

Relation between circulating biomarkers at diagnosis of early luminal-like breast cancer and subsequent risk of distant metastases.

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Background: Predicting development of distant metastases after treatment of early luminal breast cancer (BC) remains a major challenge. Besides clinical-pathological features of the primary tumor, baseline circulating factors could also play a role as prognostic biomarkers. **Methods:** Patients with newly diagnosed early BC (grade 2/3, ER+, HER2-non- amplified) were selected from our institutional BC registry, with associated blood biobank collecting baseline plasma/serum samples at diagnosis. Circulating biomarkers potentially modulating the metastatic process (chemokines, micro-RNAs (miRNAs), Leukemia Inhibitory Factor (LIF), and osteopontin), and serum-induced functional myeloid interferon (IFN)) and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) signaling-responses, were measured at early BC diagnosis (before any treatment) in patients who subsequently developed distant metastasis within five years after diagnosis and therapy (META group) and in a 1:1 control group of patients, pairwise matched for age, tumor grade, stage, and histological subtype, who remained disease-free for at least seven years (NON-META group). All blood biomarkers were analyzed pair-wisely using the univariable Wilcoxon signed rank test (two-tailed). Multiple testing correction was done by applying a false discovery rate (FDR) of 0.05. In addition, a multivariable logistic regression analysis (MVA) was performed to find blood biomarkers signatures that can predict the development of metastases at first diagnosis of early BC. **Results:** 102 matched patient pairs were included. Univariable paired analysis showed significantly increased baseline expression of LIF (p=0.012) and six miRNAs (miR-143-3p: p=0.015; miR-197-3: p:<0.001; miR-223-3p: p=0.006; miR-223-5p: p=0.045; miR-338-3p: p=0.045; miR-365a-3p: p=0.025), and decreased serum-induced myeloid -IFN-responses (p=0.023) and ten miRNAs (let-7b-5p: p=0.006; miR-106a-5p: p=0.045; miR-106b-5p: p=0.015; miR-107: p=0.014; miR-144-3p: p=0.015; miR-15a-5p: p=0.045; miR-15b-3p: p=0.032; miR-185-5p: p=0.045; miR-18a-5p: p=0.015; miR-30b-5p: p=0.045) in the META group compared to the NON-META group. MVA yielded a seven-biomarker signature, which includes miR-197-3p (p=0.008), miR-139-5p (p<0.001), LIF (p=0.007), miR-106b-5p (p=0.003), serum-induced IFN/ISG response (p=0.006), miR-652-3p (p=0.015), and miR-133b (p=0.025) with a C-index of 0.79 (0.70-0.88) to predict distant metastases. After 5-fold internal cross-validation, C-index was 0.63 (0.52-0.74). **Conclusions:** Baseline circulating miRNAs, LIF, and serum-induced IFN-response levels at early luminal BC diagnosis are associated with subsequent distant metastases. Further external validation is required to confirm the prognostic value of these biomarkers. Research Sponsor: Kom op Tegen Kanker.

Alpelisib + endocrine therapy in patients with *PIK3CA*-mutated, hormone receptor–positive, human epidermal growth factor receptor 2–negative, advanced breast cancer: Analysis of all 3 cohorts of the BYLieve study.

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Background: The phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) gene is mutated in ~40% of patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC). Alpelisib (ALP), an α-selective PI3K inhibitor and degrader, is indicated in combination with fulvestrant (FUL) for pts with HR+, HER2− ABC following progression on/after endocrine therapy (ET)-based treatments (tx). Primary analyses from the 3 cohorts of the Phase 2, open-label, noncomparative BYLieve study demonstrated the efficacy of ALP + ET in pts with HR+, HER2–, *PIK3CA*-mutated ABC who progressed on/after other tx, including immediately after a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). Presented here are efficacy and safety data from the full 3 cohorts of the BYLieve study. **Methods:** Pts in all 3 cohorts completed ≥18 mo follow-up plus 1 mo safety follow-up. Efficacy assessments included DoR, BOR, PFS, PFS2, and OS. Safety/tolerability of ALP were also assessed. Median (m) PFS, PFS2, and OS were assessed by Kaplan-Meier methodology per local investigator assessment. **Results:** Cohort A (ALP + FUL) comprised 127 pts whose immediate prior tx was CDK4/6i + aromatase inhibitor (AI); Cohort B (ALP + letrozole) enrolled 126 pts whose immediate prior tx was CDK4/6i + FUL. In Cohort C (ALP + FUL), 126 pts had disease progression on/after AI and received CT or ET as immediate prior tx. Median follow-up for the 3 cohorts was 21.8, 25.3, and 18.5 mo, respectively. mPFS in Cohorts A, B, and C was 8.0 mo (95% CI, 5.6-8.6), 5.6 mo (3.7-7.1), and 5.6 mo (5.4-8.1), respectively; mPFS2 was 15.2 mo (95% CI, 11.4-21.7), 13.0 mo (10.2-13.9), and 13.5 mo (11.5-17.3), respectively. mOS in Cohorts A, B, and C was 27.3 mo (95% CI, 21.3-32.7), 29.0 mo (24.5-34.8), and 20.7 mo (16.9-28.1), respectively. Efficacy of ALP + ET in 2nd and 3rd lines will be presented. In Cohorts A, B, and C, respectively, 29 (22.8%), 19 (15.1%), and 23 (18.3%) pts discontinued tx due to adverse events (AEs). The most common any grade AEs in all 3 cohorts (A; B; C) were diarrhea (n = 82, 64.6%; n = 86, 68.3%; n = 68, 54.0%), hyperglycemia (n = 76, 59.8%; n = 82, 65.1%; n = 85, 67.5%), nausea (n = 59, 46.5%; n = 69, 54.8%; n = 51, 40.5%), rash (n = 40, 31.5%; n = 39, 31.0%; n = 51, 40.5%), and fatigue (n = 39, 30.7%; n = 39, 31.0%; n = 44, 34.9%). Hyperglycemia was the most common grade ≥3 AE, observed in 37 (29.1%), 32 (25.4%), and 30 (23.6%) pts in Cohorts A, B, and C, respectively. **Conclusions:** After ≥18 mo follow-up, with mature data, ALP + ET demonstrated clinical activity in BYLieve Cohorts A, B, and C. Within the trial, ALP + ET showed median OS between 20.7 mo and 29.0 mo following prior CDK4/6i, chemotherapy, or ET. AEs associated with ALP were well defined and manageable, with no new safety signals observed in any cohort. Clinical trial information: NCT03056755. Research Sponsor: Novartis Pharmaceuticals Corporation.

1079 **Poster Session**

A phase I trial of palbociclib (palbo) and bosutinib (bos) with fulvestrant (fulv) in patients (pts) with hormone receptor–positive, HER2-negative (HR+/HER2-) metastatic breast cancer (MBC) refractory to an aromatase inhibitor (AI) and a CDK4/6 inhibitor (CDK4/6i).

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Background: Standard therapy for HR+/HER2- MBC includes a CDK 4/6i with endocrine therapy (ET). Eventual resistance results in progression of disease (PD). A potential mechanism of CDK4/6 resistance is through Src activation. Targeting Src and ET suppresses proliferation of ER+ hormone independent breast cancer cells. Therefore, adding bos, a Src inhibitor, to palbo + fulv may overcome this resistance and restore sensitivity to CDK4/6i. **Methods:** This is a single arm, 3+3 dose escalation phase I trial (NCT 03854903) of bos + palbo + fulv for pts with HR+/HER2- MBC who have PD after $\geq$ 1 AI, $\geq$ 1 CDK4/6i, and $<$ 3 lines of chemo for MBC. Pts were enrolled in two cohorts, A and B, with two dose levels in cohort B. Fulv was given at standard dose. Cohort A: bos 300mg (D1-5/wk), palbo 75mg D1-21 q28 days, fulv; cohort B1: bos 300mg (D1-5/wk), palbo 100 mg D1-21 q28 days, fulv; cohort B2: bos 500mg (D1-5/wk), palbo 100 mg D1-21 q28 days, fulv. Primary objective was safety and tolerability, including MTD and recommended phase 2 dose (RP2D). Secondary objectives included ORR, and CBR 24 wks. Serum, plasma, and peripheral blood mononuclear cells were collected for Src activation, cell cycle profile arrays, and cytokine array screens. **Results:** 18 evaluable pts were enrolled between 4/2019 – 11/2022. To date, 16pts have completed and 2 pts remain on treatment. All pts had received prior palbo and 15/18 (83%) had received prior fulv. Median number of prior therapies in the metastatic setting was 3.2. The combination in cohort A and B1 was well tolerated. The combination in cohort B2 (bos 500mg D1-D5/wk) was toxic which resulted in bos dose reduction in all pts in the B2 cohort. There were no DLTs. The RP2D was bos 300 mg D1–5/wk, palbo 100 mg D1-21 q28 days, and standard dose fulv. No pts came off treatment due to adverse events (AEs). Most common AEs were G1/2 (9 pts) and G3/4 (7 pts) neutropenia (no neutropenic fever); G1 nausea (8 pts); G1/2 (12pts) and G3 (1pt) diarrhea; G1/2 rash (4 pts), and no G5 events. Median PFS was 5.9 months with 95% CI (3, 10.1). CBR at 6 months was 50% (9/18) (95% CI (0.26, 0.74)). The ORR was 6% (0 CR, 1 PR cohort B2), but best response was SD in 11 pts. Correlative studies underway include assessment pre and post treatment of 1) Src levels and activity to confirm that bos is acting on target and 2) RNA sequencing of Src activation and cell cycle profiles and 3) cytokine array screens to test if Bos affects inflammatory markers. **Conclusions:** Bos + palbo + fulv was well tolerated at the RP2D. A robust CBR of 50% was seen despite all patients having prior PD on palbo and 83% on fulv. This is an effective combination for HR+/HER2- MBC which warrants further investigation and may represent a mechanism to overcome resistance to CDK4/6i and provide another oral treatment option. Clinical trial information: NCT03854903. Research Sponsor: Pfizer-Aspire award.

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Phase 1/2 dose expansion study evaluating first-in-class eIF4A inhibitor zotatifin in patients with ER+ metastatic breast cancer.

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Background: Zotatifin (eFT226) is a first-in-class, potent and sequence selective inhibitor of RNA helicase eIF4A that promotes a stable mRNA:eIF4A:drug ternary complex at specific polypurine motifs within the 5'-UTR, preventing translation of select transcripts. In preclinical models zotatifin treatment simultaneously down-regulated translation of numerous oncogenes including CDK4, ERα, ERBB2, KRAS, and CCND1. **Methods:** Following a 3+3 dose escalation portion of the protocol (Part 1), Part 2 is a Simon's two-stage design of cohorts of up to 18 patients (pts) with ER+ metastatic breast cancer enrolled at the recommended phase 2 dose of zotatifin (0.07 mg/kg IV two weeks on/one week off) in combination with fulvestrant (ful) (ECBF: Expansion, Combination, Breast, Ful) or in combination with ful and abemaciclib (abema) (ECBF+A: Expansion, Combination, Breast, Ful + Abema). Key eligibility criteria included at least one line of therapy for advanced/metastatic disease, progression on hormone therapy, and in addition, the ECBF cohort required prior CDK 4/6 inhibitor (CDKI). Primary endpoint was objective response rate (ORR) per RECIST v1.1. Additional endpoints included safety, other efficacy analyses, and for Parts 1 and 2, characterization of pharmacodynamic (PD) markers and pharmacokinetics. **Results:** As of a data cut-off of Jan 31, 2023, 18 pts were enrolled in each cohort. Median prior metastatic lines of therapy were 3 and 7 in ECBF+A and ECBF, respectively. In 16 evaluable pts in ECBF+A cohort, there were two confirmed partial responses (PR), two additional PRs awaiting confirmatory scans, and 8 pts with best overall response (OR) of stable disease (SD). All pts with PR/unconfirmed PR received prior CDKI and ful, including one pt with disease progression on combination abema and ful as the last therapy prior to enrollment. In 18 evaluable pts in ECBF, there was one confirmed PR and six SD as best OR. There were no dose-limiting toxicities or grade (Gr) 5 adverse events (AEs) in either cohort. In ECBF+A the most common AEs (all Gr 1/2) were diarrhea (44%) and nausea (31%) and 21% of pts had Gr 3/4 AEs. The most common AEs in ECBF (all Gr 1/2) were nausea (39%) and constipation (27%), and 28% of pts had Gr 3/4 AEs. Blood-based PD markers and ctDNA in Part 1 showed dose-dependent evidence of target engagement and anti-tumor activity. **Conclusions:** In dose expansion cohorts of heavily pre-treated metastatic breast cancer pts, eIF4A inhibitor zotatifin showed evidence of anti-tumor activity in combination with fulvestrant and abemaciclib and had a favorable safety profile consisting of primarily grade 1/2 adverse events. Clinical trial information: NCT04092673. Research Sponsor: eFFECTOR Therapeutics, Inc.

Real-world (RW) outcomes of patients (pts) with advanced breast cancer (aBC) with and without resistance alterations (alts) detected in cell-free circulating tumor DNA (ctDNA) prior to CDK4/6 inhibitor (CDK4/6i) plus endocrine therapy (ET) treatment.

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Background: CDK4/6i plus ET is standard of care first-line (1L) therapy for hormone receptor positive (HR+), HER2- aBC. While molecular analyses from trials and pts have identified several mechanisms of resistance to CDK4/6i plus ET, currently, no biomarkers (outside of hormone status) are used for therapy selection. We utilized RW data to assess impact of putative baseline CDK4/6i+ET resistance alts (CDK4/6i+ET-R) on clinical outcomes among pts with aBC treated with CDK4/6i. **Methods:** Pts with aBC were identified via the Guardant INFORM database; those with a ctDNA test within 90 days prior to CDK4/6i start were included in this analysis. Based on previous studies, oncogenic or likely oncogenic alterations (as characterized by OncoKB) in the following genes were considered CDK4/6i+ET-R alts: RB1, PTEN, AKT1, CCNE1, ERBB2, FGFR1, FGFR2, and KRAS. Pts with >1 CDK4/6i+ET-R alt were compared to pts without any CDK4/6i-R alts. Kaplan-Meier plots, log-rank tests (LR) and multivariate Cox proportional hazards models (HR) adjusted (adj) for age, sex, year of ctDNA test and line of therapy were used to assess differences in time to next treatment (TTNT) and overall survival (OS). **Results:** 1075 pts with aBC treated with CDK4/6i (27% receiving 1L treatment) met inclusion criteria, 293 of whom (27%) had >1 alt in a CDK4/6i+ET-R gene. Pts with CDK4/6+ETi-R alts had significantly shorter TTNT (8.7 mos vs 14.2 mos, LR p=0.001; adj HR 1.36, 95%CI 1.11-1.66, adj p=0.003) and OS (28.3 mos vs 60.9 mos, LR p=<0.0001; adj HR 2.19, 95%CI 1.69-2.82, adj p=<0.0001) compared to those without. This divergence was more pronounced for patients receiving 1L CDK4/6i (TTNT: 10.7 mos vs 24.6 mos, LR p=0.006, adj HR 1.84, 95%CI 1.18-2.87, adj p=0.007; OS: 23.8 mos vs 67.3 mos, LR p<0.0001, adj HR 3.27, 95%CI 1.89-5.62, adj p<0.0001). Individual gene contributions towards less favorable TTNT are shown. **Conclusions:** We demonstrate via RW data that patients with >1 pre-treatment ctDNA alt in a curated list of CDK4/6i+ET-R genes have significantly worse outcomes on CDK4/6i plus ET treatment, a difference more pronounced among patients receiving 1L therapy. This data is among the first successful efforts to validate a clinically useful multi-gene clinical biomarker that has the potential to predict CDK4/6i plus ET resistance. Further exploration of this signature's prognostic and predictive utility for CDK4/6i plus ET use is ongoing to better refine personalized treatment selection in HR+/HER2- aBC. Research Sponsor: None.

Gene	Total N	TTNT multivariate model adj HR (95%CI)	p-value
CCNE1	18	1.82 (0.98-3.38)	0.06
ERBB2	36	1.74 (1.09-2.76)	0.02
RB1	11	1.64 (0.72-3.73)	0.24
KRAS	59	1.63 (1.15-2.29)	0.006
AKT1	39	1.61 (1.01-2.56)	0.05
FGFR1	121	1.10 (0.83-1.47)	0.51
PTEN	52	0.98 (0.61-1.57)	0.92
FGFR2	10	0.76 (0.28-2.11)	0.60

1082 **Poster Session**

Trop-2 mRNA expression and association with clinical outcomes with sacituzumab govitecan (SG) in patients with HR+/HER2– metastatic breast cancer (mBC): Biomarker results from the phase 3 TROPiCS-02 study.

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Background: SG is a Trop-2–directed antibody-drug conjugate approved in multiple countries for patients with metastatic triple-negative breast cancer who received at least 1 prior systemic therapy and in the US for patients with pretreated HR+/HER2– mBC. In the TROPiCS-02 study, SG significantly improved progression-free survival (PFS; median, 5.5 vs 4.0 mo; HR, 0.66 [95% CI, 0.53-0.83]; *P*=0.0003) and overall survival (OS; median, 14.4 vs 11.2 mo; HR, 0.79 [95% CI, 0.53-0.83]; *P*=0.020) over treatment of physician's choice (TPC) in patients with pretreated, endocrine-resistant HR+/HER2– mBC. In TROPiCS-02 post hoc analyses, SG improved OS regardless of Trop-2 expression by immunohistochemistry (IHC; Rugo HS, et al. SABCS 2022), but association using more sensitive assays are lacking. Here, we examine efficacy outcomes for SG versus TPC by Trop-2 gene (*TACSTD2*) mRNA expression and the correlation of *TACSTD2* expression with other genes. **Methods:** Patients with HR+/HER2– mBC who received ≥1 prior taxane, endocrine therapy and a CDK4/6 inhibitor, and 2-4 prior chemotherapy regimens for mBC were randomized 1:1 to SG or TPC. The primary endpoint was PFS by central review per RECIST v1.1. RNA was isolated from archival tumor tissue samples using AllPrep DNA/RNA kits and libraries prepared with TruSeq RNA Exome Prep Kit. Sequencing was via NovaSeq (2x150bp). Gene expression quantitation was performed using Salmon. *TACSTD2* expression was defined as high or low via median cut. **Results:** In the mRNA analytical cohort (N=197), 49% had *TACSTD2* high expression (SG, n=51; TPC, n=46), and 51% had *TACSTD2* low expression (SG, n=47; TPC, n=53). Baseline characteristics were generally consistent between *TACSTD2* expression subsets and the intention-to-treat population. A positive concordance between *TACSTD2*expression and Trop-2 IHC (H-score) was observed (categorical concordance 71%; Cohen's kappa = 0.41). *TACSTD2* expression was similar across HER2 IHC0 and HER2-Low subgroups (log2 transcripts per million [TPM] of 3.36 [IQR, 2.76-4.22] and log2TPM of 3.44 [IQR, 2.59-4.22], respectively). SG showed a numerically higher median PFS (*TACSTD2* high, 7.3 vs 5.6 mo; *TACSTD2* low, 5.6 vs 2.8 mo) versus TPC regardless of *TACSTD2* expression. Similarly, for OS, outcomes favored SG over TPC regardless of *TACSTD2* expression. **Conclusions:** This mRNA-based biomarker analysis demonstrated that SG improves PFS and OS outcomes in patients with pretreated, endocrine-resistant HR+/HER2– mBC regardless of Trop-2 mRNA expression. There was no correlation between Trop-2 mRNA expression and HER2 status. Trop-2 mRNA expression was not predictive of benefit with SG. Additional studies are needed to determine whether Trop-2 mRNA expression has a prognostic role in mBC. Clinical trial information: NCT03901339. Research Sponsor: Gilead Sciences, Inc.

1083 **Poster Session**

Discovery of CDK4/6 bifunctional degraders for ER+/HER2- breast cancer.

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Background: CDK4/6 inhibitors (CDK4/6i) such as palbociclib and ribociclib are used to treat ER+/HER2- breast cancer, but patients can develop resistance via many mechanisms, several of which converge on the upregulation of CDK6. This has been shown to limit the effectiveness of CDK4/6i in ER+ breast cancer with up to 20% patients exhibiting innate resistance and up to 70% patients developing acquired resistance after 3 years on therapy (Scheidemann, 2021, doi:10.3390/ijms222212292). **Methods:** To address this limitation, we utilized our PRODEGY platform of Cereblon (CRBN) binders to synthesize CRBN mediated CDK4/6 bifunctional degraders to potently inhibit tumor growth for treatment of naïve ER+/HER2- breast cancer and CDK4/6i resistant tumors. **Results:** Target degradation by immunoblot analysis of the triple negative breast cancer (TNBC) cell line, MDA-MB-231, treated with our CDK4/6 bifunctional degraders for 6 hours showed up to 85% degradation of CDK4 and CDK6 with DC_{50}s of 1-100nM. CDK4/6 phosphorylates the protein RB which releases the transcription factor E2F, inducing the expression of genes which promote cell cycle progression. Analysis of RB phosphorylation by in-cell western upon 24 hours of CDK4/6 degrader treatment showed phospho-RB IC_{50}s at $<$30nM. Cell cycle analysis by staining with propidium iodide after 24 hours of treatment with CDK4/6 degraders induced G0/G1 cell cycle arrest at concentrations as low as 10nM. We used a 2D colony formation assay (CFA) as a readout for inhibition of proliferation by cell cycle arrest. Our CDK4/6 degraders showed potent inhibition of cell proliferation with CFA IC_{50}s of $<$100nM in TNBC cell lines and $<$25nM in ER+ cell lines, including MCF7, T47D and ZR751 compared to CDK4/6i which ranged from 200nM to 500nM in MCF7 cells. We demonstrated that our CDK4/6 bifunctional degraders were significantly more potent in vitro than the CDK4/6i ribociclib and palbociclib, and the increased activity was due to CRBN mediated target degradation. Our CDK4/6 bifunctional degraders display excellent pharmacokinetic properties in mice with half-lives between 2-10 hours, oral bioavailability between 50-96%. MCF7 xenograft results with our proof-of-concept CDK4/6 degrader showed dose-dependent tumor growth inhibition and greater potency compared to the clinical CDK4/6i ribociclib. We saw tumor regression with our degrader at higher doses which we did not see at any dose of CDK4/6i. **Conclusions:** Our CDK4/6 bifunctional degraders display excellent single agent activity in vitro and in vivo particularly in comparison to clinically approved CDK4/6i, indicating that using a degrader approach to targeting this pathway may be more effective than current inhibitor therapies. Research Sponsor: Biotheryx, Inc.

1084 **Poster Session**

Targeting squalene epoxidase in breast-to-brain metastasis: A new therapeutic target for brain extravasation and colonization using animal models.

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Background: Brain metastasis is the most common malignancy of the central nervous system which causes severe morbidity and mortality in multiple cancer types of patients and represents an unmet medical need. Several critical steps are required for a successful brain metastasis, including local invasion, intravasation, dissemination, extravasation, and colonization. Extensive research has been conducted to elucidate the mechanism of cancer metastasis with limited information toward how cancer cells extravasate and colonize. **Methods:** To understand the underlying molecular mechanisms and applications of molecular targets for brain metastasis therapy, murine models are employed for investigation of brain extravasation and colonization. To investigate the roles of SQLE in breast-to-brain metastasis *in vivo*, we silenced *SQLE* expression directly with lentiviral shRNA in the brain metastatic MDA-MB-231-BR cell line (231-BR/shSQLE) and used 231-BR cells expressing a scramble shRNA (231-BR/shScr) as the control. Brain metastases were induced by intracardiac, orthotopic, or direct intracranial injections of 231-BR/shSQLE or 231-BR/shScr cells into immune deficient mice. The essential roles of SQLE in the specific step(s) of breast-to-brain metastatic process were evaluated by *ex vivo* immunofluorescence analysis of brain slices from the animals. To verify SQLE as an oncogenic factor that can be selected as a potential therapeutic target in suppressing breast-to-brain metastasis, we evaluated the inhibitory effects of NB-598 (a SQLE inhibitor) in both the 231-BR orthotopic and intracardiac mouse models. **Results:** Recently, we identified a novel mechanism by which squalene epoxidase (SQLE), the second rate-limiting enzyme in the cholesterol biosynthesis, plays a critical role in the processes of breast cancer metastasized to the brain, especially in brain extravasation and colonization. Interestingly, the pharmacologic inhibition of SQLE has been widely used against fungal infections, and the next-generation SQLE inhibitors have been recently shown to exert an anticancer effect. Our data demonstrated that SQLE is essential for 231-BR cells to extravasate into the parenchyma as well as the formation of micro and macro-metastases in the brain. Interestingly, we found that astrocytes play a key role in supporting 231-BR-developed brain macro-metastasis. *In vitro* blood-brain barrier (BBB) models further demonstrated the critical roles of SQLE in promoting 231-BR cell invasion and penetration through BBB. Inhibition of SQLE by NB-598 demonstrated anti-tumor proliferation and anti-metastasis. **Conclusions:** Pharmacologic inhibition of SQLE by NB-598 suppressed 231-BR tumor growth at the mammary fat pad and distal metastases to organs, suggesting that targeting SQLE represents a therapeutic opportunity for breast cancer metastases. Research Sponsor: Pharmacology Discovery Services Taiwan, Ltd., New Taipei City, Taiwan; Institute of Biomedical Sciences, Academia Sinica, Taiwan and Institute of Translational Medicine and New Drug Development, China Medical University, Taiwan.

1085 **Poster Session**

Influence of chromatin remodeling molecule ARID1A on metastatic heterogeneity in triple negative breast cancer: Binding of YAP.

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Background: Heterogeneity is the prominent character of TNBC and one predominant cause of treatment failure. As a key nuclear SWI/SNF protein complex subunit, ARID1A plays a critical role in tumor identity determining by manipulating gene expression. The present study aimed to investigate whether and how ARID1A determined the metastatic heterogeneity of triple-negative breast cancer. **Methods:** This study retrospectively collected and analysed clinical and pathological data from 258 patients diagnosed with triple-negative breast cancer at Fudan University Cancer Hospital from August 2015 to June 2016 to define the prognostic ability of ARID1A.CRISPR/Cas9 or plasmids-mediated ARID1A were used to determine the ARID1A function in regulating the metastatic character in TNBC. Cell morphology, tumor invasion, and metastasis were analyzed in terms of ARID1A status both in vitro and in vivo experiments. The molecular mechanism of ARID1A determining metastasis potential of TNBC was explored by RNA-Seq and nuclear positioning. **Results:** ARID1A low expression was found to have independent prognostic value for poor OS (43.9 vs 53.6 months, P=0.0001) and RFS (31.0 vs 45.5 months, P=0.0029) in TNBC patients. Both nuclear and cytoplasmic protein analysis and Immunofluorescent localization assay confirm that ARID1A recruits the Hippo pathway effector YAP into nucleus in human triple negative breast cancer cells. Next we designed the YAP truncator plasmid and confirmed by Co-Immunoprecipitation that ARID1A could competitively bind to the WW domain of YAP to form the ARID1A/YAP complex. Furthermore, down-regulation of ARID1A promoted migration and invasion both in human triple negative breast cancer cells and xenograft model through Hippo/YAP signaling axis. **Conclusions:** Our study provides new insights into the previously unrecognized role of ARID1A in TNBC metastasis, which might provide new therapeutic options for patients with TNBC. Research Sponsor: National Science and Technology Major Project [grant number: 2020ZX09201-013].

1086 **Poster Session**

The overall survival analysis of FUTURE-C-PLUS: Combination of famitinib with camrelizumab plus nab-paclitaxel as first-line treatment for advanced, immunomodulatory triple-negative breast cancer—An open-label, single-arm, phase 2 trial.

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Background: Camrelizumab and nab-paclitaxel demonstrated promising anti-tumour activity in refractory metastatic immunomodulatory triple-negative breast cancer (TNBC) in FUTURE trial. Anti-angiogenic agents have been reported to facilitate immune infiltration. Famitinib is a tyrosine kinase inhibitor targeting VEGFR-2, PDGFR and c-kit. The FUTURE-C-PLUS trial (NCT04129996) which added famitinib to camrelizumab and nab-paclitaxel is a single-arm, phase 2 trial evaluating this novel triplet combinatorial strategy in patients with advanced immunomodulatory TNBC. Study design and the primary endpoint ORR has been reported previously (Zhi-ming Shao, et al. ASCO 2021, Abstract 1007). The final PFS data had been published in Clinical Cancer Research (Clin Cancer Res 2022;28: 2807–17). Here, we reported the final overall survival of this trial. **Methods:** Briefly, this study enrolled women aged 18-70 years, with previously untreated, histologically confirmed, unresectable, locally advanced, recurrent or metastatic immunomodulatory TNBC. Immunomodulatory TNBC was defined as CD8 expression on at least 10% of cells using immunohistochemistry analysis. Eligible patients received the triple therapy. **Results:** Forty-eight patients were enrolled and treated between Oct 2019 and Oct 2020. The median follow-up was 33.1 months (range, 31.8–34.4). 39 (81.3%, 95% CI 70.2-92.3) patients had a confirmed objective response which has been reported in ASCO 2021. At this updating data cutoff (Feb 1, 2023), the median progression-free survival was 13.6 months (95% CI, 8.4-18.8). While overall survival was 29.4 months (95% CI, 23.3-35.5). The disease control rate was 95.8% (46/48). The most common treatment-related grade 3 or 4 adverse events were neutropenia (16 [33.3%]), anemia (5 [10.4%]), febrile neutropenia (5 [10.4%]), and thrombocytopenia (4 [8.3%]). No new safety concerns were detected. No treatment-related deaths were reported. **Conclusions:** These data, combined with those from our previous reports, provide further evidence for the triplet combination of famitinib, camrelizumab and nab-paclitaxel as an active therapy in advanced Immunomodulatory TNBC. To our knowledge, this is the best overall survival reached in first-line treatment of advanced TNBC. A randomized controlled FUTURE-Super trial is ongoing to further validate these findings. Clinical trial information: NCT04129996. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co. Ltd. China.

1087 **Poster Session**

Olaparib (O) + ceralasertib (C) in patients (pts) with metastatic triple-negative breast cancer (mTNBC): Translational analysis of the VIOLETTE trial.

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Background: O is a PARP inhibitor approved in a number of tumor types and for use in pts with germline (g) mutations in *BRCA* (*BRCA*m) HER2-negative metastatic breast cancer. C is an inhibitor of DDR kinase ATR. Analysis of VIOLETTE (NCT03330847) in pts with mTNBC showed no improvement in PFS with a combination of C and O vs. O, whether in the context of pathogenic BRCAm, non-BRCA HRR pathway mutations (HRRm), or homologous recombination repair (HRR) wildtype (HRRwt) tumors. We report an exploratory translational analysis of predictive genomic biomarkers of response to O ± C beyond g*BRCA*m. **Methods:** Pts received O (300 mg twice daily) ± C (160 mg daily; days 1–7; 28-day cycles) as a second- or third-line treatment option. Pts were prospectively stratified into molecular strata based on pathogenic/likely pathogenic alterations in *BRCA*1/2 (*BRCA*m; n=83) or in ≥1 of 13 selected non-*BRCA* HRR genes (HRRm; n=40) or HRRwt (n=103) using FoundationOneCDx (F1CDx) sequencing assay of archival tumor sample. Advanced genomic analysis included genome-wide loss of heterozygosity (a marker of HRR deficiency [HRD] with a 16% cut-off to define HRD+ [≥16%] vs HRD− [<16%]), zygosity, and predicted g/somatic (s) status of *BRCA* and HRR alterations based on a validated computational FMI algorithm. Efficacy was evaluated by blinded independent central review of PFS, RECIST response, and best percentage change from baseline in target lesion size. **Results:** Out of evaluable pts for origin of *BRCA*m (n=42), 81% (n=34) were of germline, and 19% (n=8) were of somatic origin. Of pts evaluable for zygosity (n=48), most *BRCA* alterations were biallelic (90%; n=43), and of pts evaluable for HRD status (n=47), most were HRD+ (94%; n=44). Of HRRwt pts evaluable for HRD status (n=79), 57% were HRD+ (n=45). Responses by biomarker are shown. Responses in *BRCA*m pts were seen in all subgroups (zygosity, HRD, or g/s origin of mutation), including s*BRCA*m (ORR: n=3/4 on O; n=2/4 on O+C). Responses were also seen in patients with heterozygous *BRCA* alteration (n=3/5) by genomic result and in *BRCA*m/HRD− pts (n=3/3) across both arms. Pts with select HRR genes (*BARD1*, *RAD51C/D, ATM, CDK12*) also achieved responses on O or O+C. **Conclusions:** Responses to O were seen in pts with both g*BRCA*m and s*BRCA*m. Beyond *BRCA*m, the efficacy of O was observed in pts with alterations in select HRR genes, such as *BARD1* or *RAD51C/D*; further clinical investigation is required. Small sample size and HRD analysis performed on archival tumor samples should be considered limitations. Clinical trial information: NCT03330847. Research Sponsor: AstraZeneca.

Overall response rate in selected biomarker subsets; n/N (%).

Strata	Subgroup	O	O+C
***BRCA*m**	Predicted s*BRCA*m	3/4 (75)	2/4 (50)
	Predicted g*BRCA*m	9/16 (56)	8/18 (44)
	Unknown	7/23 (30)	10/18 (56)
HRRm	*BARD1*m	2/3 (67)	0/1 (0)
	RAD51C/*D*m	1/3 (33)	2/2 (100)
	*ATM*m	0/3 (0)	1/4 (25)
	CDK12 (co-occurring *PPP2R2A*)	0/1 (0)	1/3 (33)
HRRwt	HRD+	2/22 (9)	4/23 (17)
	HRD−	0/17 (0)	1/17 (6)

1088 **Poster Session**

ARID1A deficiency in triple-negative breast cancer induces adaptive immune resistance and sensitivity to immune checkpoint inhibitors.

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Background: Adaptive immune resistance (AIR) is pivotal to triple-negative breast cancer (TNBC) progression. Although immune checkpoint inhibitors (ICIs) shed new light on reversing AIR, the treatment effect and predictive markers of immunotherapy remain controversial. The present study focused on epigenetic regulation for TNBC AIR and explored whether this could be clinically targeted. **Methods:** Through screening an epigenetic gene set in TNBC patients from The Cancer Genome Atlas (TCGA), ARID1A was pinpointed as most significantly correlated with AIR. Humanized immune system (HIS) mice were adopted for TNBC transplantation, identifying $CD8^+$ T cells as most significantly correlated with TNBC ARID1A. To probe the mechanism underlying TNBC ARID1A deficiency-induced $CD8^+$ T cell malfunction and AIR, RNA-seq of both TNBC patients and TNBC cell lines were analyzed and the candidate mediator gene, PD-L1, was identified and verified through western blot, qPCR, IHC, dual luciferase reporter assay and cell co-culture. Chromatin immunoprecipitation and ATAC-seq further demonstrated direct binding of ARID1A to *NPM1* promoter to regulate PD-L1 expression. Finally, HIS mice were treated with ICI and the clinical trial CTR20191353 was retrospectively analyzed. **Results:** Among a series of epigenetic modulators, we first observed that ARID1A, a core subunit of the chromatin remodeling complex SWI/SNF, demonstrated highest correlation with AIR in TNBC patients. This was verified in HIS TNBC mice and a patient cohort from Fudan University Shanghai Cancer Center by higher malignancy observed in ARID1A-deficient TNBC. Both bulk and single-cell RNA-seq in TNBC patients uncovered an immunosuppressive microenvironment induced by TNBC ARID1A deficiency, and $CD8^+$ T cells was identified as the immune cell type most significantly correlated with TNBC ARID1A. $CD8^+$ T cell malfunction and AIR in ARID1A-deficient TNBC was induced by upregulated PD-L1, but ARID1A did not directly regulate PD-L1 expression. We found that ARID1A bound to the *NPM1* promoter and that ARID1A deficiency increased *NPM1* chromatin accessibility as well as gene expression, further activating PD-L1 transcription. In HIS mice, ICI demonstrated the potential to reverse TNBC ARID1A deficiency-induced AIR manifested by reducing tumor malignancy and activating antitumor immunity. In CTR20191353, a phase 1b clinical trial of pucotenlimab combined with chemotherapy for TNBC, patients with ARID1A deficiency demonstrated significantly better prognosis and the longest progression-free survival was found in ARID1A-low/PD-L1-high group. **Conclusions:** In AIR epigenetics, TNBC ARID1A deficiency induced AIR via the ARID1A/NPM1/PD-L1 axis, leading to poor outcome. While ARID1A deficiency provided survival advantage for TNBC cells, it simultaneously left the Achilles' heel which could be targeted with ICI. Research Sponsor: This work was supported by the National Science and Technology Major Project [grant number: 2020ZX09201-013].

1089 **Poster Session**

The case for acceleration of prospective multi- stakeholder led community-based research in young Black women with triple negative breast cancer (TNBC).

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Background: Black women face a three- fold increase in TNBC BRCA1 gene mutations. In TNBC, there is a higher rate of recurrence and metastasis to other organs. Lower access to timely care and more advance stage at diagnosis contribute to poorer outcomes. Black women have the lowest survival rate at each stage of TNBC diagnosis compared to other demographic groups. Research Question: Over the past 10 years, what real world community interventions have been published regarding risk for and diagnosis with TNBC in Black or African American women? **Methods:** Using the following keywords: TNBC, diversity, health equity, young adults, Black, African American, authors conducted PUBMED and Google Scholar searches for years 2011 to 2022 to summarize publications on community-based interventions with Black or African American women at risk of or diagnosed with TNBC. **Results:** A validated publication assessment revealed 70 publications: 63 retrospective and 7 prospective studies. Prospective studies were categorized using the NASEM cancer continuum of care domains. The number of studies that addressed the domains included: risk=1, screening =1, diagnosis=3, treatment=2, survivorship=1 end of life=0, outcomes=1. No studies reported the following criteria: A co-creation approach with community-based participatory research principles; interventions led by patients and Black women who are at risk for TNBC; multi stakeholder interventions led by community leaders or patient organizations with long-standing trust of diverse populations; addressing and resolving social drivers of health inequities, mental health, palliative care services or implicit bias; or inclusion in clinical studies. **Conclusions:** It is critical to address the disproportionate impact of TNBC in partnership with Black women. To achieve equitable health outcomes, we advise public and private sector leaders to make more funding available to support community-engaged approaches in high prevalence geographic areas. 1) Provide CBPR training and opportunities for diverse investigators and patient- and community-based organizations. 2) Build capacity for social needs assessment and interventions. 3) Employ community-based implementation science focused on all care continuum domains including the gaps between domains. 4) Increase public awareness of health issues in Black women and address resistance, access and eligibility for participation in clinical research. 5) Offer RFPs to transform care through collaboration between researchers, providers, patient and community-based organizations, health departments, and payers; engaging clinical and lay navigators and community health workers; design solutions that address barriers; and development and implementation of policy with a focus on standardization, accountability, and enforceability. Research Sponsor: None.

1090 **Poster Session**

Sociodemographic and clinicopathologic factors of triple negative breast cancer at an academic urban safety-net hospital.

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Background: Racial disparities in breast cancer in the United States is a persistent and ongoing problem. Decades of research is derived from large population based data sets and little is published with granular detail of specific, actionable factors to target for interventions. From a large urban safety-net hospital, we evaluate sociodemographic and clinicopathologic factors on survival outcomes of triple negative breast cancer. **Methods:** We conducted a single-institution retrospective study of patients with invasive breast cancer, diagnosed and treated between January 2010 and December 2021 at an academic safety-net hospital where insurance systems allow for access and treatment for all patients. Demographic, tumor and treatment characteristics were obtained. Chi-square and ANOVA were used to examine associated factors among White, Black, and other races. Survival was analyzed using the Kaplan-Meier estimator and log-rank test. Significant risk factors were identified with Cox regression analysis. **Results:** 251 women with invasive triple negative breast cancer were diagnosed and treated during the study period. Median age was 58 years, 68.9% were non-white, and 64.9% were publicly insured or uninsured patients. Median time from diagnosis to treatment initiation was 29 days and follow up period was 1392 days. Having a non-English primary language and living in areas with lower socioeconomic indices are observed in non-White patients (P=0.003, 0.033) and predictive of a higher clinical stage at presentation (P=0.011, 0.021). Black patients were diagnosed at higher histologic grade (Black: 82.4%, White: 79.7%; P=0.003) and White patients were more likely to change facility during the treatment course (White: 32.4%, Black: 16.03%; P=0.005). No significant racial disparities were observed in time to treatment, recurrence rate, and overall survival. Among patients indicated for adjuvant therapies, including chemotherapy, immunotherapy, and radiation, rates of recommendation and completion of therapy did not vary by race. Five year survival did not significantly vary by race when adjusted for demographic and clinicopathologic factors. **Conclusions:** At an academic urban safety-net hospital where access to diagnostic and treatment resources are comparable across patient populations, no racial disparities were seen in treatment, recurrence, and survival outcomes. Further research on racial differences in breast cancer biology and health behaviors may improve understanding of triple negative disease or mitigate later stage diagnosis. Research Sponsor: None.

1091 **Poster Session**

Phase Ib study of talimogene laherparepvec (T-VEC) in combination with chemotherapy (CT) or endocrine therapy (ET) in patients with metastatic, unresectable, or locoregionally recurrent HER2-negative breast cancer (BC).

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Background: Talimogene laherparepvec (TVEC) is a modified oncolytic herpes simplex 1 (HSV1) virus that may enhance tumor immune infiltration and is currently FDA-approved for the treatment of unresectable cutaneous, subcutaneous, and nodal melanoma. Anti-tumor responses have been seen both locally and systemically, and an abscopal systemic effect has been described in distant organ metastases. **Methods:** In this single arm, open label Phase 1b study, patients received intra-tumoral TVEC (first dose 10^6 PFU/mL followed by 10^8 PFU/mL q2-3 weeks; volume based on tumor size up to max 4mL) in combination with CT (gemcitabine/carboplatin [GC], nab-paclitaxel [Nab-P], or paclitaxel [P]) or ET at the discretion of the treating physician. All patients had at least one 1 cm lesion that was injectable at the bedside. The primary endpoint was safety and tolerability. The secondary endpoint was response by RECIST 1.1. Blood and tissue-based immune correlates including injected and neighboring non-injected lesions were evaluated. **Results:** 19 pts were enrolled on this study (2/5/20 – 1/25/23) and evaluable for toxicity with 1 pt non-evaluable for efficacy due to early discontinuation. Median age was 52.1 years. Nine pts (47%) had HR+/HER2- BC and 10 pts (53%) had TNBC. Injected lesions included intact subcutaneous skin nodules (7), non-fungating breast or chest wall lesions (12), and fungating breast or chest wall lesions (9). Pts had a median of 3 prior lines of systemic therapy in the metastatic setting (range 0-9). 13 pts (74%) had visceral metastases. Pts received TVEC with the following treatment partners: GC (n=8, 42%), Nab-P (n=7, 37%), P (n=2, 11%), ET (n=2, 10%). Median treatment duration was 11.6 weeks (range 1.0-45.0 weeks). Grade 3-4 treatment-related adverse events included neutropenia (n=5, 26%), anemia (n=1, 5%), thrombocytopenia (n=1, 5%), and injection site skin ulceration (n=1, 5%). Three pts (16%) had Grade 1-2 injection site skin ulceration. Response per RECIST 1.1 was evaluated in 16 pts (2 pts had rapid progression prior to first response evaluation): PR (n=2, 13%), SD (n=5, 31%), and PD (n=9, 56%). Disease response at the site of TVEC injection was clinically evaluated in 18 pts, with response rates (RR) as follows: partial response (PR) (n=11, 61%), stable disease (SD) (n=4, 22%), and progressive disease (PD) (n=3, 17%). Mass cytometry (CyTOF) analysis demonstrated a decrease in HLA-DR expression circulating lymphocytes and in TIM3 expression across multiple cell types in responders vs. non-responders; updated correlative analyses will be presented. **Conclusions:** The addition of intra-tumoral TVEC to CT or ET is safe and tolerable in pts with advanced BC. This treatment induces changes in circulating immune responses. Clinical trial information: NCT03554044. Research Sponsor: Amgen.

1092 **Poster Session**

Early efficacy evaluation of ORIN1001, a first in class IRE1 alpha inhibitor, in advanced solid tumors.

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Background: ORIN1001 is a first-in-class small molecule targeting a novel enzyme with a unique mode of inhibition that selectively blocks the Inositol Requiring Enzyme 1α (IRE1) RNAse and blocks X-Box Binding Protein 1 (XBP1) activation in the endoplasmic reticulum. ORIN1001 is now undergoing Phase 1/2 clinical testing in advanced solid tumors. **Methods:** In a Phase 1 dose escalation trial (3+3 design), ORIN1001 was administered PO daily as a single agent in patients (pts) with advanced solid tumors and in combination with Abraxane in pts with relapsed, refractory breast cancer. Safety, tolerability, pharmacokinetics, and preliminary efficacy of ORIN1001 was evaluated and a RP2D determined. **Results:** As of Jan, 2023, 30 patients with advanced cancer have received ORIN1001 as a single agent at doses up to 650 mg per day in 21-day continuous cycles and 13 patients with breast cancer have received ORIN1001 at doses up to 400 mg in combination with Abraxane in 28-day continuous cycles. For single agent, DLTs consisting of thrombocytopenia were observed at 200 mg (2 pts) and 650 mg (2 pts) and, rash was observed at 200 mg (1 pt) and 500 mg (1 pt). For combination treatment, DLTs consisting of thrombocytopenia were observed at 300 mg (1 pt), fatigue/ rash at 400 mg (1 pt), febrile neutropenia/low WBC at 400/500 mg (1 pt at each dose). Common ($>$ 15%) adverse events were predominantly nausea and/or vomiting (Grade 1-2 in severity). ORIN1001 exposure increased in a dose proportional manner with a mean $T_{1/2}$ at steady state of approximately 20 hours. For single agent, best response per RECIST 1.1 was partial response (PR) in 2 of 30 pts. These PRs included a stage IV colon cancer pt exceeding 44 months on treatment at 100 mg, and stage IV ER-/PR-/HER2+ breast cancer pt with 5 months on treatment at 500 mg. Stable disease (SD) was observed in a total of 16 of 30 pts with breast, colorectal, mesothelioma, liver, prostate, kidney or ovarian cancer. For combination therapy with Abraxane, a PR was observed in one ER+/PR-/HER2- breast cancer pt at 300 mg ORIN1001 and SD was observed in 5 of 13 pts. SD included both triple negative and ER+/HER2- breast cancer pts at 300 or 400 mg with ongoing treatment exceeding 5 months. Of note, in a separate Phase 1 oncology basket trial in China, there were 2 PRs; 1 pt with stage IV NSCLC at 300 mg and 1 pt with metastatic castrate resistant prostate cancer at 100 mg exceeding 9 and 5 months of treatment with ORIN1001 in combination with Abraxane, respectively. **Conclusions:** Phase 1 clinical evaluation of ORIN1001 has demonstrated tolerability and dose proportional PK. The proposed RP2D is estimated to be 500 mg and 300 mg ORIN1001 for single agent and in combination with Abraxane, respectively. Early efficacy data with ORIN1001 demonstrate clinical responses (SD and PR) in multiple pts with heavily-pretreated advanced solid tumors as a single agent or in combination with Abraxane in breast cancer patients. Clinical trial information: NCT03950570. Research Sponsor: Fosun Orinove.

Olaparib (O) in advanced triple negative breast cancer (aTNBC) patients (pts) with BRCA1/2 promoter methylation: GEICAM/2015-06 study (COMETA-Breast).

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Background: Epigenetic silencing by aberrant *BRCA1/2* promoters' methylation (*BRCA*-meth) can be responsible for a dysfunctional BRCA protein. *BRCA*-meth occurs in 15-57% of TNBC pts. *BRCA*-meth breast cancer (BC) display pathologic features and genetic profiles like germline *BRCA1/2*-mutated (g*BRCA1/2*m) carriers. O is a PARP inhibitor approved for treating g*BRCA*m HER2-negative advanced BC (aBC) pts. These are the results of a phase II study assessing the O efficacy in aTNBC pts with *BRCA1/2*-meth (NCT03205761). **Methods:** We included aTNBC pretreated pts (≥1 line) with centrally confirmed somatic *BRCA1/2-meth* (in most recent lesion(s) available) and no g*BRCA1*/2m. O 300mg b.i.d. was administered. *BRCA1/2* CpG island was considered methylated if value was ≥25%. Overall response rate (ORR) (complete response [CR] + partial response [PR]) according to RECIST 1.1) was the primary objective. Thirty-one evaluable pts were required based on an optimal 2-stage Simon's design (α error=0.05, 1-β error=80%), estimating an ORR increase of 24%, with a null hypothesis of 30%. Whole exome/transcriptome and 105-genes NGS assays (Tempus xE & xF) were performed on pretreatment tumor and sequential ctDNA of a long-term responder. **Results:** Eleven pts received ≥1 cycle of O (ITT population). Median age was 51 years (37-64), and 8 pts were postmenopausal. All M0 pts at diagnosis had neo-/adjuvant chemotherapy (CT). Median O exposure duration was 8 (1-88) weeks and relative dose-intensity was 97% (76-100), with any dose modifications in 6 pts. ORR was 9% (1 PR/11; 95% CI, 0.2-41). Clinical benefit rate (CR + PR + stable disease of any duration) was 36% (4/11; 95% CI, 11-69). Most pts (n=9) discontinued O due to BC progression. Median PFS was 2 months (95% CI, 1-4), and median OS was 9 months (95% CI, 1-14). One pt with confirmed PR was on O for >20 months. AEs were reported in 3 pts in line with O safety profile. No AE led to O discontinuation and no SAEs were reported. The statistical assumptions for the 1st Simon's model stage were not met (≥ 4/12 pts with CR or PR), so the recruitment did not proceed onto the 2nd stage. Preliminary NGS analysis on the long-term responder identified alterations on tumor (TP53, BCL11A, MYC) and on-treatment ctDNA (PMS2). **Conclusions:** In this proof-of-concept study, O did not show clinically nor statistically significant antitumor activity in pretreated aTNBC pts with *BRCA1/2*-meth. Clinical trial information: NCT03205761. Research Sponsor: None.

Methylation, n	
BRCA1	**7**
BRCA2	**2**
BRCA1/2	**2**
Proportion of BRCA1/2 promoter methylation, median (range); %	
BRCA1	37 (15 – 53)
BRCA2	6 (2 – 53)
Time since BC diagnosis to study inclusion, median (range), months	
M0 (n=7)	63 (11; 231)
M1 (n=4)	33 (3; 75)
No. of metastatic sites, n	
1	2
2	3
3	4
4	2
Visceral involvement, n	9
Prior therapies for aBC, n *	7
CT	3
CT + BT (biological therapy)	1
CT + BT + endocrine therapy	

*7 pts had ≥3 CT lines.

1094 **Poster Session**

The impact of social determinants of health (SDOH) on use of germline genetic testing for triple-negative breast cancer (TNBC) in the community oncology setting.

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Background: TNBC presents at an earlier age of onset and at a more advanced stage, and is associated with a worse outcome in African American women. In a subset of patients, TNBC is associated with germline BRCA1 and/or BRCA2 mutations. Genetic testing improves breast cancer and other surveillance as well as treatment outcomes. Current NCCN Guidelines recommend germline testing for all patients with any stage TNBC. Previous versions recommended testing in patients aged 60 years or younger. This study aimed to identify factors associated with receiving genetic testing among patients with TNBC in the community oncology setting. **Methods:** This was a retrospective observational cross-sectional study examining patient profiles, demographics, SDOH indicators, and germline genetic testing data. Patients in The US Oncology Network diagnosed with any stage TNBC between 3/31/2017 and 9/30/2021 aged 60 years or younger were identified.Data from the iKnowMed EHR was used for patient identification, baseline characteristics, and social determinants, including area deprivation index (ADI), a validated measure of socioeconomic status (SES) based on address. Mean ADI percentile scores using national and state level benchmarks were calculated as well as stratifications above and below the 80^{th} percentile (where higher scores $>$ 80 are markers of low SES). Evidence of germline genetic testing (yes/no) was compiled from iKM, network genetic databases, and confirmatory chart audits. Only US Oncology Network sites participating in confirmatory audits were included in this analysis. **Results:** Among participating sites, 1318 patients with TNBC were identified with a mean age of 49 years; 58% were White, 22% Black, 3% Asian, and 16% other/unknown; and evidence for germline genetic testing was found for 981 (74.4%). Statistically significant differences in germline testing rates were found for age (48.4 years for tested, 50.7 years for not tested); race (67% for Black patients, 77% for White); US census region (68% in South, 70% in Midwest, 83% in Northeast, and 87% in West); practice size (mean number of physicians: 32.8 per practice for testing group, 29.2 for untested); and for nationally benchmarked ADI score (mean ADI of 42.3: tested and 47.1 for not tested). No significant difference was seen across the spectrum of ethnicity, with 82% testing among Hispanic or Latino patients compared with 74% for non-Hispanic or Latino, $p = 0.074$. No significant differences were observed for clinical variables. **Conclusions:** We report that 75% of patients with TNBC in our community oncology network received genetic testing. However, significantly lower testing rates were observed for patients who were Black, had lower SES, and resided in the South and Midwest geographic regions. Further research should be performed to understand reasons why testing was not done, to address barriers. Research Sponsor: None.

1095 **Poster Session**

Phase II study of pembrolizumab plus mifepristone in patients with advanced HER2-negative breast cancer.

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Background: Metastatic breast cancer is incurable, and novel treatment (tx) strategies are needed. Single agent immune checkpoint inhibitor (ICI) tx has limited efficacy; combination approaches may yield better results. Multiple mechanisms of glucocorticoid-induced immunosuppression have been proposed, including the suppression of the cytotoxic Th1 cytokine response via glucocorticoid receptor (GR) activation. We hypothesize that pretreatment with a GR antagonist shifts the cytotoxic immune response toward Th1, thus enhancing response to ICIs. We present the safety and efficacy of the combination of pembrolizumab and mifepristone in advanced HER2-negative breast cancer. **Methods:** This (NCT03225547) was a phase II non-randomized study of pembrolizumab and mifepristone in patients (pts) with advanced HER2-negative breast cancer. Pts with prior ICI tx were excluded. Pts received mifepristone 300mg daily and pembrolizumab 200mg every 3 weeks; mifepristone was started 7 days prior to pembrolizumab. The primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and safety and tolerability. **Results:** 18 patients were enrolled from March 2018 – November 2020; 10 patients with TNBC (cohort 1) and 8 patients with HR+ BC (cohort 2). Mean age was 53 yrs (range 33-74) and 33% of patients were self-reported Black. In cohort 1, 50% of patients were tx naive in this advanced setting, and 90% of patients had < 2 prior lines of tx. In cohort 2, 25% of patients had not received prior chemo in the metastatic setting. The overall ORR was 6%. One pt with TNBC had a complete response (CR). She received 36 cycles of tx; tx was discontinued due to mucositis and rash, and she remains in CR at $>$48 mos from start of tx. No patients in cohort 2 had a partial or complete response. The most common treatment-related adverse events were rash (61%), thyroid abnormality (17%), and pruritis (17%). 45% of patients experienced a grade 3 or 4 adverse event; all except one (hypokalemia) were due to rash. Rash was described as maculopapular dermatitis. The DCR at 18 weeks was 33.3% in the overall population; it was 44.4% in cohort 1 and 16.7% in cohort 2. Overall median PFS was 1.9 months [95% CI 1.8 – 3.6]. Overall median OS was 12.9 months [95% CI 5.8 – 23.0]. **Conclusions:** While this regimen demonstrated efficacy in a small subset of patients, including one pt with long-term CR, given the non-randomized design, we cannot determine if mifepristone enhanced the efficacy of ICI. In addition, a higher than anticipated rate of skin toxicity, possibly related to mifepristone enhancing the activity of ICI, was observed in the study, leading to early closure. While the benefit/risk analysis of this combination does not support further evaluation, additional investigation of alternative chemotherapy-free, immunomodulatory strategies is warranted. Clinical trial information: NCT03225547. Research Sponsor: Corcept Pharmaceuticals, Merck; U.S. National Institutes of Health.

Efficacy of oral selective estrogen receptor degraders (SERD)s in the treatment of estrogen receptor positive (ER+), HER2-negative metastatic breast cancer (MBC): A stratified analysis of the ESR1 wild type (wt) and mutant (mt) subgroups.

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Background: Oral SERDs are a novel drug class developed to counteract endocrine resistance due to ESR1 mutations. Several SERDs have emerged from phase 2 and 3 trials, and the FDA has most recently limited approval for Elacestrant to patients with ESR1mt tumours despite PFS benefit in the overall population. Questions remain on whether patients with ESR1wt tumours stand to benefit from SERDs. We conducted an IPD meta-analysis of the trials EMERALD, SERENA2, ACELERA and AMEERA3 to compare survival outcomes of SERDs in the 2nd or 3rd line setting against endocrine therapy (ET), using KMSubtraction to unveil HRs of unreported ESR1wt subgroups from AMEERA3 and EMERALD. Meta-analysis results were stratified by ESR1 status. **Methods:** RCTs investigating the efficacy of novel SERDs versus ET for ER+, HER2- MBC, and which reported the Kaplan Meier (KM) plots of progression free survival (PFS) were selected after a systematic search of Embase and PubMed from inception until January 21,2023. A graphical reconstructive algorithm was applied to estimate time-to-event outcomes from reported KM plots in all overall and reported subgroup cohorts, deriving IPD. A bipartite matching algorithm, KMSubtraction was used to subtract patients in the reported subgroup from the overall cohort, to derive survival data for unreported ESR1wt subgroups. An IPD meta-analysis was then performed, pooling data by ESR1 mutation. **Results:** A total of 1216 patients were included in this analysis. In the pooled analysis of the overall cohort, PFS benefit was observed with SERDs compared to treatment of physician's choice (TPC) (HR 0.787, 95%CI 0.683-0.908, $p<0.001$). In the ESR1mt subgroup SERDs demonstrated improved PFS (HR 0.557, 95%CI 0.440-0.705, $p<0.001$) compared with TPC. In the ESR1wt subgroup, SERDs demonstrated no significant PFS benefit (HR 0.948, 95%CI 0.790-1.137, p=0.565) when compared to TPC. KMSubtraction was implemented on AMEERA3 to reveal survival data in ESR1wt subgroup. Amcenestrant revealed no significant PFS difference in the ESR1wt population (HR 1.197, 95% CI 0.857-1.670, p=0.291) when compared to ET. Additionally, a separate analysis of EMERALD was performed using KMSubtraction to derive survival data of the ESR1wt subgroup comparing Elacestrant vs Fulvestrant. No significant PFS difference was observed between the 2 agents in the ESR1wt population (HR 0.832, 95% CI 0.587-1.178, p=0.299). **Conclusions:** Our results suggest that PFS benefit in the overall population is mainly driven by the ESR1mt subgroup. These findings are in line with the recent FDA approval of Elacestrant for patients with ESR1mt tumours. Research Sponsor: None.

Subgroup	HR (CI)	P value
Overall	0.787 (0.683-0.908)	<0.001
ESR1mt	0.557 (0.440-0.705)	<0.001
ESR1wt	0.948 (0.790-1.137)	0.565

1097 **Poster Session**

High dose alkylating chemotherapy for patients with oligometastatic breast cancer harboring homologous recombination deficiency: Results from the randomized phase 3 OLIGO study.

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Background: Oligometastatic breast cancer (OMBC) is a clinical entity with favorable prognosis compared to MBC in general, but the optimal treatment for individual patients remains unclear. We compared high dose chemotherapy (HDCT) to conventional dose chemotherapy (CDCT) in patients receiving local ablative therapy (LAT) of all disease sites in HER2-negative OMBC that harbors homologous recombination deficiency (HRD). **Methods:** In this open-label phase 3 study, we randomly assigned patients with OMBC after 3 cycles of induction CDCT to either continue with CDCT (up to a maximum total of 8 cycles) or switch to HDCT. OMBC was defined as 1-3 distant metastatic lesions, with or without locoregional disease, all amenable to LAT. Main eligibility criteria included pathologic proof of a distant metastatic lesion, HRD (based on either germline *BRCA1/2* mutation and/or a BRCA-like profile in the tumor), and a favorable response to induction CDCT. The primary endpoint was event-free survival (EFS), defined as time since randomization to recurrence or death. Overall survival (OS), safety and quality of life (QoL) were key secondary endpoints. Following the advice of the independent data monitoring committee, analyses were performed before the prespecified number of events was reached. **Results:** Between November 2012 and May 2022, 36 patients were allocated to HDCT and 39 to CDCT. 52 (69%) tumors were triple negative and 23 (31%) were hormone receptor positive; 39 patients (52%) had a solitary metastasis and 43 (57%) had synchronous OMBC. After a median follow-up of 52 months (interquartile range 28-97), 42 EFS-events had occurred. Median EFS in the HDCT-group was 28 months (95% CI 21 – not reached (NR)) compared to 25 months (95% CI 14 – NR) in the CDCT-group (hazard ratio (HR) 0.78 (95% CI 0.42 – 1.42, p = 0.411). Median OS was 67 months (95% CI 37 – NR) in the HDCT-group versus 36 months (95% CI 26 – NR) in the CDCT-group (HR 0.74, 95% CI 0.37 – 1.48, p = 0.398). 5-year EFS was 40% and 30%, and 5-year OS was 51% and 49% in the HDCT- and CDCT-group, respectively. 34 (94%) patients in the HDCT-group experienced grade 3 or higher adverse events, compared to 25 (64%) patients in the CDCT-group; no grade 5 adverse events occurred. QoL was comparable between groups at 12 months. **Conclusions:** HDCT does not improve outcome compared to CDCT in patients with OMBC harboring HRD and can therefore not be recommended. Survival in this highly selected group of patients with OMBC, all receiving LAT, compares favorably to survival in the overall MBC population. The optimal systemic therapy for patients with OMBC requires further study. Clinical trial information: NCT01646034. Research Sponsor: Dutch Cancer Society.

Prognostic value of tumor-derived extracellular vesicles and circulating tumor cells in metastatic breast cancer (BC): A focus on inflammatory BC.

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Background: Circulating tumor cells (CTCs) are an independent prognostic factor in metastatic breast cancer (MBC). The prognostic value of CTCs and the optimal cutoff for patients (pts) with inflammatory breast cancer (IBC), one of the most aggressive types of BC, has not been fully established. Recent evidence showed the complementary prognostic value of tumor-derived extracellular vesicles (tdEVs) to CTCs in MBC. The significance of tdEVs in IBC is unexplored. This study aimed to assess the prognostic value of CTCs and tdEVs in metastatic IBC. **Methods:** This study retrospectively analyzed 308 pts with MBC enrolled at Northwestern University (Chicago, IL) before starting a new line of therapy between 2016 and 2021 (NU16B06 trial). Blood samples were processed for CTCs using the CellSearch system. We applied the open source ACCEPT software to archived CellSearch images to enumerate CTCs and tdEVs. TdEVs cutoff levels were $<$20 (low), 20-79 (intermediate), and $\geq$80 (high), as previously reported. The association of CTCs and tdEVs with overall survival (OS) was tested in the overall population (OvP) and IBC pts. **Results:** Of the 308 pts, 69 were diagnosed with IBC. 51% of pts received first-line therapy. CTCs enumerated by ACCEPT were strongly correlated with manual count (r=0.86) and hence used for this analysis. Median CTC count was 1 [interquartile range (IQR) 0-7] in IBC pts and 3 (IQR 0-14) in non-IBC (p=0.11). A significantly lower median tdEVs count was observed in IBC (7; IQR 3-45) than in non-IBC (22; IQR 4-137) pts (p=0.03). In IBC, higher CTC and tdEV counts were seen in the triple negative subtype (p=0.03) and non-visceral involvement (p=0.02), respectively. In the OvP median OS (mOS) was worse among pts with $\geq$5 CTCs (HR 2.6; p=0.001) and with elevated tdEVs (HR 3.3; p$<$0.001). Only tdEVs were independently associated with poorer OS in multivariable analysis. In pts with $<$5 CTCs there was a stepwise decrement in OS with increased tdEVs count (p=0.3); in pts with $\geq$5 CTCs, elevated tdEVs levels were associated with significantly worse OS (p=0.03). IBC pts with $\geq$5 CTCs had shorter mOS (8 vs 47 months; HR 3.6; p$<$0.001); this association was weaker using $\geq$1 as CTC cutoff (HR 2.4; p=0.01). OS was adversely associated with increasing tdEVs levels (33 vs 23 vs 7 months for low, intermediate, and high subgroups, respectively; HR 3.7; p=0.001). Furthermore, elevated tdEVs were associated with shorter mOS in pts with $\geq$1 (p=0.055) and $\geq$5 CTCs (p=0.6). Among pts with $<$5 CTCs no significant difference emerged among tdEVs subgroups (p=0.6). **Conclusions:** This study confirmed the strong prognostic significance of CTCs and tdEVs in MBC, including IBC. Pts with IBC had fewer CTCs and tdEVs compared to non-IBC, probably due to the predominant lymphatic spread of IBC. tdEVs offer the possibility to better define prognosis of IBC pts. Further studies are needed to evaluate their complementarity to CTCs. Research Sponsor: None.

1099 **Poster Session**

Phase II study of trifluridine/tipiracil (FTD/TPI) in HER2-negative metastatic breast cancers with or without prior exposure to fluoropyrimidines.

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Background: Fluoropyrimidines are commonly used in the treatment of patients (pts) with metastatic breast cancers (MBC). FTD/TPI is an oral drug combination of trifluridine with tipiracil, a thymidine phosphorylase inhibitor preventing rapid degradation of trifluridine, thus allowing for increased exposure to active agent, and has showed activity in pts with colorectal and gastric cancers despite prior exposure to fluoropyrimidines. We investigate the role of FTD/TPI in MBC pts with (Cohort A) or without (Cohort B) prior exposure to fluoropyridines in a single arm phase II study. **Methods:** Pts were treated with FTD/TPI, and enrolled first into a lead-in dose confirmation phase, followed by two parallel cohorts based on prior exposure to fluoropyrimidines. Primary objectives for each cohort included determination of progression-free survivals (PFS), and secondary objectives included determination of objective response rates (ORR), safety and tolerability. **Results:** A total of 74 pts were recruited (42 for Cohort A, 32 for Cohort B), of whom 4 belonged to lead-in phase. Dosing was confirmed at FTD/TPI 35mg/m^2 days 1-5 and 8-12 of 4-weekly cycles based on lead-in phase with no dose-limiting toxicities observed, and recruitment then proceeded in 2 parallel cohorts. All pts were evaluable for toxicity and survival analyses, and 72 were evaluable for ORR. Median age at enrolment was 62 years (range 32-85), with median of 4 (range 0-14) prior lines therapy in the metastatic setting, and 47% had de novo metastatic disease. Median PFS was 5.7 months (95% CI 3.8 to 8.3) and 9.4 months (95% CI 5.5 to 14.0) respectively in Cohorts A and B. Similar response rates were observed regardless of prior exposure to fluoropyrimidine, with ORR of 19.5% (95% CI 8.8 to 34.9) and 16.1% (95% CI 5.5 to 33.7) in Cohorts A and B, with 6-month clinical benefit rates of 56.1% (95% CI 39.7 to 71.5) and 61.3% (95% CI 42.2 to 78.2) respectively. Safety profile was consistent with known toxicities of FTD/TPI, with most common treatment-related adverse events of neutropenia, fatigue, nausea and anorexia. 64% of pts required dose modifications during study treatment, most commonly due to neutropenia, that could be overcome by dose reduction or prolongation from 4- to 5-weekly cycles. Only 1 pt required discontinuation due to toxicity from therapy. **Conclusions:** FTD/TPI showed promising anti-tumor activity with meaningful clinical benefit even among pts with prior exposure to fluoropyrimidines, and has a reasonable toxicity profile with appropriate dose modification. An oral chemotherapy option with good disease control provides an attractive treatment alternative to pts with MBC where quality of life is paramount, warranting further investigation in randomised studies. Clinical trial information: NCT04280536. Research Sponsor: National Medical Research Council, Singapore; Taiho pharmaceuticals.

Preliminary results from a first-in-human study of ESG401, a trophoblast cell-surface antigen 2 (TROP2) antibody drug conjugate (ADC), in patients with locally advanced/ metastatic solid tumors.

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Background: ESG401 is an innovative ADC composed of a humanized anti-TROP2 IgG1 monoclonal antibody conjugated to topoisomerase I inhibitor SN-38 via a proprietary stable-cleavable linker with DAR of 8. **Methods:** Patients (pts) aged ≥18 years with locally advanced/metastatic solid tumors refractory to/relapsed from standard treatment with measurable disease (RECIST v1.1) were eligible. ESG401 is administered intravenously by designated dose and regimen until unacceptable toxicity or progressive disease. The Bayesian Optimal Interval (BOIN) design was used to establish the MTD. **Results:** As of Feb 3, 2023, 35 pts with a median age of 53 were treated with ≥1 dose of ESG401 during escalation at doses of 2-20 mg/kg once Q3W (Regimen A), or 12-16 mg/kg D1,8,15 in a 4-week cycle (Regimen B). 80% of pts were ECOG = 1, 63% of pts were 3L+; median 4 (2-10) prior lines, 94% of pts had visceral metas (11% brain, 63% liver, 60% lung) at baseline. Only one patient treated with 20 mg/ kg experienced DLT. The MTD has not reached either regimen. The most common TRAEs were leukopenia (80%), neutropenia (69%), anemia (66%), fatigue (54%), nausea (51%), and vomiting (46%). The most common ≥ Grade 3 TRAEs were leukopenia (29%) and neutropenia (31%). There was no ≥ Grade 3 thrombocytopenia, diarrhea, skin rash, or oral mucositis. No Interstitial Lung Disease (ILD) was observed. Of 33 efficacy evaluable (EE) pts, 12 partial responses (PR) were observed and 4 pts had achieved SD ≥24 wks. The first dose level found PR (16 mg/kg Q3W) and afterward were taken as therapeutically relevant doses (TRD). The ORR and DCR were 36% (4/11) and 64% (7/11) in 11 TRD pts with TNBC, while 62% (8/13) and 77% (10/13) in 13 TRD pts with HR+/HER2-BC. Two pts with brain metas both got an obvious intracranial response (one pt whose intracranial lesion was significantly reduced to too small to measure). Until the cut-off date, 11 (31%) pts remained on treatment. Three pts were treated over 12 mons and the longest on-treatment duration was 12.9 mons. One pt had consistent PR up to 10.8 mons. **Conclusions:** The preliminary data demonstrated that ESG401 is safe and well-tolerated with promising signals of efficacy in heavily pretreated pts. These encouraging findings warrant further clinical evaluation. Clinical trial information: NCT04892342. Research Sponsor: Shanghai Escugen Biotechnology Co., Ltd.

Summary of tumor response per investigator.

	Regimen A				Regimen B			
	8mg/kg (N=3)	12mg/kg (N=3)	16mg/kg (N=5[a])	20mg/kg (N=5)	12mg/kg (N=5)	14mg/kg (N=6)	16mg/kg (N=6)	Total (N=33)
PR[b], n (%)	0	0	2 (40.0)	2 (40.0)	3 (60.0)	1 (16.7)	4 (66.7)	12 (36.4)
SD, n (%)	1 (33.3)	0	1 (20.0)	1 (20.0)	1 (20.0)	4 (66.7)	1 (16.7)	9 (27.3)
PD, n (%)	2 (66.7)	3 (100)	2 (40.0)	2 (40.0)	1 (20.0)	1 (16.7)	1 (16.7)	12 (36.4)

[a] Includes pts who were assigned to 2mg/kg (N=1) and 4mg/kg Q3W (N=1) while eventually intra-pt escalated to 16mg/kg Q3W.
[b] Per RECIST 1.1, but including single-point PRs, not confirmed responses.

1101 **Poster Session**

Actionability of comprehensive genomic profiling compared to the tissue-based and plasma-based assay in patients with metastatic breast cancer: A real-world study.

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Background: Comprehensive genomic profiling (CGP) was officially approved in August 2021 in Japan under the national health insurance system with three CGP tests in June 2019: FoundationOne CDx (F1CDx), OncoGuide NCC Oncopanel (NCC), which are tissue-based assay (TBA), and FoundationOne Liquid CDx (F1LCDx, starting in August 2021) which is plasma-based panel (PBA). The Center for Cancer Genomics and Advanced Therapeutics (C-CAT) has collected genomic and clinical data of 2,617 Japanese breast cancer patients as of October 2022. Here we assess these PBA and TBA to detect pathogenic or driver alterations informative for matched therapy in patients with metastatic breast cancer (mBC). **Methods:** We queried consecutive mBC patient clinical-genomic data through the C-CAT Research-Use Portal from June 2019 to October 2022 were categorized based on PBA or TBA. We used ClinVar to identify if the called somatic alterations were pathogenic or likely pathogenic, and BoostDM (https://www.intogen.org/boostdm/search) to identify potential driver mutations of breast cancer. The proposed rate of matched therapy was determined. The incidence rates were compared using the Pearson $\chi 2$ test. **Results:** Of 2,617 pts who underwent the CGP test, 2,259 (86%) received TBA (74% F1CDx and 12% NCC). The proportion of pts with ≥ 1 pathogenic variant with PBA and TBA was not significant (71.5%vs.72.7%; p=0.88), but the proportion of pts with ≥ 1 driver mutation was significantly higher with PBA than TBA (75.4% vs. 69.8%; $p = 0.03$). Regarding the proportion of pts who matched therapy or clinical trials presented among the pts for whom data were available, PBA was significantly lower than TBA (27.7% vs.38.5%, $p < 0.001$). Although data on post-treatment is still being collected, the proportion of tested patients that received matched therapies recommended by molecular tumor boards of each institute was significantly lower for PBA (4.2%vs. 8.3%; $p = 0.007$). **Conclusions:** This study is the first analysis of CGP for mBC in Japan using the C-CAT utilization program. Although significant alterations were well-detected in PBA, the proportion of pts who received matched-therapy post-testing was low for PBA. Possible causes include that PBA has fewer companion diagnoses than TBA in Japan and that PBA is more often used in later lines. Research Sponsor: None.

1102 **Poster Session**

Social determinants of health factors and palliative care services use among patients with metastatic breast cancer in Florida.

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Background: ASCO recommends palliative care (PC) as an adjunct to the oncologic standard of care for patients with metastatic cancer. However, current evidence on PC utilization in patients with breast cancer and its relationship with area-level social determinants of health (SDoH) factors is limited. Therefore, we examined the associations between county-level factors and PC utilization among patients with metastatic breast cancer (mBC) in Florida. **Methods:** We extracted patient-level data (n = 23,539 patients diagnosed with mBC between 2012 and 2021) from the OneFlorida+ Data Trust and linked it to county-level data (67 Florida counties) from the AHRQ-SDoH Database. PC utilization since cancer diagnosis was identified using ICD-9 code V66.7 or ICD-10 code Z51.5. We assessed differences in PC utilization with county-level SDoH factors (e.g., poverty rate, transportation resource, provider supply, racial segregation) using bivariate analysis. Multivariable Poisson regression, including significant factors from bivariate analysis, was used to compare the PC utilization for the SDoH factors. **Results:** Our study population's overall prevalence of PC utilization was 16.1%. PC utilization was higher for patients with mBC residing in counties with a higher proportion of residents living in poverty and with a greater supply of advanced practice providers (APP: NP, PA), general surgeons, and nursing homes. Patients with mBC in counties with higher proportions of residents who identified as immigrants, with limited English proficiency, without personal transportation, and having higher racial segregation had lower PC utilization. In adjusted analysis, the supply of APP (coefficient:0.12) and nursing homes (coefficient:0.09) was associated with increased PC utilization. Conversely, racial segregation (White vs. non-White) was associated with decreased PC utilization (coefficient: -0.07). **Conclusions:** PC utilization among patients with mBC was associated with several SDoH at the county level. Notably, low PC utilization was associated with racial residential segregation and fewer APPs and nursing homes. Further research is needed to identify mediators in these relationships to improve PC effectiveness for patients with mBC in Florida. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

1103 **Poster Session**

Association between baseline radiological tumor burden and outcomes in patients with metastatic breast cancer treated with an immune checkpoint inhibitor.

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Background: Lower baseline radiological tumor burden is associated with more favorable outcomes for patients with metastatic non-small cell lung cancer and melanoma treated with immunotherapy. However, minimal data is available for metastatic breast cancer patients. This is despite immunotherapy, in combination with chemotherapy, now being standard-of-care for a subset of metastatic breast cancer patients who have triple-negative disease and are PD-L1 positive. **Methods:** We reviewed data of 82 patients with metastatic breast cancer consecutively treated at our institution from August 2015 to October 2021, who received >1 dose of an immune checkpoint inhibitor (anti-PD-1 or -PD-L1) within the context of a clinical trial. Baseline tumour burden was assessed by a single radiologist and calculated as sum of Response Evaluation Criteria in Solid Tumours 1.1 baseline target lesions (baseline tumour size [BTS]) or as sum of all measurable baseline lesions (total tumour burden [TTB]); the impact of both parameters on treatment outcomes was investigated. Treatment outcomes assessed were clinical benefit rate (complete response, partial response or stable disease for 6 months or more [CBR6]), disease free survival (DFS) and overall survival (OS). Multivariate analysis adjusted for ECOG status, line of treatment (first line vs second line or beyond), and whether immunotherapy was given in combination with chemotherapy or as monotherapy. **Results:** A total of 82 patients were included in the analysis. 43 patients (52%) received combination chemotherapy with immunotherapy, 39 patients (48%) received immune checkpoint inhibitor monotherapy. Median BTS and TTB were 36.5mm (range 0 -204mm) and 43mm (range 0 – 1123mm) respectively. CBR6 was significantly associated with BTS ($p=0.004$) and TTB ($P=0.002$) quartiles, with clinical benefit time progressively increasing with decreasing tumor burden quartiles. Both increasing BTS ($p<0.001$) and TTB ($p<0.001$) across quartiles were significantly associated with shorter OS. There was a numerical, but not statistically significant, association between both parameters as quartiles (BTS, $p=0.25$; TTB, $p=0.07$) and PFS. In the bottom BTS quartile, 32% of patients were progression-free and 95% alive at 12 months, compared with 15% and 40% respectively in the top quartile. Similar results were seen when TTB was used as the baseline measurement: 32% progression-free and 95% alive at 12 months in the bottom quartile compared with 1% and 33% in the top quartile. Multivariate analysis confirmed that both BTS and TTB, considered as continuous variables, are independently associated with OS. **Conclusions:** Lower baseline radiological tumor burden is associated with better outcomes in patients with metastatic breast cancer treated with immune checkpoint inhibitors. Research Sponsor: None.

Prognostic value of HER2-low status in breast cancer: A systematic review and meta-analysis.

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Background: HER2-Low breast cancer (BC) has been recently identified as a new therapeutic target. However, it is unclear if HER2-Low status has an independent impact on prognosis, both in metastatic and early settings. **Methods:** A systematic literature research of PubMed, Cochrane and conference proceedings (ASCO meetings, SABCS and ESMO congress) up to December 8, 2022 was performed to identify studies comparing survival outcomes of patients affected by HER2-Low BC vs. HER2-zero BC. HER2-Low status was defined as immunohistochemistry score 1 + or 2+ without in situ hybridization amplification. Pooled hazard ratios (HRs) for survival endpoints in the metastatic [progression-free survival (PFS), overall survival (OS)] and in the early [disease free-survival (DFS) and OS] settings as well as their 95% confidence intervals (95%CI) were calculated using the random-effect model of Der Simonian and Laird. The above-mentioned endpoints were also assessed according to estrogen receptor (ER) status. **Results:** Among 1,916 identified records, 42 studies including 1,797,377 patients were eligible for this analysis. We show the pooled HRs in the overall population and specific subgroups. In the early setting, HER2-Low status was associated with significant improved DFS (HR 0.86, 95%CI 0.79-0.92, p<0.001) and OS (HR 0.84, 95%CI 0.77-0.92, p<0.001) when compared to HER2-zero status. Improved OS was observed in subgroup analysis for both ER-positive and ER-negative HER2-Low populations, while DFS improvement was observed only in the ER-positive subgroup. Similarly, in the metastatic setting, patients affected by HER2-Low BC showed better OS when compared to those with HER2-zero BC (HR 0.94, 95%CI 0.89-0.98, p=0.008). HER2-Low metastatic BC was associated with significant improvement in OS compared to HER2-zero BC also in ER-positive and ER-negative subgroups. No significant differences were found in terms of PFS. **Conclusions:** Compared with HER2-zero status, HER2-Low status appears to be associated with an increased OS both in the advanced and early settings, regardless of hormone-receptor expression. Research Sponsor: None.

Setting	Population	OS HR (95%CI)	p value	DFS HR (95% CI)	p value	PFS HR (95% CI)	p value
Early	Overall	0.84 (0.77-0.92)	<0.001	0.86 (0.79-0.92)	<0.001		
	ER-positive	0.85 (0.78-0.93)	0.001	0.86 (0.80-0.93)	<0.001		
	ER-negative	0.87 (0.84-0.89)	<0.001	0.90 (0.78-1.04)	0.155		
Metastatic	Overall	0.94 (0.89-0.98)	0.008			0.99 (0.96-1.03)	0.710
	ER-positive	0.92 (0.87-0.98)	0.013			1.13 (0.94-1.35)	0.192
	ER-negative	0.91 (0.87-0.95)	<0.001			0.92 (0.84-1.02)	0.103

1105 **Poster Session**

Biomarker analysis of phase II pembrolizumab maintenance treatment after chemotherapy response in patients with HER2-negative inflammatory breast cancer and triple-negative breast cancer.

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Background: Accumulating toxicities make indefinite chemotherapy unfeasible for many patients with metastatic/recurrent HER2-negative inflammatory breast cancer (IBC) or triple-negative breast cancer (TNBC). We conducted a single-arm phase II trial of pembrolizumab monotherapy to determine the efficacy of maintenance immunotherapy in patients with metastatic HER2-negative aggressive breast cancer and to identify biomarkers correlated with disease control. **Methods:** The study enrolled patients who had a complete response, partial response, or stable disease after a minimum of 3 cycles of chemotherapy for metastatic TNBC/IBC regardless of PD-L1 expression between 2015 and 2022. Pembrolizumab was administered at 200 mg every 3 weeks until disease progression, intolerable toxicity, or 2 years of exposure to the drug. The primary endpoint was the 4-month disease control rate (DCR), and the secondary endpoint was progression-free survival (PFS). Correlative studies were performed to determine associations between clinical response, and immune profiling consisting of T-cell clonality, immunophenotyping, and dendritic cell (DC) function with blood collected at baseline and after 2 cycles of pembrolizumab treatment. **Results:** Of 43 treated patients, 11 had metastatic IBC and 32 had TNBC. The median number of prior lines of chemotherapy for metastatic disease was 1. During a median follow-up of 11.4 months, 33 patients had progressive disease and 25 were deceased. The 4-month DCR was 58.1% (95% CI: 43.4%-72.9%) and the median PFS was 4.8 months (95% CI: 3.0-7.1 months). The median PFS of the metastatic IBC group (2.2 months) and TNBC group (4.8 months) did not differ significantly (p = .12). Thirty-one patients discontinued treatment due to progressive disease rather than toxicity. Observed toxicities were consistent with the known profile of pembrolizumab. Correlative blood studies showed availability of PD-1 on CD8 T cells decreased on therapy. T-cell exhaustion markers 2B4, CTLA4, and TIM3 decreased in patients who had therapeutic benefit, while LAG3 increased in patients without benefit. During therapy, *ex vivo* cytokine synthesis (IL-6/IL-12/TNFα) by DCs was superior in patients who benefited from therapy and increased from pretreatment samples. High T-cell clonality at baseline predicted response to immunotherapy (10.4 vs 3.6 months, p = .04). Additionally, patients exhibiting the greatest clinical benefit also had a significant increase in T-cell clonality over the course of therapy (20% vs 5.9% mean increase, p = .04). **Conclusions:** Increased T-cell clonality and DC activity, along with reductions in T-cell exhaustion, were associated with prolonged disease control following pembrolizumab maintenance therapy, achieving acceptable disease control with manageable toxicity. Clinical trial information: NCT02411656. Research Sponsor: Merck.

Association of pretreatment chest CT abnormalities with trastuzumab deruxtecan–associated pneumonitis.

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Background: Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate approved for HER2+ metastatic breast cancer (MBC) and HER2-low (IHC 1+ or 2+ with FISH-) MBC . Pneumonitis with T-DXd has been observed in 13.6% of patients (pts) on DESTINY-Breast 01 (including 2.2% fatal events) and 12.1% in pts on DESTINY-BREAST 04 (including 0.8% fatal events). There is an unmet need to determine if pts with baseline lung abnormalities are at increased risk for development of pneumonitis from T-DXd. **Methods:** This retrospective cohort study included all pts treated with T-DXd for MBC at an academic institution from 1/2020 to 2/2023 for more than 1 cycle (>21 days). Outcomes were evaluated from treatment initiation until 2/1/2023. Two board-certified radiologists blinded to outcomes reviewed staging chest CTs performed before initiating T-DXd and graded each scan on 16 parenchymal abnormalities, including presence of interstitial lung abnormalities (ILA). Pneumonitis was retrospectively adjudicated by an independent oncologist using chart review and graded according to CTCAE v5.0 and compared to the treating physician's assessment. The difference of proportions was analyzed with the Pearson Chi-Square test. Significance was declared at the 0.05 type I error threshold. **Results:** A total of 68 pts (median age 57.3 years) were included (30 = HER2+, 24 = HR+/HER2 low, 14 = TNBC/HER2 low). By independent assessment, 16 pts (23.5%) had grade 1 pneumonitis and 3 pts (4.4%) grade 2 pneumonitis. Median time from treatment initiation to pneumonitis was 83 days (range 35-266). By treating physician assessment, 5 pts (7.4%) developed grade 1 pneumonitis and 3 pts (4.4%) developed grade 2 pneumonitis. 16 of 68 pts (23.5%) had baseline ILA and 62 pts (91.2%) had at least one other parenchymal abnormality. As assessed by an independent oncologist, of pts with baseline ILA (N = 16), 12.5% developed T-DXd related pneumonitis, compared to 32.7% of pts without pre-existing ILA (N=52), p=0.16. There was no statistical difference in T-DXd related pneumonitis assessed by treating physician between pts with baseline ILA (2/16 patients, 12.5%) compared to pts without baseline ILA (7/52 pts, 13.5%), p=0.68. **Conclusions:** In this study, presence of baseline ILA was not associated with subsequent pneumonitis from T-DXd. Notably, the rate of independently assessed pneumonitis was higher than treatment-attributed pneumonitis as defined by the treating physician. Further research is needed to validate these findings and define predictors of treatment-associated pneumonitis. Research Sponsor: U.S. National Institutes of Health.

Rate of pretreatment abnormalities on CT chest in pts with MBC prior to treatment with T-DXd.

Finding	Patients meeting criteria (Total N=68)
Interstitial lung abnormalities	16 (23.5%)
Radiation changes	48 (70.5%)
Bronchial wall thickening	55 (80.1%)
Emphysema	9 (13.2%)
Infectious or inflammatory ground-glass opacities	15 (22.1%)

1107 **Poster Session**

Pilot study of a micro-organosphere drug screen platform to lead care in advanced breast cancer (MODEL-ABC).

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Background: ASCO guidelines suggest using single agent chemotherapy for patients with advanced breast cancer (ABC). Single agent chemotherapy provides modest response rates in ABC, causing patients to be exposed to unnecessary toxicity without benefit. Thus, there is an unmet clinical need to develop a clinically applicable assay to guide treatment. We recently reported the use of MicroOrgano-Spheres (MOS), which are gel droplets that encapsulate tumor cells creating miniature avatars of a patient's tumor and are amenable to high throughput dispensing and drug studies. In our current study, we evaluated the feasibility of generating and dosing MOS from ABC samples as a novel drug screen platform that led to the development and enrollment of a precision oncology trial, known as MODEL-ABC. **Methods:** We first performed a proof-of-concept study on 21 samples from patients with ABC and generated MOS. Drug screens were then performed on these MOS across 7 standard of care (SOC) chemotherapies commonly prescribed for ABC. These data resulted in a platform for the MODEL-ABC study that enrolled patients with ABC of any ER, PR, or HER2 subtype who were eligible for single agent chemotherapy to determine the feasibility of using MOS to predict response to therapy. In this study, biopsies from lesions $\geq$ 2 cm were obtained as part of SOC to generate MOS and perform drug screens. The patient subsequently received single agent chemotherapy per physicians' choice with either carboplatin, capecitabine, paclitaxel, eribulin, liposomal doxorubicin, gemcitabine, or vinorelbine. MOS were treated using the same chemotherapy as the patient along with 1-3 alternative single agent chemotherapies. **Results:** We generated MOS from 19/21 samples (90% success rate) across several breast cancer subtypes. Dose response curves of MOS were successfully generated across the 7 chemotherapies with a mean turnaround time of 21$\pm$7 days validating the clinical applicability of MOS and leading to the MODEL-ABC trial. As of February 14, 2023, 4 of 15 patients have enrolled onto MODEL-ABC. All biopsies provided sufficient tissue for MOS generation, and drug screens were performed in 14-28 days across 2-4 chemotherapies. Two patients received capecitabine, one patient received eribulin, and one patient received paclitaxel. Full results of MODEL-ABC including correlation between MOS drug response and patient outcomes will be reported at the meeting. **Conclusions:** Our platform enables efficient establishment of MOS from ABC patient samples and allows for drug dosing studies to be performed in a clinically meaningful timeframe. Our preliminary data suggests it is feasible to obtain biopsies for MOS development and perform drug screens within 14 days. These findings provided the foundation for evaluating this technology as a potential ABC diagnostic tool and warrants further clinical development in ABC. Clinical trial information: NCT04655573. Research Sponsor: Xilis.

1108 **Poster Session**

Demographic and clinical characteristics of patients with metastatic breast cancer and leptomeningeal disease: A single center retrospective cohort study.

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Background: Patients (pts) with metastatic breast cancer (MBC) and leptomeningeal disease (LMD) have a poor prognosis with limited therapeutic options. It is critical to better understand the risk factors and natural history of this condition, including pts in a modern cohort. **Methods:** In this single center retrospective cohort study, we identified pts with radiographic and/or cytologic evidence of LMD who received care at the University of California San Francisco (UCSF) from 2000-2023. To identify pts, we used the UCSF Pathology Database, the UCSF Radiation Oncology Database, and EMERSE, a searchable copy of the medical record. We conducted chart review to identify demographic and clinical characteristics, treatment history, and overall survival (OS). **Results:** 106 pts with MBC and radiographic and/or cytologic evidence of LMD were identified. All but one pt was female (n=105; 99.1%); most pts were non-Hispanic (n=93, 87.7%) and white (n=74, 69.8%). Median age at the time of MBC diagnosis was 51.9 years; 25 pts (20%) had de novo metastatic disease. Most pts had invasive ductal carcinoma (n=71, 66.9%), with invasive lobular carcinoma making up 21.7% (n=23) of cases. Pts presented with the following BC subtypes: Hormone receptor (HR) positive, HER2 negative (n=50, 47.1%), HR+/HER2+ (n=19, 17.9%), HR-/HER2+ (n=9, 8.5%), and triple negative (TNBC; n=23, 21.7%). Most pts had brain metastasis (n=78, 73.6%) in addition to LMD. Median time from diagnosis of MBC to LMD was 17.6 months (0-101.2 months). Pts received a median of 3.0 lines of therapy prior to the diagnosis of LMD (range 0-11.0) and 1.0 lines after the diagnosis of LMD (range 0-4.0). Many pts received intrathecal (IT) therapy (n=42, 39.6%) and/or whole brain radiation therapy or spinal radiation (n=49, 46.2%). Median OS from the diagnosis of LMD to death was 3.3 months. There was no significant difference in median OS by subtype: HR+/HER2- 3.5 months, HER2+ 4.7 months, and TNBC 2.2 months (p=0.45). There was no significant difference in median OS by histology: ductal (3.3 months) vs. lobular (4.7 months) (p=0.56). Pts who received IT therapy survived longer than those not treated with IT therapy (4.7 vs. 2.5 months, p=0.01). There was no significant difference in median OS among pts diagnosed with LMD between 2000-2015 (2.9 months) vs. 2016-2023 (3.6 months) (p=0.74). **Conclusions:** This study represents one of the largest reported case series of pts with MBC and LMD, including a more modern cohort. There appeared to be an over-representation of pts with lobular cancer and those with de novo metastatic disease. Most pts had brain metastases in addition to LMD. Survival was short in all pts, particularly those who did not receive IT therapy. There was no significant difference in median OS in pts diagnosed with LMD from 2000-2015 vs. 2016-2023; this remains an area of unmet clinical need. Research Sponsor: None.

1109 **Poster Session**

Distribution and outcomes of HER2-low and HER2-zero metastatic breast cancer in Black and younger women.

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Background: Black and younger patients with breast cancer (BC) have higher mortality. This racial disparity has been attributed to different BC biology, access to care, and treatment. With the advent of new antibody-drug conjugates (ADC) for metastatic BC (MBC), "HER2-negative" has been subdivided into HER2-low (IHC 1+ or 2+/ISH-negative) and HER2-0 (IHC 0). Little is known about these subcategories among Black and younger women with MBC. **Methods:** Clinical characteristics, treatment, and outcomes of patients diagnosed with HER2-negative MBC between 2011-2022 and with follow-up through a progression-free survival event on first-line therapy (PFS1) were retrieved from the UNC Metastatic Breast Cancer Database; hormone receptor (HR) and HER2 categories were by clinical criteria from the pathology report. Analyses were limited to HER2-negative BC and stratified/controlled by HR status. Fisher's exact tests were used to compare HER2 status across race and age. The Kaplan Meier method and log-rank tests, as well as Cox proportional hazards models estimated PFS1. **Results:** The cohort included 772 MBC patients (56% HER2-low and 44% HER2-0), 22% Black women and 30% $<$ 50 years old at MBC diagnosis. There were no differences in proportion with HER2-low by race or age ($p>0.5$). Patients with HER2-low had better observed median PFS1 compared to HER2-0, however, most of these differences were non-significant: overall (HR+ 12.2 vs 9.8m, p=0.11, HR- 4.3 v 3.3m, p=0.29) and within race and age categories (see table). In Cox modeling, Black women had worse PFS1 (p=0.03), that was no longer apparent after adjusting for HR status (p=0.1), there was no difference by age. Patients with HER2-0 had worse PFS1 (p=0.0005), which remained after adjusting for HR status (p=0.05). In a multivariable model comparing HER2-0 to HER2-low, adjusting for race and HR status, PFS1 remained shorter in the HER2-0 group (hazard ratio: 0.84, CI 0.692 – 1.015, p=0.07). Among those treated with uniform first-line therapy, better PFS1 was observed in HER2-low disease. This included 137 HR+ MBC treated with ET + CDK4/6i (mPFS1 14.3 v 10.3m, p=0.33) and 170 HR- MBC treated with chemotherapy (mPFS1 4.0 v 3.1m, p=0.22) with no variation by race or age. **Conclusions:** Within HER2-negative MBC, distribution of HER2-low and HER2-0 cancers does not differ by race and age. The clinical benefit of first-line therapy is strongly driven by HR status regardless of race and age, and is greater in HER2-low cancers although this cohort did not include HER2-directed ADCs. Research Sponsor: None.

Median PFS (in months) and 95% CIs.

	HR-positive			HR-negative		
	HER2-0	HER2-low	p-value	HER2-0	HER2-low	p-value
<50	6.2 (3.4-13.5)	13.5 (7.3-19.2)	0.36	2.9 (2.1-4.22)	4.0 (2.0-6.0)	0.31
≥50	10.3 (7.2-15.3)	12.2 (9.2-14.9)	0.23	3.9 (2.0-4.6)	4.3 (2.6-6.1)	0.65
Black	13.5 (3.4-22.3)	11.2 (6.9-15.4)	0.70	2.9 (1.6-4.5)	3.0 (1.7-5.2)	0.95
Non-Black	9.5 (6.8-12.5)	12.7 (9.4-15.5)	0.04	3.9 (2.6-5.4)	4.3 (2.6-7.5)	0.26

Imbalance in treatment discontinuation without progression between experimental and control arms among randomized trials in advanced breast cancer.

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Background: In Randomized Controlled Trials (RCT), treatment discontinuation (TD) can result in censoring. Imbalanced frequency of TD between arms could impact interpretation of results. Here, we quantify TD between the experimental and control arms among RCT supporting registration of drugs for advanced breast cancer. **Methods:** We identified RCT supporting US Food and Drug Administration's approval of drugs for advanced breast cancer between 2013 and 2023. We extracted data for the number of participants with TD for reasons other than disease progression (PD), death, or completion of treatment. Odds ratio (OR) for TD comparing experimental to control arms were determined for each trial. To assess progression-free survival (PFS) translation into an overall survival (OS) benefit, we calculated hazard ratio (HR) for PFS/OS. Then we assessed whether there was quantitative association between the OR for TD and the ratio of HR for PFS/OS. Quantitative significance was defined according to the criteria of Burnand. **Results:** Analysis included 22 RCT comprising 13853 participants and supporting approval for 18 distinct drugs. TD was reported in 2212 (16.0%) participants. Among these participants, the leading causes of TD were withdrawal of consent (27.8%), site termination (20.7%), adverse events (17.2%), and loss of follow-up (10.9%). There was a statistically significant imbalance in the experimental arm in 4 RCT (18%) (Table), which was observed for everolimus, ribociclib (with fulvestrant), alpelisib, and neratinib. The OR for TD showed quantitative, but not statistically significant negative association with the ratio of the HR for PFS/OS (Beta -0.393; p=0.18). **Conclusions:** TD without PD, death, or completion of treatment occurs in a substantial proportion of participants of several RCT supporting approval of drugs for advanced breast cancer. all the statistically significant imbalanced TD in the RCT were in experimental arms. Quantitative association between imbalanced TD and the ratio of HR for PFS/OS suggests imbalanced TD may impact ability to translate improvements in PFS to OS. Results of RCT with imbalance in TD should be interpreted cautiously. Research Sponsor: None.

OR for TD comparing experimental to control arms.

RCT	OR [95% CI]
OlympiAD	0.66 [0.24, 1.79]
ALTERNATIVE	0.72 [0.29, 1.77]
EMBRACA	0.73 [0.47, 1.13]
EMBRACE	0.74 [0.54, 1.02]
CONFIRM	0.76 [0.53,1.07]
SOPHIA	0.89 [0.54, 1.48]
CLEOPATRA	0.90 [0.59, 1.37]
MONARCH 3	0.90 [0.48, 1.72]
MONARCH 2	0.90 [0.53, 1.54]
MONALEESA-7	0.92 [0.57, 1.49]
PALOMA-3	1.10 [0.53, 2.30]
EMILIA	1.27 [0.98, 1.65]
DESTINY-Breast03	1.33 [0.86, 2.06]
PALOMA-2	1.34 [0.90, 1.99]
ASCENT	1.43 [0.95, 2.16]
NALA	1.45 [1.02, 2.07] *
MONALEESA-2	1.55 [0.98, 2.47]
HER2CLIMB	1.60 [0.58, 4.43]
KEYNOTE-355	1.77 [0.70, 4.43]
SOLAR-1	1.93 [1.19, 3.12] *
MONALEESA-3	1.94 [1.19, 3.13] *
BOLERO-2	4.04 [2.33, 7.00] *

*Significant p-value.

TPS1111 **Poster Session**

Randomised open-label phase II study of induction standard of care fulvestrant and CDK4/6 inhibition with addition of ipatasertib in metastatic ER+/HER2- breast cancer patients without circulating tumour (ct) DNA suppression (FAIM).

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Background: The combination of fulvestrant and one of the three approved CDK4/6 inhibitors (i) is the standard of care for patients with ER+/HER2 metastatic breast cancer progressing on first-line endocrine therapy, or relapsing on or within a year of completing adjuvant endocrine therapy. AKT inhibition combined with fulvestrant has recently demonstrated clinically important activity in patients with advanced ER+/HER2- breast cancer progressing on first-line CDK4/6i plus an AI. Monitoring ctDNA dynamics has potential utility as an early response evaluation tool: Lack of suppression of ctDNA at day 15 in patients treated with palbociclib and fulvestrant in the PALOMA-3 trial was predictive for shorter PFS. We designed FAIM to establish whether the addition of the AKT inhibitor, ipatasertib, improves PFS in patients with poor ctDNA suppression during cycle 1 of fulvestrant and CDK4/6i.
Methods: FAIM is a phase 2 multi-centre, randomised, open-label superiority trial in patients with ER+/HER2- advanced breast cancer, recruiting at centres in the UK. Patients will undergo ctDNA testing at days 1 and 15 of cycle 1 fulvestrant and CDK4/6 inhibitor. Eligible patients must be aged $\geq$18, have ER+ ($\geq$1% or Allred score 3/8 or greater) and HER2- advanced breast cancer, measurable disease or assessable bone disease (RECIST 1.1), adequate organ function, fasting glucose $\leq$150mg/dL and HbA1c $\leq$7.5% and be eligible for NHS treatment with fulvestrant and CDK4/6i. Patients with diabetes requiring insulin, significant cardiac disease, a history of pneumonitis, or prior exposure to CDK4/6i are excluded. The FoundationOne Liquid CDx assay will be used for ctDNA analysis, a pan-cancer, tumour-agnostic liquid biopsy test that uses error-corrected next-generation sequencing. Patients with poor ctDNA suppression at day 15 will be eligible for the randomised (minimisation) study. Up to 483 patients starting fulvestrant andCDK4/6i will enroll for ctDNA screening to allow 174 patients to enter the randomised study. The primary endpoint of the study is to compare PFS in patients randomised to palbociclib/fulvestrant +/- ipatasertib. Secondary endpoints include safety, overall survival and overall response rate in all randomised patients and PFS in the sub-group of patients with alterations in the PIK3CA/AKT1/PTEN pathway. One hundred patients with ctDNA suppression at day 15, and up to 50 patients with no detectable ctDNA at day 1, will form additional control groups for exploratory outcome comparison to patients with poor ctDNA suppression. Enrolment began in December 2022 and is anticipated to continue for 2 years (NCT04920708). Clinical trial information: NCT04920708. Research Sponsor: Roche; Pfizer.

TPS1112 **Poster Session**

Phase IIa study of αDC1 vaccines targeting HER2/HER3 combined with pembrolizumab in patients with asymptomatic brain metastasis from triple negative breast cancer or HER2$^+$ breast cancer.

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Background: Brain metastases develop in up to 50% patients (pts) with metastatic triple negative breast cancer (TNBC) and HER2$^+$ BC, constituting an increasing source of morbidity and mortality. HER3, overexpressed in triple negative and HER2$^+$ brain metastatic breast cancer (BMBC), is a resistance factor to HER2-targeted therapies and a driver of CNS metastasis. Disease progression is associated with loss of anti-HER2 and anti-HER3 immunity. Previously, we have demonstrated that glioma-specific peptide-loaded αDC1 which produce CXCL9, CXCL10, CXCL11, CCL5, the chemokines which attract CXCR3- and CCR5- expressing cytotoxic T-lymphocytes (CTLs) and T-helper 1 (Th1) cells, induce clinical responses and long-term disease stabilization in pts with aggressive recurrent primary brain tumors (Okada et al. JCO 2011. PMID: 21149657). We hypothesized that anti-HER2/3-loaded αDC1 in combination with PD1 blockade will result in strong Th1/CTL response against HER2/3 epitopes (Basu A et al. Cancer Immunol Res. 2022 PMID: 34785506), being effective against brain lesions and systemic disease. **Methods:** This is a phase II single-arm, non-randomized multicenter study (NCT04348747). Eligibility includes pts with triple negative and HER2$^+$ BMBC ≥18 years, ECOG PS ≤1, normal marrow and organ function with asymptomatic untreated brain metastases ≥ 5 mm who will receive αDC1 q3 weeks x 3 along with pembrolizumab every 3 weeks. Thereafter, αDC1 booster doses (if available) would be administered every 3 months until disease progression, intolerable side effects or withdrawal from study, up to 24 months. Baseline and 9-week post-αDC1 peripheral biopsies (non-CNS) are required for six pts. 1 of the planned 21 pts have been enrolled and is undergoing treatment. Primary endpoint is CNS response rate (RR) by RANO-BM criteria. If no CNS response is observed after 12 pts, study will be terminated. If ≥ 1 response observed, then 9 more pts will be enrolled, for a total of 21 pts. If ≥ 3 CR are observed, the proposed therapy will be considered as promising for further evaluation. Secondary endpoints include non-CNS RR per RECIST v1.1, median CNS, non-CNS and overall progression-free survival, overall survival and safety. Exploratory endpoints include changes in intratumoral biomarkers (CTLs, PDL1, chemokines) in pre- and post-treatment peripheral tumor biopsies and immune changes in the blood. Clinical trial information: NCT04348747. Research Sponsor: Department of Defense.

TPS1113 **Poster Session**

Phase I study of adoptive T cell therapy following HER2-pulsed dendritic cell vaccine and pepinemab/trastuzumab in patients with metastatic HER2-positive breast cancer (MBC).

Hyo S. Han, Ricardo L Costa, Hatem Hussein Soliman, Aixa Soyano, Hung T. Khong, Loretta S. Loftus, Kimberley T Lee, Avan J. Armaghani, Hien Liu, Jessica Malka, Frederick L. Locke, Qianxing Mo, Junmin Whiting, Lavakumar Karyampudi, Elizabeth E. Evans, Terrence Lee Fisher, Maurice Zauderer, Brian J. Czerniecki; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; H. Lee Moffitt Cancer Center, Tampa, FL; Vaccinex, Inc., Rochester, NY

Background: Despite major improvement of overall survival of HER2+ MBC with effective HER2 targeted therapies, many patients experience significant toxicities and develop progressive disease during treatment. Therefore, new and more effective therapeutic options are needed. This novel approach will evaluate whether the combination of three immunotherapies in addition to trastuzumab: dendritic cell (DC) vaccination, anti-SEMA4D blocking antibody (pepinemab) and CD4+ T cell adoptive transfer can lead to improved outcomes for patients with MBC refractory to HER2-targeted agents. BC have been considered as immunologically cold which is attributed to immune evasion and suppression of host effector immune cells homing into tumor bed. Progressive loss of Th1 immunity against HER2 oncodriver correlates with poor prognosis. HER2 peptide pulsed type I dendritic cells (HER2-DC1) restored anti-HER2 CD4+ Th1 immune response and improved pathologic complete response (pCR) in HER2+ BC. Antibodies to SEMA4D have been shown to modulate the TME by increasing effector cell infiltration and reducing immunosuppression. In preclinical studies, treatment with anti-SEMA4D and HER2-DC1 in mice bearing established HER2+ tumors improved DC homing, expansion of CD4+ T cells, and complete tumor regression, compared to treatment with anti-SEMA4D or HER2-DC1 alone. Further, subsequent expansion and adoptive transfer of CD4+ T cells induced synergistic anti-tumor activity by activating CD8+ T mediated cytotoxicity. Pepinemab was well-tolerated and showed signs of anti-tumor activity in in immunotherapy-resistant and PD-L1 negative/low non-small cell lung cancer patients when combined with checkpoint inhibitor (avelumab). **Methods:** This open label Phase 1 study is enrolling up to 28 patients with HER2+ MBC. Patients will be treated with 6 weekly injections of dendritic cell (DC1) vaccines in combination with trastuzumab and pepinemab. We hypothesize these therapies may elicit CD4+ HER2-specific T cell responses. HER2-specific T cells will be expanded ex vivo and subsequently infused to patients following lymphodepletion with cyclophosphamide. Trastuzumab and pepinemab will be given as maintenance in addition to booster DC1 vaccines. Patients (ECOG 0,1) must have had disease progression while on trastuzumab for the treatment of HER2+ MBC and received no more than 3 lines of chemotherapy in the setting of metastatic disease. Dose escalation will consist of 3-6 patients each with increasing amounts of transferred CD4+ T cells, followed by dose expansion of 10 patients at the MTD. The primary objective is safety and tolerability; secondary objectives will include evaluation of T cell immunity and immune subsets, efficacy, PK/PD/ADA of pepinemab, and biomarker assessments. Clinical trial information: NCT05378464. Research Sponsor: Moffitt Cancer Center Breast Cancer Funding; Bankhead and Coley Cancer Research Grant.

TPS1114 **Poster Session**

A phase 1, first-in-human, open label, escalation and expansion study of ORM-5029, a highly potent GSPT1 degrader targeting HER2, in patients with HER2-expressing advanced solid tumors.

Sara A. Hurvitz, Erika P. Hamilton, Alexander I. Spira, Paula R Pohlmann, Antonio Giordano, Katherine Clifton, Barry Douglas Anderson, Sujoy Dutta, Umesh Mangipudi, Shikha Saini, James Palacino, Tina Karunaratne, Dennise Greensmith, Olaf Christensen, Sharon Wilks; Division of Hematology/Oncology, David Geffen School of Medicine at the University of California Los Angeles/ Jonsson Comprehensive Cancer Center, Los Angeles, CA; Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN; NEXT Oncology - Virginia Cancer Specialists, Fairfax, VA; University of Texas MD Anderson Cancer Center, Houston, TX; Dana-Farber Cancer Institute, Boston, MA; Washington University School of Medicine, St. Louis, MO; Theradex Oncology, Princeton, NJ; Orum Therapeutics, Cambridge, MA; NEXT Oncology, San Antonio, TX

Background: Targeted protein degradation (TPD) molecules have expanded the therapeutic options through their catalytic mechanism of action (MOA) and ability to degrade "undruggable" proteins. To increase the efficacy versus tolerability window of protein degradation and improve drug delivery, ORM-5029 uses a Dual-Precision TPD (TPD^2) approach combining the catalytic mechanism of TPDs with the precision of tumor-targeting therapeutic antibodies. ORM-5029 is a first-in-class human epidermal growth factor receptor 2 (HER2)-targeted antibody-drug conjugate (ADC) comprised of SMol006, a highly potent GSPT1 degrader, conjugated to pertuzumab, a clinically validated antibody. HER2 is overexpressed in cancers such as breast, ovarian and gastric, and associated with early-onset aggressive disease. ORM-5029 is in development for treatment of HER2-expressing solid tumors. The MOA is mediated by targeted uptake of the ADC, release of the TPD payload, and cell death by GSPT1 degradation. ORM-5029 showed robust *in vitro* and *in vivo* efficacy in multiple HER2-expressing models with comparable activity to trastuzumab deruxtecan and strong activity in trastuzumab emtansine-refractory models. **Methods:** This phase 1 first-in-human study evaluates the safety, tolerability, and efficacy of ORM-5029 administered by intravenous infusion in patients (pts) with HER2-expressing advanced solid tumors (NCT05511844). The escalation, guided by the Bayesian Optimal Interval design, explores cohorts of ORM-5029 to identify the maximum tolerated dose (MTD) and/or expansion dose level (EDL). Each cohort will enroll ≥3 breast cancer pts with at least HER2 1+ (HER2 low) or greater by immunohistochemistry or positive by *in situ* hybridization. Expansion cohort A (HER2+ breast cancer) may enroll in parallel to escalation evaluating doses showing pharmacodynamic activity or efficacy. Up to 10 pts may be enrolled at each dose explored in cohort A. Enrollment into expansion cohort B (up to 21 pts) and cohort C (up to 22 pts) will begin once the EDL has been determined to further assess the safety, tolerability and efficacy of ORM-5029 using a Simon's optimal 2-stage design. Cohort B will enroll pts with HER2+ breast cancer refractory or intolerant to standard treatment after ≥2 HER2 therapies in the metastatic setting. Cohort C will enroll pts with advanced solid tumors that are refractory or intolerable to standard treatment or for which no standard treatment is available, including HER2+ gastric or gastroesophageal junction adenocarcinoma or tumors with HER2 expression, amplification or mutations (e.g., colorectal, bile duct, ovarian, bladder, non-small cell lung). Study enrollment began in October 2022 in the United States. Escalation cohort 1 was completed without DLT; enrollment in cohort 2 began as of December 2022. Clinical trial information: NCT05511844. Research Sponsor: Orum Therapeutics USA, Inc.

TPS1115 **Poster Session**

HER2CLIMB-05: Phase 3 study of tucatinib or placebo in combination with trastuzumab and pertuzumab as maintenance therapy for HER2+ metastatic breast cancer.

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Background: The current first-line (1L) standard of care (SOC) for human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (MBC) is trastuzumab (T) plus pertuzumab (P) and a taxane. Despite advances in 1L SOC, most patients progress during maintenance therapy with T + P. Tucatinib is a tyrosine kinase inhibitor (TKI) approved in combination with T and capecitabine for adults with HER2+ MBC, with and without brain metastases (BM). In HER2CLIMB, the addition of tucatinib significantly prolonged progression-free survival (PFS) and overall survival (OS) in patients with HER2+ MBC and was well tolerated. Adding tucatinib also reduced the risk of disease progression or death in patients with untreated and/or active BM (Murthy et al. 2020, Curigliano et al. 2021). HER2CLIMB-05 investigates whether adding tucatinib to 1L SOC as maintenance therapy will extend PFS while maintaining quality of life (QOL). **Methods:** HER2CLIMB-05 (NCT05132582) is a phase 3, randomized, double-blind study evaluating tucatinib plus T + P as maintenance therapy for HER2+ MBC. Approximately 650 patients will be enrolled. Eligible patients will have advanced HER2+ disease, no progression on 4–8 cycles of prior 1L SOC, Eastern Cooperative Oncology Group Performance Status of 0 or 1, and no or asymptomatic BM. Exclusion criteria include prior treatment with anti-HER2 and/or anti-epidermal growth factor receptor TKI (prior SOC for early BC is permitted) or inability to undergo contrast magnetic resonance imaging of the brain. Patients will be randomized 1:1 to receive either tucatinib or placebo twice daily, with T + P once every 21 days. Patients with hormone receptor-positive disease may receive endocrine therapy. The primary endpoint is investigator-assessed PFS. Secondary endpoints include OS (key endpoint), PFS by Blinded Independent Central Review (BICR), time to deterioration of health-related QOL, central nervous system PFS, safety, and pharmacokinetic (PK) parameters. PFS and OS will be compared using a 2-sided stratified log-rank test between treatment groups. Time-to-event endpoints will be summarized using the Kaplan–Meier method. PK and safety data will be summarized using descriptive statistics. Enrollment is ongoing in the US, Canada, Brazil, APAC and EU countries with additional sites planned. Clinical trial information: NCT05132582. Research Sponsor: Seagen, Inc.

TPS1116 **Poster Session**

UCLA B-13: A phase 1b trial evaluating the safety of ribociclib, tucatinib, and trastuzumab in patients with metastatic, HER2+ breast cancer and a multicenter, randomized, open-label, phase 2 study of preoperative treatment with ribociclib, trastuzumab, tucatinib, with or without fulvestrant versus docetaxel, carboplatin, trastuzumab, and pertuzumab in HR+/HR-, HER2+ breast cancer.

Nicholas Patrick McAndrew, Sara A. Hurvitz, Merry L. Tetef, Christine Kivork, Larissa Ikenouye, Dennis J. Slamon; David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA

Background: Overexpression of the HER2 protein is an important prognostic and predictive biomarker in about 20% of breast cancers, and while trastuzumab-based regimens are still considered standard of care in the early and metastatic settings, these regimens require chemotherapy co-administration. Pre-clinical mouse models suggest that a tucatinib/CDK 4/6 inhibitor combination regimen may be equally effective as standard regimens. Thus, finding more effective/tolerable therapies for this disease remains an area of unmet need. This randomized, open label, phase II clinical trial will explore the safety and efficacy of two novel, chemotherapy free combination drug regimens, given neoadjuvantly, in patients with anatomic stage I-III, HER2+ breast cancer. **Methods:** Phase 1b dose escalation trial: To establish the safety profile of the combination of ribociclib and tucatinib, an initial dose-finding phase 1b trial will be performed in patients with metastatic HER2+ breast cancer before moving into the larger phase 2 trial. 3-6 patients will be assigned sequentially to groups of increasing doses of ribociclib (200mg-600 mg) with fixed doses of tucatinib (300mg) and trastuzumab (SOC dosing) for a total of four 28-day cycles. The recommended phase 2 dose will be established when 6 patients have been treated at the highest dose level cohort. As of January 2023, 1 participant has been enrolled in dose level 1. Phase 2 neoadjuvant trial: Following MTD determination and approval from regulatory boards and funding partners, a total of 100 patients will be enrolled in the phase 2 portion of the study. Enrollment will be stratified by hormone receptor status. Patients will be randomized 1:1 (25 in each group) to receive six cycles of one of the following regimens: ribociclib/trastuzumab/tucatinib/+/- fulvestrant (28 day cycles) or docetaxel/carboplatin/trastuzumab/pertuzumab (SOC, 21 day cycles), preceded by one run-in cycle of trastuzumab/pertuzumab. To assess for changes in predictive molecular biomarkers, biopsies pre-and-post cycle 1 will be planned in all arms. Early imaging response assessments in the experimental arms will be planned after 2 cycles. Other endpoints include safety, changes in Ki67 expression, RCBi, biomarker analysis, and health-related quality of life. Clinical trial information: NCT05319873. Research Sponsor: Novartis, Seagen Inc.

TPS1117 **Poster Session**

EPIK-B6: A phase 2, open-label, 2-part, multicenter study of alpelisib in combination with fulvestrant for men and postmenopausal women with PIK3CA mutation HR–positive, HER2-negative, advanced breast cancer, which progressed on/after aromatase inhibitor treatment in Japan.

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Background: The *PIK3CA* oncogene mutation, seen in ~40% of patients with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2-) advanced breast cancer (aBC), is associated with endocrine treatment resistance and shorter survival. Alpelisib, an α-selective PI3K inhibitor and degrader, was established as standard therapy in combination with fulvestrant for patients with HR+, HER2-, *PIK3CA*-mutated aBC following progression on/after endocrine-based regimen based on the phase 3 SOLAR-1 study. However, alpelisib is not yet approved in Japan. In the SOLAR-1 study, a high percentage of Japanese patients experienced dose reductions/interruptions (78.5% vs 84.4%), and/or discontinuation (56.3% vs 25.0%) of alpelisib in early stages compared with overall population, due to adverse events such as rash and hyperglycemia. Thus, it is difficult to assess the consistency of the benefit of alpelisib + fulvestrant in Japanese patients as compared to overall population due to the short duration of alpelisib exposure and low-dose intensity. The EPIK-B6 study aims to determine the recommended dose (RD) of alpelisib in Japanese patients as well as assess the efficacy and safety of alpelisib + fulvestrant in Japanese men and postmenopausal women with HR+, HER2-, *PIK3CA*-mutated aBC, which progressed while on/after aromatase inhibitor treatment, prior/post CDK 4/6i use. **Methods:** The EPIK-B6 study is designed as a phase 2, open-labelled, 2-part, multicenter study. Part 1 is to determine RD of alpelisib to be used in part 2. Part 2 is designed to assess the efficacy and safety of alpelisib (RD starting on cycle 1 day 1 [C1D1]) + fulvestrant (500 mg on C1D1 and C1D15, and D1 of subsequent cycles) after completion of part 1, in participants with/without prior CDK 4/6i use. Adult Japanese men or postmenopausal women with confirmed HR+, HER2-, *PIK3CA*-mutated aBC and $\geq$1 measurable lesion as per RECIST 1.1 criteria are eligible. Patients previously treated with fulvestrant, any PI3K, mTOR or AKT inhibitors are excluded. Use of prophylactic antihistamine is highly recommended for prevention of rash. The primary endpoint for part 2 is overall response rate based on assessments per RECIST 1.1. Secondary endpoints include progression free survival, overall survival, clinical benefit rate, duration of response, time to response, time to deterioration of ECOG performance status, safety, tolerability, and pharmacokinetics. Part 1 has been completed, and recruitment for part 2 is ongoing until August 2023 approximately. As of December 2022, 9 and 8 patients are enrolled in part 1 and 2, respectively. The study will include approximately 50 participants. Primary Analysis is planned in 2024 after at least 6 months follow-up period. Clinical trial information: NCT04524000. Research Sponsor: Novartis.

TPS1118 **Poster Session**

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

Sara A. Hurvitz, Fabrice Andre, Massimo Cristofanilli, Giuseppe Curigliano, Antonio Giordano, Hyo S. Han, Miguel Martin, Barbara Pistilli, Hope S. Rugo, Robert Wesolowski, Samuel Suzuki, Sarah Mutka, Igor Gorbatchevsky, Sibylle Loibl; David Geffen School of Medicine; University of California, Los Angeles; Jonsson Comprehensive Cancer Center, Santa Monica, CA; Gustave Roussy Institute, Villejuif, France; Weill Cornell Medicine, New York, NY; European Institute of Oncology, IRCCS and University of Milano, Milan, Italy; Dana-Farber Cancer Institute, Boston, MA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Servicio Oncología Médica, Hospital General Universitario Gregorio Marañon, IiSGM, Universidad Complutense, Ciberonc, GEICAM, Madrid, Spain; Breast Cancer Unit, Gustave Roussy, Villejuif, France; University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Ohio State University Comprehensive Cancer Center, Columbus, OH; Celcuity, Inc., Minneapolis, MN; German Breast Group, Neu-Isenburg, Germany; Centre for Haematology and Oncology Bethanien, Frankfurt, Germany

Background: Patients who receive frontline CDK4/6 inhibitor (CDK4/6i) therapy eventually experience disease progression. Resistance to CDK4/6i is likely a transient adaptive mechanism that may be reversed by inhibition of the PI3K/mTOR pathway. Thus, combination of CDK4/6i and PI3K/mTORi after disease progression on CDK4/6i could restore sensitivity to CDK4/6i and prevent activation of the PI3K/mTOR pathway. This hypothesis was evaluated in a Phase 1b study (Layman SABCS 2021) of gedatolisib (geda), a potent inhibitor of PI3K and mTOR. Subjects with HR+/HER2- ABC with prior CDK4/6i received geda (180 mg IV weekly for 3 weeks, then one week off) with palbociclib (palbo) and fulvestrant (FUL). Median PFS was 12.9 months with 63% overall response rate. Efficacy was observed regardless of *PIK3CA* mutation status (Wesolowski SABCS 2022). Geda was well tolerated, with few discontinuations due to treatment-related adverse events (4%). The most common AE was stomatitis; hyperglycemia of any grade occurred in 26% of patients. This preliminary data, dosing schedule, and study population characteristics form the basis for the Phase 3 trial, VIKTORIA-1 (NCT05501886).
Methods: This Phase 3 multinational clinical trial will evaluate geda and FULwith or without palboin patients with HR+/HER2- ABC previously treated with any CDK4/6i in combination with a non-steroidal aromatase inhibitor (AI) therapy. Those without tumor *PIK3CA* mutations will be assigned to Study 1 (n=351) and randomized to Arm A (geda, palbo, and FUL), Arm B (geda and FUL), or Arm C (FUL). Those with *PIK3CA* mutations will be assigned to Study 2 (n=350) and randomized to Arm D (geda, palbo, and FUL), Arm E (alpelisib and FUL), or Arm F (geda and FUL). Key eligibility criteria include adults with confirmed metastatic or locally advanced breast cancer, any menopausal status, radiologically evaluable disease, and prior CDK4/6i treatment in combination with a non-steroidal AI. Prior hormonal therapy, including SERDs, is allowed. Key exclusion criteria include prior treatment with a PI3K, Akt, or mTOR inhibitor, prior treatment with chemotherapy for advanced disease, more than two lines of prior endocrine therapy, bone only disease with no soft tissue components, active CNS metastases, and type 1 diabetes or uncontrolled type 2 diabetes. The primary endpoint is PFS assessed by blinded independent central review per RECIST v1.1. Secondary endpoints included overall survival, safety and tolerability, ORR, duration of response, time to response, CBR, quality of life, and pharmacokinetics. The trial is open for enrollment. Clinical trial information: NCT05501886. Research Sponsor: Celcuity, Inc.

TPS1119 **Poster Session**

evERA Breast Cancer (BC): Phase III study of giredestrant + everolimus vs exemestane + everolimus in patients (pts) with estrogen receptor-positive, HER2-negative locally advanced or metastatic BC (ER+, HER2– LA/mBC).

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Background: Endocrine therapy (ET) + a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is the standard of care in pts with ER+, HER2– mBC in the first-line setting. Fulvestrant ± a CDK4/6i, and everolimus + exemestane are the current approved second-line regimens. However, therapeutic resistance to some ETs, such as aromatase inhibitors, can arise from *ESR1* mutations (m) driving estrogen-independent transcription and proliferation. Current post-CDK4/6i treatment options are suboptimal. New therapy options are therefore needed to reduce this risk and to improve outcomes, tolerability, quality of life, and adherence to treatment. Giredestrant is a highly potent, nonsteroidal oral selective ER antagonist and degrader (SERD) that achieves robust ER occupancy and is active regardless of *ESR1*-mut status. While Phase I SERD combination data in the post-CDK4/6i setting are encouraging, there are no randomized combination data. Combining giredestrant and everolimus may improve outcomes after CDK4/6is and in pts with *ESR1*m tumors. **Methods:** evERA BC (NCT05306340), a Phase III, global, randomized, open-label, multicenter study will evaluate the efficacy and safety of giredestrant + everolimus vs. exemestane + everolimus in pts with ER+, HER2– LA/mBC who had previous treatment with a CDK4/6i and ET in the LA/mBC or adjuvant setting. Pts will be randomized to either giredestrant (30 mg) + everolimus (10 mg) by mouth (PO) every day (QD), or exemestane (25 mg) + everolimus (10 mg) PO QD. Pts will receive treatment until disease progression or unacceptable toxicity. Pts will use a dexamethasone mouth rinse 4 times QD for 8 weeks concurrently with study treatment. Eligibility: Female/male pts ≥ 18 years with ER+, HER2– LA/mBC and disease progression ≥ 6 months (mo) after initiating ET + CDK4/6i in the LA/mBC setting (and ≥ 4 mo on most recent ET, if ET + CDK4/6i was not the most recent therapy received), or relapsed either while taking or within 12 mo of exposure to combination adjuvant ET (≥ 12 mo) + CDK4/6i (≥ 6 mo), and available blood sample for circulating tumor DNA central testing for *ESR1*m status. Men and pre-/perimenopausal women will receive a LHRH. Co-primary endpoints: Investigator-assessed progression-free survival (per RECIST v1.1) in the intent-to-treat and *ESR1*m populations. Secondary endpoints: Overall survival; objective response rate; duration of response; clinical benefit rate; pt-reported outcomes; safety; pharmacokinetics. Co-primary endpoint analyses will use a two-sided stratified log-rank test at an overall 0.05 significance level. An independent data monitoring committee will be in place for safety. Target enrollment is 320 pts, and this study is currently recruiting. Encore from SABCS 2022 (OT2-01-07). Clinical trial information: NCT05306340. Research Sponsor: F. Hoffmann-La Roche Ltd.

TPS1120 **Poster Session**

AIPAC-003: A randomized, double-blind, placebo-controlled phase 3 trial testing eftilagimod alpha (soluble LAG-3) in patients with HER2-neg/low metastatic breast cancer receiving paclitaxel, following an open-label dose optimization.

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Background: Eftilagimod alpha (efti), a soluble LAG-3 protein, acts as an MHC class II agonist that enhances immunity by mediating antigen presenting cell and CD8 T-cell activation. Data from a randomized, phase 2b trial of efti plus paclitaxel compared to placebo plus paclitaxel in patients (pts) with HR+ HER2– metastatic breast cancer (MBC) (AIPAC; NCT02614833) showed sustained pharmacodynamic activity that was linked to improved overall survival (OS) in the efti arm. AIPAC-003 is a randomized, double-blind, placebo-controlled phase 3 trial testing efti plus paclitaxel in HER2-neg/low MBC pts, including an initial open-label dose optimization lead-in (DOL) component to determine the optimal biological dose (OBD) of efti in this combination. **Methods:** Enrolment for the DOL will begin in March 2023 in max. 66 pts. Primary endpoints (EP) in the DOL include safety and tolerability of 90 mg vs 30 mg efti and defining the OBD of efti in combination with weekly paclitaxel. Determination of the OBD will be based on the totality of safety and tolerability data together with overall response rate (ORR) and pharmacodynamic marker (CD8+ T cells, absolute lymphocyte count) data. In the Phase 3 component approx. 771 pts are randomized to receive either paclitaxel + efti or paclitaxel + placebo in a double-blinded fashion. The primary EP for the proposed Phase 3 is OS. Key secondary EPs include progression free survival and ORR by RECIST 1.1, quality of life and safety. Pts will receive paclitaxel (80 mg/m^2 I.V. on D1, 8 and 15 in a 4-week cycle), followed by efti or placebo (DOL: 30 or 90 mg efti; Phase 3: OBD of efti or placebo) S.C. on D1 and 15 in a 4-week cycle for up to 12 months. Key inclusion criteria: Pts with either a) HR+ and HER2-neg/low and endocrine therapy-resistant MBC or b) TNBC not eligible for anti-PD-1-based therapy. Pts must have measurable disease, ECOG PS 0-1 and no prior chemo for metastatic disease. Research Sponsor: Immutep S.A.

TPS1121 **Poster Session**

TACTIVE-U: Phase 1b/2 umbrella study of ARV-471, a proteolysis targeting chimera (PROTAC) estrogen receptor (ER) degrader, combined with other anticancer treatments in ER+ advanced or metastatic breast cancer.

Rachel M. Layman, Katarzyna Joanna Jerzak, John Frederick Hilton, Katherine Clifton, Baha Alkuzweny, Gary Mo, Olga Valota, Julia Perkins Smith, Sibyl Anderson, Cynthia X. Ma; University of Texas MD Anderson Cancer Center, Houston, TX; Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada; The Ottawa Hospital and University of Ottawa, Ottawa, ON, Canada; Washington University School of Medicine, St. Louis, MO; Pfizer, San Diego, CA; Pfizer, Inc., La Jolla, CA; Pfizer, Milano, MI, Italy; Pfizer, Inc., New York, NY; Arvinas Operations, Inc, New Haven, CT

Background: ARV-471, an oral PROTAC ER degrader, was well tolerated and showed evidence of clinical activity in a phase 1/2 study in heavily pretreated patients with ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer. The CDK4/6 inhibitors abemaciclib and ribociclib are approved in combination with endocrine therapy as first- and second-line treatment for ER+/HER2- advanced or metastatic breast cancer; abemaciclib is also approved as monotherapy and in combination with other agents in additional breast cancer settings. ARV-471 combined with abemaciclib or ribociclib showed evidence of synergistic interactions in ER+ breast cancer cells and greater tumor growth inhibition in a xenograft breast cancer model compared with fulvestrant in combination with these agents. Here we describe the first sub-studies of the open-label, phase 1b/2 TACTIVE-U umbrella study, which evaluate the safety and clinical activity of ARV-471 plus abemaciclib (sub-study A; NCT05548127) and ribociclib (sub-study B; NCT05573555) in patients with ER+/HER2- advanced or metastatic breast cancer. Future combination sub-studies will be included in TACTIVE-U. **Methods:** Patients eligible for sub-studies A and B are aged $\geq$18 years, have histologically or cytologically confirmed ER+/HER2- advanced or metastatic breast cancer not amenable to surgical resection with $\geq$1 measurable lesion by RECIST 1.1, and have received $\leq$2 lines of prior therapy for advanced or metastatic disease and 1 line of any CDK4/6 inhibitor–based regimen in any setting. In sub-studies A and B, patients will receive ARV-471 orally once daily (QD) continuously in a dose escalation/de-escalation approach. In sub-study A, abemaciclib will be given orally twice daily continuously, and in sub-study B, ribociclib will be given orally QD for 21 days followed by 7 days off treatment. For both sub-studies, the primary endpoint of the phase 1b portion is dose-limiting toxicities to determine the recommended phase 2 dose of ARV-471 in combination with abemaciclib or ribociclib. Secondary endpoints of phase 1b are antitumor activity (overall response rate [ORR], clinical benefit rate [CBR], and duration of response [DOR]), progression free survival (PFS), safety (type, frequency, and severity of adverse events and laboratory abnormalities), and plasma concentrations of study drugs. Phase 2 further evaluates the antitumor activity of the combinations; the primary endpoint is ORR and secondary endpoints include antitumor activity (CBR and DOR), PFS, overall survival, safety, plasma concentration of study drugs, and changes in circulating tumor DNA. Clinical trial information: NCT05548127, NCT05573555. Research Sponsor: Arvinas Estrogen Receptor, Inc.

TPS1122 **Poster Session**

VERITAC-2: A global, randomized phase 3 study of ARV-471, a proteolysis targeting chimera (PROTAC) estrogen receptor (ER) degrader, vs fulvestrant in ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer.

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Background: ARV-471 is an oral PROTAC ER degrader that binds to and degrades wild-type ER and clinically relevant mutants. ARV-471 directly recruits the ubiquitin-proteasome system to degrade ER, whereas selective ER degraders (SERDs) indirectly cause ER degradation. In a first-in-human phase 1/2 study, ARV-471 monotherapy was well tolerated and showed clinical activity in heavily pretreated patients with ER+/HER2- advanced breast cancer. The phase 3 monotherapy dose (200 mg once daily [QD]) was chosen due to comparable efficacy and favorable tolerability relative to 500 mg QD and robust ER degradation in paired tumor biopsies. The randomized phase 3 VERITAC-2 study (NCT05654623) will compare efficacy and safety of ARV-471 vs the SERD fulvestrant in patients with ER+/HER2- advanced breast cancer after prior combination cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy and endocrine therapy (ET). **Methods:** Eligible patients (aged $\geq$18 years) have a confirmed diagnosis of ER+/HER2- locoregional recurrent or metastatic breast cancer not amenable to surgical resection or radiation; 1 prior line of combination CDK4/6 inhibitor therapy and ET; $\leq$1 additional line of ET; most recent ET given for $\geq$6 months before disease progression; and radiological disease progression during or after the last line of therapy. Prior chemotherapy in the locally advanced or metastatic setting and prior fulvestrant are not permitted. Patients (N~560) are randomized 1:1 to receive 200 mg ARV-471 orally QD continuously or fulvestrant intramuscularly on days 1 and 15 in the first 28-day cycle and on day 1 in subsequent cycles; patients are stratified by *ESR1* mutation status and presence of visceral disease. The primary endpoint, progression-free survival, will be assessed by blinded independent central review in the intention-to-treat population and the *ESR1* mutation sub-population. Secondary outcome measures include overall survival, antitumor activity (objective response rate, duration of response, and clinical benefit rate), safety, and quality of life assessments. Clinical trial information: NCT05654623. Research Sponsor: Arvinas Estrogen Receptor, Inc.

TPS1123 **Poster Session**

INAVO121: Phase III study of inavolisib (INAVO) + fulvestrant (FUL) vs. alpelisib (ALP) + FUL in patients (pts) with hormone receptor-positive, HER2-negative (HR+, HER2–) *PIK3CA*-mutated (mut) locally advanced or metastatic breast cancer (LA/mBC).

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Background: Standard-of-care (SoC) endocrine therapy (ET) for pts with HR+, HER2– LA/mBC was transformed by combinations with cyclin-dependent kinase 4/6 inhibitors (CDK4/6is); a CDK4/6i-based combination is approved in high-risk early BC. However, in most pts, mechanisms of resistance that emerge during or after treatment with a CDK4/6i and ET combination lead to relapse/disease progression. Dysregulating mutations in *PIK3CA,* occurring in ~40% of HR+, HER2– BCs, represent a common mechanism of resistance to CDK4/6is and ET combinations. ALP (a selective PI3Kα inhibitor; PI3Kαi) + FUL is approved for pts with HR+, HER2–, *PIK3CA*mut LA/mBC, but its widespread implementation in clinical practice has been challenging. As such, there is a significant need to develop PI3K$\alpha$is with a better therapeutic index. INAVO is a highly potent and selective PI3Kαi that also facilitates the degradation of mutated PI3Kα isoform. INAVO has demonstrated manageable safety/tolerability, alone and in combination with SoC treatments in HR+, HER2–, *PIK3CA*mut LA/mBC. Moreover, an ongoing Phase I trial showed that INAVO + FUL elicited encouraging preliminary antitumor activity in heavily pretreated pts, including a CDK4/6i-based regimen. **Methods:** INAVO121 (NCT05646862) is a Phase III, randomized, open-label study evaluating INAVO + FUL vs. ALP + FUL in pts with HR+, HER2–, *PIK3CA*mut LA/mBC (confirmed by circulating-tumor DNA or tumor tissue), who progressed during or after a CDK4/6i-based regimen with adequate hematologic and organ function. Up to two prior lines of systemic therapy in LA/mBC, including one line of chemotherapy are allowed. Pts are randomized 1:1 to receive INAVO (9 mg oral daily; PO QD) + FUL (500 mg intramuscularly on Days [D] 1 and 15 of Cycle [C] 1, then D1 of subsequent cycles), or ALP (300 mg PO QD) + FUL. Randomization is stratified by visceral disease (yes vs. no) and prior CDK4/6i therapy (adjuvant vs. metastatic setting). Pts will receive treatment until disease progression or unacceptable toxicity. The primary endpoint is progression-free survival (PFS) by blinded independent central review (BICR). Secondary endpoints include overall survival, BICR-objective response rate, BICR-best overall response, BICR-duration of response, BICR-clinical benefit rate, safety, tolerability, pt-reported outcomes, and pharmacokinetics. The study is open for enrollment, targeting 400 pts at ~200 sites globally. A stratified log-rank test at an overall 0.05 significance level (two-sided) will be used for the primary endpoint analysis. Median PFS will be estimated using Kaplan–Meier methodology. An independent data monitoring committee will be in place for safety and efficacy. Clinical trial information: NCT05646862. Research Sponsor: F. Hoffmann-La Roche Ltd.

TPS1124 **Poster Session**

CAPTOR-BC: Comprehensive analysis of spatial, temporal and molecular biomarkers predicting response and resistance to first-line treatment with ribociclib + ET in HR+, HER2- advanced breast cancer.

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Background: The combination of an oral CDK4/6 inhibitor with endocrine therapy (ET) has become the standard first-line therapy for women with advanced HR+ HER2- breast cancer. In this context, the broadest clinical trial data are available for ribociclib, a highly selective CDK4/6 inhibitor, with three phase III trials (MONALEESA-2, -3 and -7) consistently showing a significant overall survival benefit compared to ET monotherapy regardless of treatment line, menopausal status or combination partner. However, *de novo* or acquired resistance to CDK4/6 inhibitors does occur and biomarkers predicting treatment response or providing information on resistance mechanisms are only beginning to be understood. Comprehensive identification and validation of biomarkers before and during ribociclib therapy is needed to better understand mechanisms leading to disease progression, which will be the first step towards developing novel therapies and optimizing treatment sequences. **Methods:** CAPTOR-BC (NCT054552213) is a single-arm, open-label phase IV study evaluating the combination of ribociclib and ET according to SmPC in the first-line treatment of HR+ HER2- advanced breast cancer to identify and validate molecular and non-molecular biomarkers predictive of drug response and resistance. First patient first visit occurred in October 2022 and at least 1000 patients across more than 75 sites in Germany will be enrolled until October 2025. Progression-free survival (PFS) and overall survival (OS) at 12 months are the co-primary endpoints, quality of life (QoL) and toxicity are secondary endpoints. Exploratively, a comprehensive multi-omics biomarker discovery and validation program is integrated into the study: Besides tumor tissue, liquid biopsies profiling circulating tumor (ct)DNA, ctRNA, whole blood RNA, proteins from serum and plasma, and circulating immune cells will be evaluated before, during and after treatment or upon progression to determine correlations with PFS, OS, QoL and adverse events. Clinical trial information: NCT05452213. Research Sponsor: Institut fuer Frauengesundheit GmbH; Novartis.

TPS1125 **Poster Session**

Ribociclib (RIB) vs. palbociclib (PAL) in patients (pts) with hormone receptor-positive/HER2-negative/HER2-enriched (HR+/HER2-/HER2-E) advanced breast cancer (ABC): A head-to-head phase III study—HARMONIA SOLTI-2101/AFT-58.

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Background: RIB and PAL are CDK4/6 inhibitors with demonstrated efficacy in terms of progression-free survival (PFS) and similar tolerability in pts with HR+/HER2- ABC when combined with endocrine therapy (ET). Only RIB has demonstrated a consistent, statistically significant, and clinically meaningful overall survival (OS) benefit across the MONALEESA (ML) phase III trials, while PALOMA trials failed to achieve similar outcome. Given effective treatments (Tx) may change underlying tumor biology (TB), it is hypothesized that RIB changes TB, enabling a better response to subsequent therapy and thus improving OS. RNA-based intrinsic subtyping reflects differences in TB and has strong prognostic and predictive value in HR+/HER2- ABC. Non-Luminal subtypes, as HER2-E and basal-like (BL), are relatively endocrine-resistant and have poorer prognosis than luminal. Tumors can switch subtypes over time to a more aggressive and less endocrine-responsive biology, which may also be reversed by effective Tx. A retrospective analysis of pooled data from ML 2/3/7 trials showed that HER2-E tumors had surprising benefit from RIB, while BL tumors did not. Pre/clinical data and indirect comparisons suggest that RIB may outperform PAL in HER2-E. Thus, choosing pts with HER2-E tumors as a means of a well defined TB with relative endocrine resistance provides the right setup for HARMONIA study to explore likely differential re-sensitization to endocrine therapy with RIB vs. PAL and ultimately testing which CDK4/6i prepares best for continued response and OS benefit. In addition, HARMONIA explores the value of earlier Tx with chemotherapy (paclitaxel) + anti PD-1 (tislelizumab) in pts with BL tumors to leverage learnings from treating ET-insensitive triple-negative BC. **Methods:** This is an international, multicenter, randomized, open-label, phase III study, using prospective pre-selection based on TB in pts with HR+/HER2- ABC, with HER2-E tumors (main cohort) and with BL tumors (exploratory cohort). HER2-E cohort will randomized pts 1:1 to RIB+ET (letrozole or fulvestrant) or PAL+ET. As per recent protocol amendment, BL cohort pts will be treated with paclitaxel plus tislelizumab, an anti PD-1 monoclonal antibody, pts may be offered to try RIB + ET first, and will remain eligible for paclitaxel + tislelizumab upon progression. Primary endpoint (EP): PFS per RECIST v1.1. Secondary EP: OS, PFS2, clinical benefit rate, duration and time to response, quality of life, and exploratory EP, including subtype switching between primary and metastatic tumor, and after trial Tx. Interim and primary EP analysis will be performed after 224 and 310 PFS events are observed (~80% power using one-sided 5% α). HARMONIA will recruit in Spain (55 sites), Portugal (5), and US (35) within SOLTI & AFT network. Clinical trial information: NCT05207709. Research Sponsor: Novartis Pharma AG.

TPS1126 **Poster Session**

Harnessing olaparib, palbociclib, and endocrine therapy: A phase I/II trial of olaparib, palbociclib and fulvestrant in patients with BRCA mutation-associated, hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (HOPE).

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Background: Hormone receptor-positive (HR+) metastatic breast cancer (MBC) in patients (pts) with germline or somatic *BRCA1* or *BRCA2* (g/s*BRCA1/2*) mutations has dual drivers: hormone receptor signaling and homologous recombination deficiency. The PALOMA-3 trial showed superiority of fulvestrant (F) with palbociclib (P) compared to F alone. The OlympiAD trial showed the poly-ADP ribose polymerase inhibitor (PARPi) olaparib (O) to be superior to chemotherapy in *BRCA1/2*-associated MBC. However, treatment resistance inevitably develops; targeting dual therapeutic drivers concurrently may delay or circumvent resistance. O and P have overlapping hematologic toxicity and the safety of combined O, P and F is unknown. The tolerability of O + P is particularly relevant given the emergence of potentially less myelosuppressive PARPi. **Methods:** HOPE (NCT03685331) is a phase I/II trial to evaluate safety and efficacy of O, P and F in pts with g/s*BRCA1/2*-associated, HR+ MBC. Eligible pts have an ECOG performance status 0-1, measurable/evaluable breast cancer, any/no prior endocrine therapy, and 0-2 lines of chemotherapy for MBC. Prior platinum is allowed for curative intent if completed at least 12 months prior to MBC diagnosis, or for MBC if no progression during therapy. Prior PARPi and CDK4/6i are permitted on phase I, and are permitted during phase II if there was no progression on them. Treatment (28-day cycles) consists of: O orally twice daily continuously; F 500mg intramuscularly on day 1 of each cycle plus load; and P orally once daily on days 1-21. Phase I begins with a 28-day safety run-in of O and F alone. O and P doses are based on dose level (DL): DL 0 (starting level), O 300mg, P 75mg; DL 1, O 300mg, P 100mg; DL 2, O 300mg, P 125mg; DL-1, O 250mg, P 75mg and DL-2, O 200mg, P 75mg. For phase II, O and P will be dosed at MTD. Pts have tissue collection at baseline and peripheral blood cfDNA analysis at baseline, at progression, and at all scan timepoints (every 3 cycles). Phase I primary endpoint is MTD. A 3+3 dose escalation design is used with a 30% rate of dose limiting toxicity (DLT) deemed acceptable, and 6 patients treated at a dose for it to be declared MTD. A minimum of 2 and a maximum of 18 patients will be enrolled on the phase I. Phase II primary endpoint is PFS using Kaplan-Meier methods and secondary efficacy endpoints are objective response rate and 24-week clinical benefit rate. Phase II will evaluate 54 subjects to provide 80% power to detect an increase in PFS from 7 months with O monotherapy to 10 months. Exploratory objectives include examination of baseline tissue for PARPi predictive biomarkers and measures of tumor immunogenicity as well as serial serum evaluation for reversion mutations. Enrollment is ongoing. Clinical trial information: NCT03685331. Research Sponsor: AstraZeneca, Pfizer; Susan G. Komen Career Catalyst Award.

TPS1127 **Poster Session**

A phase 1b/2 dose escalation and expansion study of OP-1250 in combination with ribociclib or alpelisib in patients with advanced and/or metastatic estrogen receptor–positive (ER+)/HER2-negative (HER2-) breast cancer.

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Background: Therapies targeting the estrogen receptor (ER) are standard of care in the management of ER+/HER2- metastatic breast cancer (MBC) and when administered concurrently with cyclin-dependent kinase (CDK) inhibitors are the most effective first-line therapy. CDK 4/6 inhibitors plus endocrine therapy improve progression-free survival and, for some agents, overall survival for patients with MBC. However, most patients will acquire resistance, highlighting an unmet need for more effective endocrine options in ER+ disease. OP-1250 is a small molecule oral complete estrogen receptor antagonist (CERAN) and selective estrogen receptor degrader (SERD) that binds the ligand binding domain of ER and completely blocks ER-driven transcriptional activity. OP-1250 potently inactivates both wild-type and mutant forms of ER, the latter of which confers ligand independent activity as a mechanism of resistance to standard of care endocrine therapies. In preclinical studies, OP-1250 in combination with CDK4/6 inhibitors demonstrated synergistic activity in models of both wild-type ER and those with ESR1 (the gene that encodes ER) activating mutations, and in brain metastasis. OP-1250 is orally bioavailable with a favorable pharmacokinetic (PK) profile supportive of once-daily dosing, and a low probability of drug:drug interactions, making it an attractive agent for patients with ER+/HER2- MBC. **Methods:** The study (NCT05508906) is an open-label, multicenter, 2-part study of OP-1250 in combination with either the CDK4/6 inhibitor ribociclib or the PI3K inhibitor alpelisib for patients with MBC. Eligibility includes adults with evaluable (measurable or non-measurable) ER+/HER2- recurrent, locally advanced or MBC confirmed by histology/cytology, $\leq$2 prior hormonal regimens (prior CDK4/6 inhibitors allowed) and $\leq$ 1 prior line of chemotherapy. Patients in the alpelisib arm must have a PIK3CA mutation. A total of 30 patients will be enrolled in each arm. The dose escalation cohorts will evaluate the safety and PK of varied OP-1250 doses (30mg, 60mg, or 120mg) administered orally (PO) every day (QD) in combination with approved dosages of either ribociclib 600 mg PO QD or alpelisib 300 mg PO QD to identify the recommended phase 2 doses (RP2D). The dose expansion cohorts will assess additional safety and PK parameters and further explore the anti-tumor activity of OP-1250 in combination with ribociclib or alpelisib. Tolerability, safety and PK of OP-1250 in combination with ribociclib or alpelisib constitute the primary endpoints. Overall response rate, clinical benefit rate and duration of response are key secondary endpoints. Enrollment at approximately 20 sites in the United States and Australia is ongoing. Clinical trial information: NCT05508906. Research Sponsor: Olema Oncology; Novartis.

TPS1129 **Poster Session**

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

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Background: Alpelisib, a selective PI3K p110a inhibitor, was approved for breast cancer patients with PIK3CA mutations. An on-target toxicity of alpelisib is hyperglycemia and patients with baseline insulin resistance/elevated HbA1c are at greater risk of developing grade 3,4 hyperglycemia after receiving alpelisib. Restoring insulin sensitivity and reducing systemic insulin levels improved the efficacy of alpelisib in animal models of breast cancer. Evexomostat is a polymer-drug conjugate of a novel small molecule methionine aminopeptidase 2 (MetAP2) inhibitor. In normal mice, it reduced alpelisib-induced hyperglycemia/hyperinsulinemia and in an animal model of breast cancer synergized with alpelisib to regress tumor growth. In a Phase 1 trial, evexomostat improved insulin resistance in patients with elevated baseline insulin, reduced angiogenic factors in patients with elevated baseline levels, increased the insulin-sensitizing adipokine adiponectin and showed anti-metastatic effects in patients with advanced solid tumors. **Methods:** This is a phase 1b/2, open-label, single-arm pilot study (NCT05455619) in postmenopausal women with HR+, HER2- metastatic breast cancer with a PIK3CA mutation who progressed following treatment with endocrine therapy plus a CDK4/6 inhibitor and who are at risk for hyperglycemia (HbA1c between 5.5 and 6.4%inclusive). The primary goal is to determine the safety of evexomostat plus alpelisib and fulvestrant (the 'triplet therapy'), including the severity and number of hyperglycemic events, as well as anti-tumor benefit. The starting dose of evexomostat in the triplet therapy is 36 mg/m^2 (n=6; one dose below the monotherapy MTD of 49 mg/m^2). Once the MTD of evexomostat in the triplet therapy has been defined, up to 20 patients will be enrolled at that dose. An additional 20 patients may be enrolled to further characterize the safety and anti-tumor effect of the triplet therapy (up to 52 patients). This trial is open to accrual at multiple sites in the USA. Safety analysis includes the type, frequency, and severity of treatment-emergent adverse events (TEAEs) per NCI CTCAE, v5, and the number and proportion of patients with grade 3 or 4 hyperglycemia during the first 2 cycles of therapy, with an estimate of the exact upper one-sided 97.5% confidence bound. Efficacy analyses include objective response rate (ORR, consisting of complete response (CR) and partial response (PR)). The number of patients without disease progression six months from the start of the triplet therapy will be assessed. The CBR of CRs, PRs plus stable disease $\geq$24 weeks from C1D1 will be calculated. Overall survival data will be summarized as available. QoL will be analyzed according to functional scores and recommendations in the EORTC scoring manual. ECOG performance status and change from baseline will be summarized. Clinical trial information: NCT05455619. Research Sponsor: SynDevRx, Inc.

TPS1130 **Poster Session**

A phase 2 randomized study of magrolimab combination therapy in adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC): ELEVATE-TNBC.

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Background: Improving outcomes in patients (pts) with TNBC remains a high unmet need. Immune checkpoint inhibitors (ICIs) + chemotherapy (chemo) is approved for newly diagnosed pts with PD-L1+ tumors. Further, single-agent sacituzumab govitecan (SG), a Trop-2–directed antibody-drug conjugate, is approved for pts with mTNBC who received ≥2 prior systemic therapies (≥1 for metastatic disease). However, more options are needed for pts with PD-L1–negative mTNBC and for those with disease progression on chemo ± ICI. Magrolimab is a monoclonal antibody that blocks CD47, a "don't eat me" signal often overexpressed on TNBC cells. Magrolimab blockade of CD47 induces macrophage-mediated phagocytosis of tumor cells and has shown preclinical activity and promising clinical efficacy in hematologic malignancies. Certain chemos, including taxanes, enhance prophagocytic signals on tumor cells, which may lead to synergistic antitumor activity with magrolimab. This study is evaluating the safety, tolerability, and efficacy of magrolimab + nab-paclitaxel/paclitaxel or + SG in mTNBC. **Methods:** This open-label study has 2 cohorts (C) with safety run-in and phase (ph) 2 portions. Eligible pts are ≥18 y with measurable disease per RECIST 1.1. C1 pts have PD-L1–negative untreated mTNBC. C2 pts have mTNBC and received 1 prior line of therapy in the advanced setting, a taxane in the neoadjuvant/adjuvant or metastatic setting, and, if PD-L1+, an ICI. Exclusion criteria include active central nervous system disease, RBC transfusion dependence, and prior treatment with CD47/SIRPα-targeting agents. C1 assesses nab-paclitaxel/paclitaxel + magrolimab (safety run-in) or ± magrolimab (ph 2; randomized 1:1). C2 assesses magrolimab + SG (safety run-in and ph 2). In C1 safety run-in, magrolimab is given intravenously (IV) as a 1-mg/kg priming dose on day (D) 1 of cycle 1 to mitigate on-target anemia, followed by 30 mg/kg (cycle 1: D8, 15, 22; cycle 2: D1, 8, 15, 22; cycle 3+: D1, 15) (28-d cycles). In C2 safety run-in, pts receive a 1-mg/kg priming dose on D1, followed by 30 mg/kg (cycle 1: D8, 15; cycle 2: D1, 8, 15) and 60 mg/kg (cycle 3+: D1) (21-d cycles). The recommended ph 2 dose (RP2D) is determined in the safety run-in, with de-escalation if prespecified dose-limiting toxicity (DLT) criteria are met. Once RP2D is determined, the ph 2 cohorts will follow their respective dose schedules. Nab-paclitaxel/paclitaxel and SG are given IV per standard of care. The primary endpoints are incidence of DLTs, adverse events, and abnormal lab results by CTCAE v5.0 (safety run-in); progression-free survival by RECIST 1.1 (ph 2 C1); and confirmed objective response rate by RECIST 1.1 (C2; pooled safety run-in and ph 2). Planned enrollment is ≈144 pts. Clinical trial information: NCT04958785. Research Sponsor: Gilead Sciences, Inc.

TPS1131 **Poster Session**

The ARETHA study: A phase 2 randomized control trial of eribulin with evexomostat (SDX-7320) or placebo for patients with metastatic triple-negative breast cancer (TNBC) and metabolic dysfunction.

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Background: The prognosis for advanced/metastatic TNBC remains poor and novel therapeutic strategies are urgently needed. Insulin resistance and obesity contribute to TNBC progression and are independent predictors of worse survival. Methionine aminopeptidase 2 (MetAP2/p67) is overexpressed in many tumor types including breast. MetAP2 inhibitors exhibit broad anti-tumor activity and attenuate the effects of metabolic dysfunction on tumor growth. Evexomostat (SDX-7320) is a second-generation MetAP2 inhibitor that improved insulin sensitivity, reduced fat mass, and normalized adipokine levels in preclinical models of obesity and reduced tumor growth in TNBC preclinical models. In phase 1 trials, evexomostat monotherapy partially restored insulin sensitivity, reduced adipokines, and showed anti-metastatic effects in patients with advanced solid tumors. The goal of this phase 2 study is to test whether evexomostat prevents worsening of insulin resistance and augments tumor response in patients with metastatic TNBC and metabolic dysfunction in combination with eribulin chemotherapy, a standard of care treatment option after prior anthracycline and taxane exposure. **Methods:** This is a single-center phase 2 randomized control trial of evexomostat, a MetAP2 inhibitor, and eribulin chemotherapy. Key eligibility criteria include metastatic TNBC, measurable disease or $\geq$1 predominantly lytic bone lesion, baseline hemoglobin A1c $>$5.5% and/or BMI $\geq$30 kg/m2, and $\leq$2 prior lines of therapy in the advanced/metastatic setting. Patients with uncontrolled or insulin-dependent type II diabetes, or who require combination antihyperglycemic therapy are excluded. During the safety run-in period, 15 patients will be assigned to receive evexomostat 49 mg/m2 Q2 weeks and eribulin 1.4 mg/m2 on days 1 & 8 of a 21-day cycle. Upon safety confirmation, an additional 40 patients will be randomized 2:1 to receive evexomostat or placebo with eribulin. The primary endpoint is metabolic efficacy assessed by change in Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score. Secondary endpoints include objective response rate, progression-free survival, safety and tolerability, patient-reported outcomes, and changes in metabolic markers and body composition. Historically, HOMA-IR scores double during chemotherapy, and this trial will test whether evexomostat attenuates the expected HOMA-IR rise. This trial will have $>$90% power to detect a difference between a 1.5-fold change in HOMA-IR in the control arm vs. no change in the evexomostat arm while controlling the Type I error at 5%. As of Feb 2022, 3 patients are enrolled; total accrual of 61 patients is planned with a goal of 55 evaluable patients. Clinical trial information: NCT05570253. Research Sponsor: SynDevRx, Inc.

TPS1132 **Poster Session**

A randomized phase II clinical trial of talazoparib maintenance therapy in patients with triple-negative breast cancer who showed platinum-sensitivity on first- or second-line platinum-based chemotherapy: KCSG BR21-10.

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Background: A potent PARP inhibitor, talazoparib, demonstrated superior clinical activity compared to standard chemotherapy in germline BRCA1/2-mutant advanced breast cancer patients. However, the role of talazoparib treatment in BRCA1/2 wild-type triple-negative breast cancer (TNBC) patients remains undefined, although high incidence of homologous recombination deficiency (HRD) is one of the major characteristics of the TNBC. Previous studies indicated clinical responsiveness to platinum agents is a useful surrogate for HRD that may predict favorable PARP inhibitor response. Here, we present a phase II study to test talazoparib maintenance therapy in germline BRCA1/2 mutation unselected advanced TNBC patients after platinum-based chemotherapy. **Methods:** The KCSG BR21-10 study (NCT04755868) is a randomized double-blind placebo-controlled phase II clinical trial of talazoparib maintenance therapy in metastatic TNBC patients whose tumor showed platinum-sensitivity to first- or second-line platinum-based chemotherapy. The criteria for platinum-sensitivity were set as follows: remaining complete response (CR), partial response (PR), or stable disease (SD) after 6 to 9 tri-weekly doses or 18 to 27 weekly doses of platinum-based chemotherapy. The eligible TNBC patients are enrolled to the trial after completion of platinum-based therapy and 1:1 randomized to receive talazoparib (once daily 1.0 mg) or placebo maintenance therapy. The patient with any germline BRCA1/2 mutation status is eligible, and randomization stratification factors include line of platinum-based chemotherapy, response to platinum-based chemotherapy, and germline BRCA1/2 mutation status. The talazoparib/placebo maintenance treatment is initiated within 8 weeks after the last platinum chemotherapy. At the time of progression of disease, unblinding can be performed and patients in placebo arm may be eligible for crossover to talazoparib single treatment. The primary endpoint is progression-free survival (PFS) after randomization by RECIST 1.1, and the key secondary endpoints are overall survival, PFS2, objective response rate, adverse events by CTCAE 5.0 criteria, and quality of life. We also planned exploratory study to find predictive biomarker by tumor tissue and blood analysis. The median PFS from the randomization is expected to be 3 months in the placebo maintenance arm and we expect that talazoparib maintenance will improve PFS with hazard ratio of 0.65. It is predicted that a total of 206 patients (103 patients in each arm) are required with the α of 0.05 and power of 0.8 (1-β) by two-sided test, considering monthly 3% dropout rate. Currently, 23 of planned 206 patients have been enrolled. Clinical trial information: NCT04755868. Research Sponsor: Pfizer.

TPS1133 **Poster Session**

Phase I/II study of stereotactic radiosurgery with concurrent olaparib followed by adjuvant durvalumab and physician's choice systemic therapy in patients with breast cancer brain metastases.

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Background: Despite progress in the treatment of brain metastasis for HER2+ breast cancer, outcomes for patients with HER2-negative breast cancer brain metastases remain poor. Current standard of care consists of local therapies, including surgery and radiotherapy, followed by systemic therapy. Preclinical studies show inhibitors of poly(ADP-ribose) polymerase (PARP) are effective in combination with radiation therapy as a DNA damage response inhibitor. Triple-negative breast cancer (TNBC) has higher rates of homologous recombination deficiency compared to other breast cancer subtypes, and together with HER2-negative, BRCA-mutated breast cancer would be particularly sensitive to PARP inhibition. PARP inhibition has also demonstrated promising efficacy combined with immunotherapy in patients with germline BRCA-mutant and metastatic TNBC in clinical trials (MEDIOLA, TOPACIO). In addition, immunotherapy with stereotactic radiosurgery (SRS) is associated with favorable intracranial control and survival in patients with brain metastases. We hypothesize that this biologically-driven combination will enhance local control of SRS-treated brain metastases through synergy with PARP inhibition, while controlling micrometastatic disease in the brain and extracranial sites via potentiation of the immune response. **Methods:** We are conducting a multi-institution, Phase I/II trial of SRS plus olaparib, followed by durvalumab (with physician's choice systemic therapy), for patients with TNBC (any BRCA status) or HER2-negative with BRCA-mutated (germline or somatic) breast cancer brain metastases [NCT04711824]. A total of 41 patients are planned for enrollment at 8 sites. The primary objectives are to evaluate safety and tolerability (Phase I) and determine intracranial disease control at 6 months (Phase II) of this treatment combination. Secondary objectives include determining clinical activity via intracranial and global progression-free survival, overall survival, and intracranial and extracranial response rate. Exploratory objectives will assess potential biomarkers of treatment response, including changes in circulating tumor cells and DNA in blood and cerebrospinal fluid, germline and tumor mutations in DNA repair pathway genes, and PD-L1 expression, as well as quality of life and patient-reported outcomes. A surgical sub-study (n=5) will evaluate olaparib concentration/distribution in resected brain metastases. As of January 2023, cohort 1 of phase I has been completed without dose-limiting toxicity. Clinical trial information: NCT04711824. Research Sponsor: AstraZeneca.

TPS1134 **Poster Session**

Phase II study of a PARP inhibitor in somatic *BRCA1/2* mutant metastatic breast cancer (MBC).

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Background: While PARP inhibitors are approved for germline *BRCA1/2* mutant MBC, and are shown to improve both patient quality of life and progression-free survival (PFS), as a well-tolerated oral targeted therapy, their utility is limited as germline *BRCA1/2* mutations are present in 5-10% of breast cancer. We hypothesize that somatic *BRCA1/2* mutations may also respond to PARP inhibitors. We have demonstrated that somatic *BRCA1/2* mutations can be identified by cell-free DNA and tumor tissue genotyping assays in patients who are not known germline *BRCA1/2* carriers, and some of these are pathogenic. Using a circulating tumor cell culture model developed from a patient with a pathogenic somatic *BRCA1* mutation, we have shown that a PARP inhibitor can induce cell growth inhibition paralleling germline *BRCA1/2* mutant lines. In this trial, we are evaluating the efficacy of a PARP inhibitor in somatic *BRCA1/2* mutant MBC. Our work may help expand the number of patients with MBC who benefit from a PARP inhibitor. **Methods:** In this phase II investigator-initiated clinical trial, 30 patients with MBC harboring somatic *BRCA1/2* mutations identified via a CLIA certified cell-free DNA or tumor tissue genotyping assay are being enrolled at 7 academic centers. Mutations are evaluated for pathogenicity using validated genomic databases such as ClinVar by genetic counselors prior to enrollment. Patients may have metastatic triple-negative or hormone receptor positive (HR+)/HER2- breast cancer progressing on 1 prior therapy, and should not be known germline *BRCA1/2* carriers. Any number of prior therapies are allowed but patients must have adequate baseline performance status and organ function. Patients are treated with talazoparib 1 mg/day (a PARP inhibitor with high potency) until disease progression. Imaging (CT chest abdomen and pelvis as well as bone scan) occurs at baseline and every 3 months for disease assessment. The primary endpoint is progression-free survival (RECIST 1.1). This study has 81% power to demonstrate that talazoparib is associated with "success" (PFS $>$ 12 weeks) in $\geq$53% patients (4% alpha). Key secondary endpoints include objective response rate and toxicity (NCI CTCAE v 5.0). Correlative studies include collecting cell-free DNA at baseline and monthly to identify the emergence of resistance mutations and impact of *BRCA1/2* reversion mutations and mutant allele fraction on response, and evaluating the Cancer Risk B (CR-B) assay, a novel method that identifies double-strand break repair mutations in circulating blood cells. The study (NCT03990896) is open at Massachusetts General Hospital, MD Anderson, Emory, University of California San Francisco, and Northwestern, and pending activation at Vanderbilt and Cornell, with 11 patients enrolled as of 2/2023. Clinical trial information: NCT03990896. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; Pfizer ASPIRE Award.