1000 **Oral Abstract Session**

Trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) in patients (pts) with HER2-positive (HER2+) unresectable and/or metastatic breast cancer (mBC): Safety follow-up of the randomized, phase 3 study DESTINY-Breast03.

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Background: In the DESTINY-Breast03 (NCT03529110) primary analysis (data cutoff [DCO], May 21, 2021), T-DXd showed superiority over T-DM1 in pts with HER2+ mBC, with a significant improvement of progression-free survival by blinded independent central review (HR, 0.284; 95% CI, 0.217-0.373; $P < 0.001$), and a safety profile consistent with prior studies. This analysis provides updated safety data with longer follow-up. **Methods:** Pts were randomized 1:1 to T-DXd or T-DM1. Prespecified safety analysis of treatment-emergent adverse events (TEAEs) was conducted; endpoints included time to event, duration of event, and resolution. **Results:** At DCO (September 7, 2021), 116 (45.1%) pts vs 39 (14.9%) pts remained on treatment in the T-DXd vs T-DM1 arms; median treatment duration was 16.1 mo (range, 0.7-33.0) for T-DXd vs 6.9 mo (range, 0.7-28.5) for T-DM1. Any-grade (G), G≥3, and serious AE (SAE) rates were similar for T-DXd vs T-DM1 (99.6% vs 95.4%; 53.3% vs 49.8%; and 21.0% vs 19.2%), while exposure-adjusted incidence rates (EAIRs; per pt-year) for G≥3 and SAEs were lower for T-DXd vs T-DM1 (0.42 vs 0.70 and 0.17 vs 0.27). Median time to TEAE associated with drug discontinuation or dose reduction was longer with T-DXd vs T-DM1 (224.0 vs 147.0 d and 96.0 v 19.0 d, respectively). Most TEAEs in ≥20% of pts were hematologic or gastrointestinal. Median time to first onset of select any-G TEAEs was 70.0 vs 42.0 d for anemia, 196.0 vs 168.0 d for lymphopenia, 132.0 vs 8.0 d for thrombocytopenia, 22.0 vs 24.0 d for fatigue, 74.5 vs 92.0 d for leukopenia, and 64.0 vs 105.0 d for neutropenia, with T-DXd vs T-DM1, respectively. In both arms, most nausea and vomiting events were G1/2; while G≥3 events with T-DXd vs T-DM1 were 6.6% vs 0.4% for nausea and 1.6% vs 0.8% for vomiting, respectively. Rates of nausea, vomiting, and alopecia were highest in cycle 1 and lower in subsequent cycles for T-DXd. Rates of hematologic events were generally lower in earlier cycles vs cycle ≥8 in both arms. Rates of adjudicated, drug-related ILD/pneumonitis were 10.9% (1 G2 event since previous DCO) with T-DXd vs 1.9% with T-DM1, with no G4/5 events. Median time to first adjudicated, drug-related ILD/pneumonitis event was 5.9 vs 9.5 mo for T-DXd vs T-DM1, respectively; at DCO, most events resolved (57.1% vs 80.0%), and follow-up is ongoing. **Conclusions:** In this updated safety analysis, T-DXd demonstrated a tolerable safety profile consistent with prior studies. Despite longer treatment duration with T-DXd, EAIRs of G≥3 and SAEs were lower for T-DXd vs T-DM1. Rates of ILD/pneumonitis for T-DXd were similar to those in the previous DCO. Nausea, vomiting, and alopecia rates decreased over time. This longer safety update reinforces the consistent safety profile of T-DXd, supporting the clinical benefit of T-DXd over T-DM1 in patients with HER2+ mBC. Clinical trial information: NCT03529110. Research Sponsor: Daiichi Sankyo Inc. and AstraZeneca.

LBA1001 **Oral Abstract Session**

Primary results from TROPiCS-02: A randomized phase 3 study of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (Pts) with hormone receptor–positive/HER2-negative (HR+/HER2-) advanced breast cancer.

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1002 **Oral Abstract Session**

Results from the phase 1/2 study of patritumab deruxtecan, a HER3-directed antibody-drug conjugate (ADC), in patients with HER3-expressing metastatic breast cancer (MBC).

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Background: Patritumab deruxtecan (HER3-DXd) is a novel, investigational ADC composed of a human anti-HER3 monoclonal antibody covalently bound to a topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker. Here we report updated safety and efficacy data from this ongoing study (U31402-A-J101; NCT02980341; JapicCTI-163401) of HER3-DXd in pts with previously treated MBC. **Methods:** U31402-A-J101 is a phase 1/2, multicenter, open-label, first-in-human study of HER3-DXd in pts with HER3-expressing MBC (N = 182). The study enrolled pts in dose-escalation (3.2-8.0 mg/kg IV Q3W) and dose-finding portions across molecular subtypes (n = 66; including HER2+ MBC, n = 14) followed by dose expansion in the following subtypes: HER3 high (4.8 mg/kg [n = 33] or 6.4 mg/kg [n = 31]), HER3 low (6.4 mg/kg [n = 21]) HR+/HER2– MBC or HER3-high TNBC (6.4 mg/kg [n = 31]). HER3-high and -low were defined as ≥75% and 25% – < 75% membrane positivity. The primary objective was to assess safety and efficacy; secondary objectives included determining the relationship between efficacy and HER3 expression. **Results:** At data cutoff (16 Aug 2021), median study duration was 31.9 mo (range, 15-56). Median age was 57 y (range, 30-83); 132 (72.5%) and 50 (27.5%) pts had an ECOG PS of 0 or 1. Pts had a median of 5 (range, 1-13) prior lines of therapy for locally advanced/metastatic disease. Median treatment duration with HER3-DXd was 5.9 mo (range, 0.7-30.6). In a pooled evaluation of dose escalation/finding and expansion, efficacy is shown in pts with HR+/HER2– MBC, TNBC, and HER2+ MBC in the Table. Overall, 130 pts (71.4%) had grade ≥3 TEAEs; the most common (≥15%) were decreased neutrophil count (39.6%), decreased platelet count (30.8%), anemia (18.7%), and decreased white blood cell count (18.1%). 12 pts (6.6%) experienced treatment-related interstitial lung disease according to central adjudication, including 1 grade 5 event. **Conclusions:** A pooled analysis in this heavily pretreated population showed promising efficacy in pts with HR+/HER2– and HER2+ MBC as well as TNBC. The safety profile with longer follow-up is consistent with previous reports and showed adequate safety and tolerability. Studies are ongoing in MBC tumor types, with a focus on biomarkers associated with efficacy. Clinical trial information: NCT02980341. Research Sponsor: Daiichi Sankyo, Co., Ltd.

LBA1003 **Oral Abstract Session**

Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (ER+/HER2− ABC): Analyses from PALOMA-2.

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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, 2022, issue of the *Journal of Clinical Oncology*. Research Sponsor: Pfizer Inc.

LBA1004 **Oral Abstract Session**

A randomized, phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition (CDK 4/6i) in patients (pts) with unresectable or hormone receptor–positive (HR+), HER2-negative metastatic breast cancer (MBC): MAINTAIN 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, 2022, issue of the *Journal of Clinical Oncology*. Research Sponsor: Novartis, Glenn Family Breast Center.

1005 **Oral Abstract Session**

Fulvestrant plus capivasertib versus fulvestrant plus placebo after relapse or progression on an aromatase inhibitor in metastatic, estrogen receptor–positive breast cancer (FAKTION): Overall survival and updated progression-free survival data with enhanced biomarker analysis.

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Background: Previous results from the Phase 2 FAKTION trial (NCT01992952) showed progression free survival (PFS) in patients with aromatase inhibitor (AI) resistant ER+/HER2– advanced breast cancer was significantly longer with fulvestrant plus capivasertib vs fulvestrant plus placebo. At the time of analysis, PFS benefit associated with capivasertib was not restricted to patients with activating mutations in PIK3CA (E542K, E545K, H1047R or H1047L) or PTEN protein null. We report now mature overall survival (OS) data with enhanced biomarker analysis. **Methods:** For the enhanced analysis, available tissue and plasma samples were sent for targeted next generation sequencing (NGS) with Foundation One CDx and GuardantOMNI assays. 'Pathway altered' (PA) was defined as any activating mutation in PIK3CA (exons 1,4,7,9,20) or AKT1 (E17K only) or inactivating alterations in PTEN. For samples not tested by targeted NGS, previously reported digital droplet PCR (ddPCR) results for PIK3CA were used, in addition to tissue AKT1 ddPCR analysis performed after the initial publication. Concordance between mutations identified by ddPCR and subsequent NGS was 97%. **Results:** In January 2022, 108 OS events were reported (77% maturity) in the intention to treat (ITT) population. The median OS was 29.3 vs 23.4 months (mo) in the capivasertib (n = 69) vs placebo (n = 71) arms respectively (HR 0.66, 95% CI 0.45–0.97; p = 0.035). In the enhanced biomarker analysis, 76 participants were classified as PA compared to 59 in the original analysis. In the PA group, OS was 39.0 vs 20.0 mo in the capivasertib vs placebo arms respectively (HR 0.46, 95% CI: 0.27–0.79; p = 0.005). Within the pathway non-altered (PNA) group, median OS was 26.0 vs 25.2 mo in the capivasertib vs placebo arms respectively (HR 0.86, 95% CI: 0.49–1.52; p = 0.60). In the updated PFS analysis, the advantage in the ITT population persisted with capivasertib vs placebo (median 10.3 vs 4.8 mo, HR 0.56, 95% CI: 0.38–0.81; p = 0.002). PFS analysis against the updated biomarker subgroups shows a significant improvement in PFS in the PA group: 12.8 vs 4.6 mo in the capivasertib vs placebo arms respectively (HR 0.44, 95% CI: 0.26–0.72; p = 0.001). In the PNA group, median PFS was 7.7 vs 4.9 mo in the capivasertib vs placebo arms respectively (HR 0.70, 95% CI: 0.40–1.25; p = 0.23). **Conclusions:** Updated analysis of the FAKTION trial data show a significant improvement in OS in the ITT population. Enhanced subgroup analysis suggests that the benefit of capivasertib in both PFS and OS may be predominantly in patients with PIK3CA/AKT1/PTEN pathway altered tumours, but further elucidation will be forthcoming from the ongoing Phase 3 CAPItello-291 study in which participants with PA and PNA tumours have been recruited. Clinical trial information: NCT01992952. Research Sponsor: AstraZeneca, Cancer Research UK.

Alpelisib (ALP) + fulvestrant (FUL) in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2−) advanced breast cancer (ABC): Biomarker (BM) analyses by next-generation sequencing (NGS) from the SOLAR-1 study.

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Background: *PIK3CA* mutations (mut; ~ 40% of HR+, HER2– ABC) are linked to poor prognosis. In SOLAR-1, ALP (PI3Kα-selective inhibitor and degrader) + FUL improved progression-free survival (PFS) vs placebo (PBO) + FUL in pts with *PIK3CA*-mutated HR+, HER2– ABC. Here, we focus on efficacy data by gene alterations in SOLAR-1 *PIK3CA*-altered (alt) cohort. **Methods:** SOLAR-1 was a phase 3, randomized, double-blind study of ALP (or PBO) + FUL in HR+, HER2– ABC progressing on/after an aromatase inhibitor. Baseline tissue samples with enough quantity/quality (N = 398) were retrospectively tested by NGS (FoundationOne CDx 324-gene panel) and pts grouped by *PIK3CA*-alteration status. Clinical benefit was assessed using PFS and hazard ratio (HR) based on tumor mutational burden (TMB) and gene alteration status in the *PIK3CA*-alt cohort. No multiplicity adjustment was made. **Results:** *PIK3CA*-alt (ALP, n = 120; PBO, n = 117) and *PI3KCA*-non-alt (ALP, n = 81; PBO, n = 80) cohorts had differential gene alteration landscapes. In the *PIK3CA*-alt cohort, ALP + FUL clinical benefit was seen across TMB quartiles (Q1: 0 -<2.52, Q2: 2.52 -<3.78, Q3: 3.78 -<5.04, Q4: ≥ 5.04 mut/megabase). ALP + FUL had greater benefit in pts with alt vs non-alt *FGFR1/2* (Table). ALP + FUL benefit was independent of alterations in *TP53, ESR1, CCND1, MAP3K1*, and *ARID1A* and limited in *MYC*- and *RAD21*-alt cohorts. ALP + FUL benefit was seen in pts with alt genes in the MAPK (HR [95% CI] vs PBO: alt 0.43 [0.23 - 0.80]; non-alt 0.56 [0.40 - 0.79]) and PI3K (in addition to *PIK3CA*; alt 0.68 [0.38 - 1.23]; non-alt 0.48 [0.34 - 0.68]) pathways, and implicated in CDK4/6i resistance (alt 0.52 [0.30 - 0.89]; non-alt 0.53 [0.37 - 0.76]). **Conclusions:** The unique mut profile of *PIK3CA*-alt tumors did not affect ALP + FUL benefit in pts with HR+, HER2– ABC. Clinical benefit was maintained regardless of alterations in most BMs, including *ESR1* and genes implicated in CDK4/6i resistance, consistent with ALP targeting the *PIK3CA* driver oncogene. Clinical trial information: NCT#02437318; EUDRA CT#2015-000340-42. Research Sponsor: Novartis Pharmaceuticals Corporation.

mPFS and HR in pts receiving ALP + FUL (*PIK3CA*-alt cohort).

Genes	Alt mPFS, mo (N)	Alt HR (95% CI) vs PBO	Non-alt mPFS, mo (N)	Non-alt HR (95% CI) vs PBO
FGFR1	12.7 (22)	0.36 (0.16-0.77)	11.0 (98)	0.54 (0.39-0.75)
FGFR2	9.6 (9)	0.28 (0.09-0.88)	11.0 (111)	0.55 (0.41-0.75)
TP53	8.5 (26)	0.49 (0.28-0.87)	12.0 (94)	0.56 (0.39-0.80)
ESR1	12.0 (13)	0.70 (0.29-1.67)	11.0 (107)	0.51 (0.37-0.70)
CCND1	9.2 (31)	0.77 (0.43-1.37)	11.2 (89)	0.47 (0.33-0.66)
MAP3K1	17.3 (13)	0.44 (0.17-1.10)	10.9 (107)	0.54 (0.40-0.75)
ARID1A	22.1 (11)	0.50 (0.17-1.49)	10.9 (109)	0.51 (0.37-0.70)
MYC	5.8 (13)	1.01 (0.45-2.28)	11.6 (107)	0.49 (0.35-0.67)
RAD21	6.1 (20)	1.02 (0.54-1.95)	11.6 (100)	0.46 (0.33-0.64)

1007 **Oral Abstract Session**

NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) for newly oligometastatic breast cancer (NCT02364557).

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Background: Prospective and retrospective studies of patients (pts) with oligometastatic (OM) disease have supported that metastases (mets) directed treatment (MDT) with SBRT or SR in addition to standard of care systemic therapy (SOC ST) can improve progression-free (PFS) and overall survival (OS) compared with SOC ST alone. However, randomized evidence in oligometastatic breast cancer (OMBC) are lacking. NRG-BR002, a randomized Phase IIR/III trial, sought to determine the efficacy of SOC ST + MDT (SBRT or SR) as first line treatment of OMBC. **Methods:** OMBC pts with ≤ 4 extracranial mets on standard imaging with controlled primary disease were eligible if on first line SOC ST for ≤ 12 months without progression. Pts were randomized (1:1) to ARM 1 – SOC ST (mainly chemotherapy, endocrine therapy, anti-HER2) or ARM 2 – SOC ST with MDT of all mets. Stratification included mets number (1 vs > 1), ER/PR and Her2 status, and chemotherapy use. Phase IIR targeted sample size was 128 total/116 eligible pts, for 92% power and 1-sided significance level = 0.15 to determine if adding MDT shows a signal for improved PFS (hazard ratio [HR] = 0.55, corresponding to median PFS (mPFS) from 10.5 to 19 months), in order to continue to the full phase III trial for OS. PFS and OS were estimated by Kaplan-Meier and arms compared with log-rank. **Results:** 125 of the 129 pts randomized were eligible (ARM 1 = 65, ARM 2 = 60). Key characteristics included median age 54, 79% ER+ or PR+/HER2-, 13% HER2+, 8% triple negative. 60% had 1 metastasis and 20% presented synchronously with primary disease. Following randomization, systemic therapy was delivered to 95% in ARM 1 and 93% in ARM 2; ablation: SBRT 93%, SR 2%, and 5% none. The median follow-up was 30 mo. The mPFS (70% CI) in ARM 1 was 23 mo (18, 29) and 19.5 mo (17, 36) in ARM 2; 24 and 36-mo PFS (70% CI) for ARM 1 were 45.7% (38.9, 52.5) and 32.8% (26.0, 39.5) compared with 46.8 (39.2, 54.3) and 38.1 (29.7, 46.6) in ARM 2; HR (70% CI): 0.92 (0.71, 1.17); and 1-sided log-rank p = 0.36. As PFS did not show signal, OS reporting is included: median OS was not reached in either arm; 36-mo OS (95% CI) in ARM 1 71.8% (58.9, 84.7) and ARM 2 68.9% (55.1, 82.6; 2-sided log-rank p = 0.54). Analysis of first failure showed new mets outside index area (Arm 1) /RT field (Arm 2) developed similarly in both arms at 40%. There were fewer new mets inside treated/index area for Arm 2 6.7% vs ARM 1 29.2%, respectively. There were no grade 5 treatment-related adverse events (AEs), 1 grade 4 AE in ARM 1, and 9.7% and 5.3% grade 3 AEs in ARMS 1 and 2, respectively. Circulating tumor cell counts (0 vs ≥1) at baseline were similar in both arms and were not prognostic HR (95% CI): 1.04 (0.54, 2.02). **Conclusions:** The addition of MDT to SOC ST did not show signal for improved PFS, nor OS difference in patients with OMBC. The trial will not proceed to the Phase III component. Clinical trial information: NCT02364557. Research Sponsor: National Cancer Institute (NCI).

Contributions of screening, early-stage treatment, and metastatic treatment to breast cancer mortality reduction by molecular subtype in U.S. women, 2000-2017.

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Background: Treatment for metastatic breast cancer has advanced since 2000, but we do not know if those advances have reduced mortality in the general population. **Methods**: Four Cancer Intervention and Surveillance Network (CISNET) models simulated US breast cancer mortality from 2000 to 2017 using national data on mammography use and performance, efficacy and dissemination of estrogen receptor (ER) and HER2-specific treatments of early-stage (stages I-III) and metastatic (stage IV or distant recurrence) disease, and competing mortality. Models compared overall and ER/HER2-specific breast cancer mortality rates from 2000 to 2017 relative to estimated rates with no screening or treatment, and attributed mortality reductions to screening, early-stage or metastatic treatment. Results of an exemplar model are shown. **Results**: The mortality reduction attributable to early-stage treatment increased from 35.8% in 2000 to 48.2% in 2017, while the proportion attributable to metastatic treatment decreased slightly from 23.9% to 20.6%. The increasing contribution of early-stage treatment reflects the transition of effective metastatic treatments to early-stage disease: accordingly, ten-year distant recurrence-free survival improved (82.5% in 2000, 87.3% in 2017; for ER+HER2+, 78.2% to 90.9%). Survival time after metastatic diagnosis also increased, doubling from 1.48 years in 2000 to 2.80 years in 2017, with the best survival for women with ER+HER2+ cancers (4.08 years) and worst for ER-HER2- (1.22 years). **Conclusions**: Advances in metastatic breast cancer treatment are reflected in lower population mortality, both through transition to early-stage treatment and gains for women with metastatic disease. These results may inform patient/physician discussions about breast cancer prognosis and expected benefits of treatment. Research Sponsor: U.S. National Institutes of Health.

	Year	All Subtypes	ER+HER2+	ER+HER2-	ER-HER2+	ER-HER2-
Mortality reduction (%) from screening, early-stage and metastatic treatment (vs. estimated mortality with no screening or treatment)	2000	39.5	40.6	41.5	34.2	34.9
	2010	52.0	62.8	55.4	44.9	36.7
	2017	56.5	69.5	58.1	59.6	39.1
Fraction of mortality reduction (%) from screening	2000	40.3	41.3	36.7	45.3	50.7
	2010	31.5	27.1	29.9	32.9	45.6
	2017	31.2	25.1	30.0	31.8	44.8
Fraction of mortality reduction (%) from early-stage treatment	2000	35.8	41.5	39.9	19.1	24.1
	2010	46.3	53.7	47.5	41.6	32.3
	2017	48.2	57.6	50.4	42.1	31.0
Fraction of mortality reduction (%) from metastatic treatment	2000	23.9	17.1	23.4	35.7	25.2
	2010	22.2	19.2	22.6	25.6	22.0
	2017	20.6	17.3	19.6	26.1	24.2
Ten-year distant recurrence-free survival with early-stage disease (%)	2000	82.5	78.2	85.9	68.5	75.0
	2010	86.6	88.3	89.0	78.7	77.4
	2017	87.3	90.9	89.1	81.4	78.5
Median time (years) from distant recurrence to breast cancer death	2000	1.48	1.68	1.66	1.55	0.92
	2010	2.48	3.62	3.18	2.45	1.16
	2017	2.80	4.08	3.47	3.30	1.22

1009 **Clinical Science Symposium**

ESR1 F404 mutations and acquired resistance to fulvestrant in the plasmaMATCH study.

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Background: The selective estrogen receptor modulator (SERD) fulvestrant is commonly used to treat patients with hormone receptor positive advanced breast cancer, although potential mechanisms of acquired resistance are poorly understood. plasmaMATCH cohort A (NCT03182634) investigated the activity of fulvestrant in patients with activating *ESR1* mutations in circulating tumor DNA (ctDNA). Here we present analysis of baseline and end-of-treatment (EOT) ctDNA to identify potential resistance mutations to fulvestrant. **Methods:** Paired baseline and EOT plasma samples from patients enrolled into plasmaMATCH underwent ctDNA sequencing (Guardant360, Guardant Health) to identify acquired mutations. For F404 analysis, MCF-7 cells were transiently transfected with estrogen receptor expression constructs containing either wildtype *ESR1* (WT), single *ESR1* mutations (D538G, E380Q, F404L), or compound mutations (D538G_F404L, E380Q_F404L), alongside an estrogen response element (ERE)-luciferase reporter construct. Transfected cells were treated with or without fulvestrant and ERE-luciferase activity compared. **Results:** Of 84 patients enrolled in cohort A, 69 had paired baseline and EOT sequencing. Patients with baseline *ESR1* Y537S had shorter progression free survival (PFS), and Y537C longer PFS, than those wild-type for each respective mutation ($p = 0.03$ and $p = 0.04$). Patients frequently acquired mutations at EOT (n = 35, 51%), including potentially targetable mutations in 25% (including 3 *PTEN*, 3 *BRCA1/2*, 2 *PIK3CA*, 2 *HER2*, 1 *BRAF*). Three (4%) patients acquired *ESR1* p.F404 mutations (F404L, F404I, F404V), with 7 mutations in total. Of 26 patients with PFS of $\geq$16 weeks, 3 patients (12%) acquired *ESR1* F404. In 800 patients screened for entry to plasmaMATCH, one harbored a F404 mutation (0.13%), with a prior history of fulvestrant. F404 mutations resided in *cis* with E380Q in 6/7 assessable mutations. *In vitro* structural modelling revealed that *ESR1* p.F404 resides within the *ESR1* ligand binding domain, and contributes to estrogen and fulvestrant binding through a pi-stacking bond between the aromatic ring of phenylalanine and estrogen/fulvestrant, with all F404 mutations disrupting this bond. Transient transfection demonstrated that single mutations D538G, E380Q, F404L and wild-type *ESR1* were sensitive to fulvestrant ($p < 0.0001$, $p = 0.0006$, $p = 0.04$ and $p = 0.0001$), whereas compound mutations D538G_F404L and E380Q_F404L were resistant. Further investigation of relative sensitivity of the F404 mutant *ESR1* to other anti-estrogens will be presented. **Conclusions:** We have identified a novel resistance mechanism to fulvestrant, with F404 mutations acquired in patients with pre-existing activating *ESR1* mutations. F404 confers fulvestrant resistance through the loss of a pi-stacking bond and likely reduced fulvestrant binding affinity, identifying a new potential target to overcome endocrine therapy resistance. Research Sponsor: Cancer Research UK and Breast Cancer Now.

1010 **Clinical Science Symposium**

Allelic dosage of *RB1* drives CDK4/6 inhibitor treatment resistance in metastatic breast cancer.

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Background: We recently reported inferior outcomes to CDK4/6 inhibitors and endocrine therapy (CDK4/6i-ET) associated with germline *BRCA2* (g*BRCA2)* in a cohort of estrogen receptor (ER) positive breast cancers. Co-occurrence of *gBRCA2* with loss of heterozygosity (LOH) of neighboring *RB1* was found to portend particularly poor outcomes. Here, we sought to define the effects of pre-treatment *RB1* allelic copy number status on outcomes of CDK4/6i-ET and the likelihood of developing *RB1* loss-of-function (LOF) mutations on CDK4/6i through the analysis of an expanded cohort of metastatic ER+ breast cancer patients. **Methods:** Patients who underwent sequencing on MSK-IMPACT from April 2014 to May 2021 were included. For every sample preceding CDK4/6i-ET, we performed FACETS to infer *RB1* allele specific copy number, ploidy, tumor purity and fraction genome altered (FGA). Patients were categorized based on *RB1* allelic status: HetLoss (total of one allelic copy), copy neutral LOH (CNLOH), other allelic imbalance including all other aneuploidy states, and diploid. Progression free survival (PFS) was assessed using univariate and multivariate Cox proportional hazard models adjusted for ET partner and FGA. Firth penalized logistic regression was used to study association of pre-treatment *RB1* status with acquired *RB1* LOF variants in paired post-CDK4/6i samples. **Results:** Of 2,630 potentially eligible patients, 279 patients had genomic sequencing performed prior to 1st line CDK4/6i-ET. Of these, 75 (26.8%) exhibited *RB1* HetLoss, 39 (14.0%) had CNLOH of *RB1*, 111 (39.7%) exhibited diploid *RB1* state, while 54 (19.4%) had other patterns of *RB1* allelic imbalance. All non-diploid *RB1* states were associated with significantly shortened PFS relative to diploid (univariate HetLoss HR: 2.05, 95% CI: 1.42, 2.97; CNLOH HR: 2.08, 95% CI: 1.32, 3.25; other imbalance HR: 1.70, 95% CI: 1.11, 2.58). Only HetLoss remained significant when adjusted for FGA (HR 1.61, 95% CI: 1.09, 2.38, p = 0.017). *RB1* LOF was rare in pre-CDK4/6i tumors (< 1%); excluding these cases did not change our results. Of the 176 patients with paired pre- and post-CDK4/6i samples, only *RB1* HetLoss in pre-CDK4/6i sample was significantly associated with development of *RB1* LOF mutations in post-CDK4/6i sample (18.4%) as compared to diploid (4.2%, OR 4.25, 95% CI 1.02, 17.7, p = 0.047). These results indicate that tumors with one functional copy of *RB1* are more likely to acquire *RB1* LOF on CDK4/6i to achieve biallelic RB1 loss as a mechanism of CDK4/6i resistance. **Conclusions:** We demonstrate that LOH and allelic imbalance of *RB1* are associated with shorter PFS on CDK4/6-ET. We postulate this may occur partly as a result of more frequent acquired *RB1* LOF mutations under selective pressure of CDK4/6i. These data supports the implementation of more refined allele-specific copy number methods and identifies a high-risk population for escalated monitoring and treatment approaches. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

1011 **Clinical Science Symposium**

Use of real-world data (RWD) to assess the utility of cell-free circulating tumor DNA (cfDNA) in identifying resistance to early treatment in advanced breast cancer (aBC).

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Background: The approvals of CDK4/6 inhibitors (CDK4/6i) and alpelisib (a PI3Ka inhibitor, PI3Ki) have overhauled early treatment of hormone positive aBC. While some clinical trials have investigated mechanisms of resistance to these drugs, their impact on tumor evolution requires further exploration. Here we use cfDNA to examine molecular changes pre- and post-CDK4/6i or PI3Ki treatment and use RWD to assess the impact of putative resistance alterations on response to treatment. **Methods:** Patients (pts) with aBC were identified via the Guardant INFORM database and included if they had a cfDNA test within 90 days prior to therapy initiation and/or 90 days after therapy discontinuation with CDK4/6i or PI3Ki. Pts with *RB1* loss of function (LOF) alterations (alts) who received CDK4/6i and pts with *PTEN* LOF alts who received PI3Ki were separately identified, and these cohorts were matched 1:3 with a *RB1/PTEN* negative population respectively, by age (+/- 5 years), sex, year of cfDNA test, and line of therapy. Log-rank tests were used to assess differences in time to discontinuation (TTD) and time to next treatment (TTNT). **Results:** Differences in the frequencies of certain alts detected in pts pre- and post-CDK4/6i or PI3Ki treatment are shown (Table). Pts with *RB1* LOF alts prior to the start of CDK4/6i had significantly worse TTD and numerically worse TTNT versus controls (TTD = 3 mos vs 4.7 mos, p=0.018; TTNT = 7.3 mos vs 8 mos, p=0.082). Pts with *PTEN* LOF alts prior to start of PI3Ki had no significant difference in TTD or TTNT versus controls (TTD = 4.1 mos vs 4.1 mos, p=0.92; TTNT = 7.4 mos vs 7 mos, p=0.32). Notably, 54% of pts receiving CDK4/6i and 84% of pts receiving PI3Ki were on their third or later line of therapy. **Conclusions:** Using cfDNA, we were able to further characterize the resistance landscape of both CDK4/6i and PI3Ki, and identified specific *ESR1, RB1* and *PTEN* alterations that appear likely to occur under the pressure of therapy. Our real-world analysis examining *RB1* LOF alts added further evidence to suggest it may be both a primary and acquired resistance mechanism to CDK4/6i. As a non-invasive alternative to tissue biopsies, this data further illustrates that cfDNA can provide unique insight into tumor evolution and disease progression in the aBC setting. Research Sponsor: None.

Biomarker	N of Pts+ Pre-CDK4/6i (%) (n = 800)	N of Pts+ Post-CDK4/6i (%) (n= 2,408)	Chi-square p value	N of Pts+ Pre-PI3Ki (%) (n = 399)	N of Pts+ Post-PI3Ki (%) (n = 93)	Chi-square p value
***ESR1* Alts**	156 (20)	709 (29)	< 0.0001	195 (49)	42 (45)	0.52
D538G	75 (9)	399 (17)	< 0.001	111 (28)	21 (23)	0.31
Y537S	50 (6)	234 (10)	0.003	68 (17)	15 (16)	0.83
Y537N	24 (3)	154 (6)	< 0.001	39 (10)	7 (8)	0.50
***PIK3CA* Alts**	273 (34)	814 (34)	0.87	374 (94)	75 (81)	< 0.001
***RB1* LOF**	13 (2)	116 (5)	< 0.0001	46 (12)	7 (8)	0.26
Splice Site Mutations	5 (1)	25 (1)	0.29	13 (3)	1 (1)	0.25
****PTEN* LOF**	-	-	-	19 (5)	8 (9)	0.14
T319fs	-	-	-	3 (1)	6 (6)	< 0.001

*Detected at ≤ 2%.

Circulating tumor DNA (ctDNA) and serum thymidine kinase 1 activity (TKa) matched dynamics in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor 2–negative (HER2-) advanced breast cancer (ABC) treated in first-line (1L) with ribociclib (RIB) and letrozole (LET) in the BioItaLEE trial.

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Background: Independent early dynamic assessment (baseline [D0] and day 15 of first cycle [D15]) of both TKa and ctDNA was prognostic and predictive in pts with HR+, HER2– ABC treated with RIB+-LET enrolled in the BioItaLEE trial (NCT03439046). Here we performed a combined analysis of these two biomarkers. **Methods:** 287 pts were enrolled in the study. Overall, early dynamics were assessable for both biomarkers in 241/287 pts (84.0%). Methods applied for ctDNA and TKa evaluation were previously reported. For ctDNA, samples were defined as wild type **(**WT) if no mutations were observed at D0 and D15, ctDNA positive (+) if with or negative (-) if without a primary target mutation at D15. Samples were TKa+ or TKa- if TKa levels were above or below the limit of detection at D15. According to ctDNA and TKa pts were classified as: WT/TKa-, WT/TKa+, ctDNA-/TKa-, ctDNA-/TKa+, ctDNA+/TKa- and ctDNA+/TKa+ and then divided into 3 main study groups (GRs) WT/TKa- (GR1, n = 126), WT/TKa+, ctDNA-/TKa-, ctDNA-/TKa+, ctDNA+/TKa- (GR2, n = 96) and ctDNA+/TKa+ (GR3, n = 19). The association between biomarkers and PFS (progression-free survival) was estimated using Kaplan-Meier analysis and multivariate Cox models with 95% confidence intervals (CIs) adjusted for clinical variables. **Results**: Median follow-up was 26.9 months. In multivariate Cox models both TKa dynamics and mutational tumor burden at D15 were independently predictive of PFS. Hazard ratios (HRs) were 0.37 (95% CI: 0.23-0.60; $p < 0.0001$) for WT vs ctDNA+ and 0.56 (95% CI: 0.32-1.00; $p = 0.0506$) for ctDNA- vs ctDNA+. For TKa, HR was 0.49 (95% CI: 0.30-0.80; $p = 0.0040$) in TKa- vs TKa+. Interestingly combining the two variables further improve prediction of outcome. HRs for TKa- vs TKa+ were 0.17 (95% CI: 0.09-0.32; $p < 0.0001$), 0.28 (95% CI: 0.13-0.59; $p = 0.0009$) and 0.44 (95% CI: 0.23-0.86; $p = 0.0169$) in WT, ctDNA- and ctDNA+ pts, respectively. Considering the 3 study GRs, median PFSs (95% CI) were not reached (27.89, NE), 19.58 (13.83, 23.39) and 6.65 (2.83, 12.16) months in GR1, GR2 and GR3, respectively, $p < 0.001$. At multivariate Cox models, HRs of GR1 and GR2 compared with GR3 were 0.17 (95% CI: 0.09-0.32; $p < 0.0001$) and 0.37 (95% CI: 0.20-0.67; $p = 0.001$) respectively. **Conclusions**: These findings suggest that combining the early dynamic assessment of both ctDNA and TKa may improve outcome prediction in pts treated with RIB+LET. Pts with ctDNA+/TKa+ are strongly enriched for non-responders. TKa and ctDNA capture different features of tumor biological activity and their combination warrants further evaluation in relation to other treatments, settings, and diseases. Clinical trial information: NCT03439046. Research Sponsor: Novartis Farma SpA.

Effect of socioeconomic status as measured by Neighborhood Deprivation Index on survival in metastatic breast cancer.

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Background: Socioeconomic status (SES) and race are major determinants of health outcomes in the United States. We aim to assess the effect of SES as measured by the Neighborhood Deprivation Index (NDI) and race on outcomes in metastatic breast cancer patients at our center. **Methods:** The NDI scores for patients with metastatic breast cancer who were treated at our center between 2000 and 2017 were obtained from the Neighborhood Atlas using their Zip-Code (N = 1246). The SES groups were defined as low deprivation with an NDI score in the bottom tertile and high deprivation with NDI in the top or middle tertiles. Baseline characteristics were compared between the SES groups with Bonferroni correction. Univariate and multivariate survival analysis were performed using the R packages "survival" and "survminer". **Results:** Race was the only baseline characteristic that was significantly different between the SES groups, the high deprivation group had a higher proportion of African Americans (10.5%) than the low deprivation group (3.7%, P = 9.3e-05). In univariate Kaplan-Meier survival analysis, both SES and race had significant effect on overall survival such that the high deprivation group had worse survival than low deprivation (Log Rank P = 0.01) and African Americans had worse survival than Caucasians (P = 0.008). In multivariate Cox proportional hazard model, SES, but not race, had a significant effect on overall survival (hazard ratio for high deprivation was 1.19 [95% Confidence interval 1.04 - 1.37], P = 0.01; Table). Progression-free survival on first-line chemotherapy was not different between the SES groups or racial groups in both univariate and multivariate analysis. **Conclusions:** The current study shows that patients from the high deprivation group (i.e., low SES), have worse survival in metastatic breast cancer. Race was no longer a significant predictor of survival when SES was accounted for in the analysis. This possibly suggests that poor outcomes in the African American population is explained by the association between low SES and African American race. Based on these results, there is an urgent need for healthcare investments in the low SES neighborhoods. Research Sponsor: None.

Cox proportional hazard model for survival in metastatic breast cancer.

	Hazard ratio [95% confidence interval]	P value
Race = Caucasian	0.8145 [0.6430 - 1.0318]	0.09
SES group = High deprivation (i.e., low SES)	1.1911 [1.0367 - 1.368]	0.01
Age at metastatic diagnosis	1.0095 [1.0045 - 1.0145]	0.0002
Subtype = ER+/HER2-	0.9685 [0.7702 - 1.2178]	0.78
Subtype = ER+/HER2+	0.8140 [0.6196 - 1.0692]	0.14
Subtype = Triple negative	2.0315 [1.5827 - 2.6077]	2.64e-08

1014 **Poster Discussion Session**

Increasing Black patient participation in metastatic breast cancer clinical trials: The BECOME (Black Experience of Clinical Trials and Opportunities for Meaningful Engagement) project.

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Background: Among U.S. racial/ethnic groups, Black people with breast cancer have the highest death rate and shortest survival. Although ~15% of cancer patients in the U.S. are Black, only 4-6% of clinical trial participants are Black. Only when trial participants reflect the diversity of the general population can oncologists understand how a drug works across subpopulations. The objectives of the BECOME initiative are to understand barriers to trial participation by Black patients with metastatic breast cancer (MBC) and to identify actions to increase participation. **Methods**: BECOME is sponsored by the Metastatic Breast Cancer Alliance, a consortium of representatives from nonprofit organizations, pharmaceutical/biotech companies, and patient advocates, many of whom are living with MBC. Findings from a literature review and Key Informant interviews informed a survey of U.S. adults living with MBC. **Results**: Of 424 survey respondents, 102 (24%) self-identified as Black. Black respondents' trust and satisfaction with their oncology care team were high (> 90%), and 83% of Black respondents were somewhat or very likely to consider trial participation. However, 40% of Black respondents reported no one on their care team had discussed trials. Black respondents' reasons to not participate in a trial included concerns about side effects (73%) and effectiveness (63%). Black respondents were more likely than non-Black respondents to believe unstudied treatments may be harmful (57% vs 31%). Black respondents were less likely than non-Black respondents to indicate they trust trials (73% vs 91%) and trust that people of all races/ethnicities get fair treatment in trials (32% vs 56%). Black respondents were more likely than non-Black respondents to value receiving trial information from someone with the same racial/ethnic identity (67% vs 10%), who has had breast cancer (73% vs 44%) or MBC (73% vs 51%), or who has been in a trial (72% vs 48%). Black respondents were also more likely to be motivated to participate to ensure people with their racial or ethnic identity will benefit (83% vs 51%). **Conclusions**: Black patients with MBC are willing to consider participating in clinical trials. Actionable steps to increase Black patient participation include: 1) enhancing awareness about trials by informing patients, increasing education, training healthcare providers to deliver patient-friendly information in an unbiased manner, and providing messaging from people of shared racial/ethnic identity and health experience; 2) building trust through clear communication; 3) addressing concerns about side effects, effectiveness, harm, and fair treatment; and 4) helping patients find and access trials. All stakeholder groups have a role to play in increasing Black patient participation in MBC clinical trials. Research Sponsor: Metastatic Breast Cancer Alliance.

1015 **Poster Discussion Session**

Quality of life (QOL) with ribociclib (RIB) plus aromatase inhibitor (AI) versus abemaciclib (ABE) plus AI as first-line (1L) treatment (tx) of hormone receptor-positive/human epidermal growth factor receptor–negative (HR+/HER2−) advanced breast cancer (ABC), assessed via matching-adjusted indirect comparison (MAIC).

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Background: The combination of a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) + endocrine therapy is the recommended 1L tx for HR+/HER2– ABC. A statistically significant overall survival (OS) benefit with RIB + AI was recently reported for MONALEESA-2 (ML-2); final OS results for the MONARCH 3 (MON-3) trial of ABE + AI are pending. QoL is an important end point that affects tx decisions. Understanding the impact of CDK4/6i on QoL is of increasing importance given use in earlier tx lines for ABC and an emerging role in treating early breast cancer, where QoL considerations may be more relevant. MAIC analysis allows for comparative effectiveness in the absence of head-to-head trial data. In this analysis, patient (pt)-reported QoL for the Phase III ML-2 (RIB + AI) and MON-3 (ABE + AI) trials were compared using MAIC with a focus on individual domains; the PALOMA-2 trial could not be considered for this analysis because of the different pt-reported outcome measures evaluated in the trial compared to ML-2 and MON-3. **Methods:** An anchored MAIC of QoL with RIB + AI vs ABE + AI was performed using data from EORTC QLQ-C30 and BR-23 questionnaires, individual participant data from ML-2 (data cutoff: 6/10/2021), and published data from MON-3 (data cutoff: 11/3/2017). All available QoL data were used in this analysis; the median follow-up for ML-2 was 79.7 months, and the median duration of follow-up at which QoL data were reported for MON-3 was 26.73 months. Inclusion and exclusion criteria were generally similar. Pts in both arms of ML-2 were weighted to match baseline characteristics in the corresponding arms of MON-3. Cox proportional hazards model was used to generate hazard ratios (HRs); anchored HRs were calculated using the Bucher method. Time to sustained deterioration (TTSD) was calculated as the time from randomization to a $\geq$ 10-point deterioration with no later improvement above this threshold. **Results:** 205 and 149 pts from the ML-2 arms of RIB/PBO were matched to 328 and 165 pts from the ABE/PBO arms of MON-3. After weighting, pt characteristics were well balanced. TTSD significantly favored RIB vs ABE in appetite loss (HR, 0.46; 95% CI, 0.27-0.81), diarrhea (HR, 0.42; 95% CI, 0.23-0.79), and fatigue (HR, 0.63; 95% CI, 0.41-0.96) as measured by QLQ-C30 and arm symptoms (HR, 0.49; 95% CI, 0.30-0.79) as assessed by BR-23. TTSD did not significantly favor ABE vs RIB in any functional or symptom scale of the QLQ-C30 or BR-23. **Conclusions:** This MAIC suggests that RIB + AI is associated with better symptom-related QoL vs ABE + AI for postmenopausal pts with HR+/HER2– ABC in the 1L setting. QoL differences between CDK4/6i and their associated adverse event profiles may impact clinical decisions in HR+/HER2– ABC. Research Sponsor: Novartis Pharmaceuticals.

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Characterization of alpelisib-associated hyperglycemia in metastatic breast cancer.

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Background: For women with metastatic hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative breast cancer, the combination of alpelisib and fulvestrant improves progression-free survival in those with *PIK3CA* mutations. Hyperglycemia is a major toxicity of PI3K inhibitors including alpelisib, which limits the clinical efficacy of these drugs due to interrupted/reduced dosing and discontinuation. In the SOLAR-1 trial that led to the Food and Drug Administration (FDA) approval of alpelisib, over 60% of patients developed hyperglycemia of any grade, and over 36% developed grade 3-4 hyperglycemia. Here we describe the incidence and treatment of alpelisib-associated hyperglycemia in a single center cohort. **Methods:** Patients with metastatic breast cancer who received alpelisib on a clinical trial or as part of standard care from 2013-2021 at Memorial Sloan Kettering Cancer Center were included in this retrospective study. Patient and tumor characteristics and pre-treatment body mass index (BMI), hemoglobin A1c, and serum glucose levels were abstracted from medical records. Alpelisib dose interruptions, reductions, or discontinuation was recorded as well as endocrinology consultation and use of anti-hyperglycemic agents. Date of progression and/or death were recorded where applicable. **Results:** 247 patients were included in this study, among whom 245 (99.1%) were female and 198 (80.1%) were white. 100 (40.5%) were treated on a clinical trial. Median baseline BMI was 25.4 kg/m^2. Among 164 patients with baseline hemoglobin A1c levels available, 93 (56.7%) patients had normal hemoglobin A1c, 54 (32.9%) had prediabetes, and 17 (10.4%) had diabetes. 152 patients (61.5%) developed hyperglycemia of any grade; 56 (22.7%) developed grade 3 and 16 (6.5%) developed grade 4 hyperglycemia. The median time to onset of hyperglycemia was 16 days. BMI $\geq$25 kg/m^2 or hemoglobin A1c $\geq$5.7% were strongly predictive of development of any-grade hyperglycemia (p= 0.036 and p< 0.001, respectively) and grade 3-4 hyperglycemia (p< 0.001 for both). Among those who developed hyperglycemia, 101 (40.9%) received treatment; 69 patients (27.9%) required only 1 anti-hyperglycemic agent whereas 9 (3.6%) required $\geq$3 anti-hyperglycemic agents. 49 (19.8%) were referred for endocrinology consult. In 66 patients (26.7%), alpelisib was held until resolution of hyperglycemia; 42 patients (17%) required dose reductions, and 11 (4.5%) discontinued alpelisib due to hyperglycemia. There was no significant difference in progression-free survival by hyperglycemia status or severity of hyperglycemia. **Conclusions:** Overweight BMI and hemoglobin A1c in the prediabetes or diabetes range were strongly predictive of developing alpelisib-associated hyperglycemia. Management of these co-morbidities prior to alpelisib treatment should be strongly considered. Research Sponsor: None.

Impact of ribociclib (RIB) dose modifications (mod) on overall survival (OS) in patients (pts) with HR+/HER2- advanced breast cancer (ABC) in MONALEESA(ML)-2.

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Background: The phase 3 ML-2, -3, and -7 trials all demonstrated consistent and statistically significant OS benefit with RIB (starting dose: 600 mg/d 3 wk on/1 wk off) vs PBO in pts with HR+/HER2– ABC. RIB dose mod (reductions and/or interruptions) when needed did not impact OS benefit with RIB + endocrine therapy (ET) in previous analyses of ML-3/-7. Here we present data on the effect of RIB dose mod on OS in postmenopausal pts with HR+/HER2– ABC in ML-2. **Methods:** ML-2 (NCT01958021) enrolled postmenopausal pts randomized 1:1 to first-line RIB + letrozole (LET) or PBO + LET. Landmark (LM) analyses of OS were performed to evaluate the association between dose reductions (yes vs no) and OS. Multiple LM times were considered to determine the sensitivity of the findings. As an alternative to LM analysis, a Cox proportional hazards model with a time-varying covariate was performed. Two time-dependent variables, dose reduction (with/without mod from 600 mg starting dose) and relative dose intensity 2 (RDI2), were included in the respective model as covariates to explore the association with OS. To account for differences in time to first dose mod, RDI2 reflects the post–dose mod period. Median (m) OS was obtained using a modified Kaplan-Meier method. **Results:** At data cutoff (June 10, 2021; m follow-up, 49.35 [range, 0-86.7] mo), 209 of 334 pts (62.6%) had ≥ 1 RIB dose reduction and 125 of 334 (37.4%) had 0 RIB dose reduction. LM analyses by dose reduction are presented (Table). mOS was 66.0 (95% CI, 57.6-75.7) mo in pts with ≥ 1 RIB dose reduction vs 60.6 (95% CI, 42.5-79.2) mo in pts with no RIB dose reductions (HR, 0.87 [95% CI, 0.65-1.18]). RDI2 was classified according to tertile: low (< 64.27%), medium (64.27%-95.86%), and high (> 95.86%). In pts with low, medium, and high RDI2, mOS was 62.6 (95% CI, 50.0-80.7) mo, 63.9 (95% CI, 48.8-not reached [NR]) mo, and 65.3 (95% CI, 50.5-NR) mo, respectively (HR low vs high, 0.99 [95% CI, 0.69-1.42]; HR medium vs high, 0.97 [95% CI, 0.62-1.38]). **Conclusions:** In this exploratory analysis of ML-2, OS benefit was maintained in pts with HR+/HER2– ABC who required mod from the recommended starting dose of RIB (600 mg/d 3 wk on/1 wk off). No relationship was observed between OS and RIB dose reduction or RDI2; OS benefit with RIB was observed in all groups. Clinical trial information: NCT01958021. Research Sponsor: Novartis Pharmaceuticals.

OS analysis for 3 LMT points.

LMT, mo[a]	Pts on treatment > LMT, n (%)	Dose reductionprior to LMT	Subgroup, n (%)	No. of events	2-year post-LMT OS rate (95% CI)[b]	Post-LMT HR (95% CI): Dose reduction Yes vs No
6	261 (78.1)	Yes	120 (46.0)	63	0.86 (0.80-0.93)	1.19 (0.85-1.68)
		No	141 (54.0)	68	0.88 (0.83-0.94)	
12	211 (63.2)	Yes	117 (55.5)	53	0.89 (0.83-0.95)	1.20 (0.79-1.82)
		No	94 (44.5)	38	0.89 (0.83-0.96)	
18	176 (52.7)	Yes	101 (57.4)	37	0.90 (0.84-0.96)	0.94 (0.57-1.53)
		No	75 (42.6)	29	0.88 (0.80-0.96)	

LMT, landmark time. [a]Each LMT represents a distinct pt population treated on and after the LM. [b]OS rate 2 years after given LMT.

Alpelisib (ALP) + endocrine therapy (ET) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–), *PIK3CA*-mutated (mut) advanced breast cancer (ABC): Baseline biomarker analysis and progression-free survival (PFS) by duration of prior cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) therapy in the BYLieve study.

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Background: ALP (PI3K-α selective inhibitor and degrader) + fulvestrant (FUL) is approved for pts with HR+, HER2– ABC and a tumor mutation in *PIK3CA* (~ 40% of these pts). Primary analyses from the Phase 2 BYLieve study demonstrated efficacy and safety of ALP + ET in pts with *PIK3CA*-mut, HR+, HER2– ABC in the post-CDK4/6i setting. Post hoc analyses, including pts with disease progression within 6 mo of CDK4/6i + ET treatment (Tx), confirmed ALP benefit regardless of duration of prior CDK4/6i. Here we assess baseline biomarkers in circulating tumor DNA (ctDNA) by duration of prior CDK4/6i Tx and PFS in pts from BYLieve Cohorts A and B. **Methods:** In the BYLieve study, pts with *PIK3CA*-mut, HR+, HER2– ABC had CDK4/6i + aromatase inhibitor (Cohort A) or + FUL (Cohort B) as immediate prior Tx to receiving ALP + FUL and ALP + letrozole (LET), respectively. At data cutoff dates, pts had ≥ 18-mo follow-up in Cohort A and ≥ 6-mo in Cohort B. In each cohort, pts were grouped based on duration of prior CDK4/6i Tx (≤ 6 mo or >6 mo). Alterations were detected on ctDNA using next-generation sequencing (PanCancer V2 Panel). PFS was assessed in each cohort and by duration of prior CDK4/6i Tx. **Results:** Of 127 and 126 pts enrolled in Cohorts A and B, respectively, 98 (≤ 6-mo: 24; >6-mo: 74) and 94 (≤ 6-mo: 28; >6-mo: 66) were included in this analysis based on availability of ctDNA samples, data on duration of prior CDK4/6i, and centrally confirmed *PIK3CA*-mut disease. In this population, median (m) PFS (95% CI) was 8.2 mo (5.6 - 9.5) and 5.6 mo (3.7 - 7.1) in Cohorts A and B, respectively. In Cohort A, mPFS (95% CI) was 12.0 mo (5.5-non estimable) and 6.2 mo (5.4 - 8.5) in the ≤ 6-mo and >6-mo groups, respectively. The OncoPrint genomic profiles showed that pts in the ≤ 6-mo vs >6-mo group had a lower median ctDNA fraction and fewer detected gene alterations, including in genes associated with ET and/or CDK4/6i resistance, and fewer chromosomes 8/11 amplifications (linked to early relapse). In Cohort B, mPFS was 5.9 mo (3.5 - 11.0) and 5.6 mo (3.7 - 7.1) in the ≤ 6-mo and >6-mo groups, respectively. Both groups had high median ctDNA fractions and complex tumor mutation profiles reflecting more extensive treatment history. **Conclusions:** Lower median ctDNA fraction and lower mutational complexity observed in Cohort A ≤ 6-mo vs >6-mo group was associated with numerically longer mPFS, potentially indicating increased dependence on the mutant PI3K-α. In Cohort B, both ≤ 6-mo and >6-mo groups had high median ctDNA fractions and similar tumor mutation profiles. Additional ctDNA and tissue analyses are needed to elucidate the correlation between ALP + ET efficacy and treatment timing and baseline genomic complexity. Research Sponsor: Novartis Pharmaceuticals Corporation.

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Baseline and longitudinal ctDNA biomarkers in GEICAM/2013-02 (PEARL) trial cohort 2 comparing palbociclib and fulvestrant (PAL + FUL) versus capecitabine (CAPE).

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Background: The randomized PEARL trial found no superiority of PAL plus endocrine therapy over CAPE in patients (pts) with metastatic HR-positive, HER2-negative breast cancer resistant to aromatase inhibitors (Martin M, Ann Oncol 2020). We investigated associations between baseline genomic landscape and on-treatment plasma ctDNA dynamics with progression free survival, in pts from cohort 2 of the trial. **Methods:** Plasma was collected for ctDNA analysis from -7 days to cycle 1-day 1 (C1D1) for baseline prognostic analysis and cycle 1-day 15 (C1D15) when available, and sequenced with an in-house error-corrected targeted capture panel encompassing 21 genes commonly altered in breast cancer. For predictive ctDNA dynamics analysis, a pre-specified criteria of 14 minimum days of treatment in first cycle was required and variants with VAF <0.5% in C1D1, set as limit of detection, were excluded. The circulating DNA ratio (CDR) was calculated as a weighted mean for potentially clonal mutations at C1D1. The optimal cut-off for predicting PFS was assessed by fitting a range of cut-offs, identifying the one with lower p-value on the log-rank test. Adjusted p-values, potential overestimation corrected by a shrinkage factor and bootstrapping techniques to calculate the CI95% were used in the cutpoint Cox regression model. **Results:** A total of 201 pts had a C1D1 sample sequenced for baseline prognostic analysis, 146 (73%) had baseline mutations identified and 55 (27%) had no mutations. 187 (93%) pts had a paired C1D15 sample for CDR calculations. Of these, 134 (72%) had baseline mutations detected, 120 of them (90%) above 0.5%, 14 (10%) had no calls, 1 pair failed sequencing. Both baseline and CDR subsets were representative of the overall study population. Pts with *TP53* mutations had worse PFS in the overall population (4.4 vs 9.3 months, logrank p= 0.04), with no differences between treatments. For on-treatment ctDNA dynamic analysis, median CDR (suppression) was lower in the CAPE arm (0.07 vs 0.21, p<0.01). There was an association between optimal cut-offs predicting PFS both in CAPE (suppressed 16.6 months vs high ctDNA 4.2 months, HR 2.37, CI95% 0.96-5.83, p=0.05) and PAL + FUL arms (suppressed 15.7 months vs high ctDNA 5.5 months, HR 2.14, CI95% 0.92-5, p=0.06). More ctDNA suppression associated with likelihood of objective responses (median CDR 0.1 in objective responders vs median CDR 0.2 in progressive disease p=0.03), with no statistical significance when stratified per treatment. **Conclusions:** In PEARL cohort 2, *TP53* mutations associated with poor outcome regardless of treatment allocation, suggesting aggressive behaviour not specifically linked to endocrine resistance. Lack of ctDNA suppression associated with worse outcome in both patient groups. Capecitabine resulted in greater ctDNA suppression at C1D15, likely reflecting faster ctDNA suppression. Research Sponsor: Pfizer and AstraZeneca.

1020 **Poster Discussion Session**

Survival in patients with breast cancer and history of autoimmune disease.

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Background: Patients with autoimmune disease, specifically systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjogren syndrome, are at reduced risk of developing breast cancer compared to those without a prior history of autoimmune disease. Despite this, little is known about the survival of patients with concurrent autoimmune disease and breast cancer. This study compared outcomes in patients with breast cancer with and without autoimmune disease. **Methods:** This study was a retrospective analysis of patients from SEER-Medicare databases from 2007-2014 with breast cancer. Patients with a history of autoimmune disease were identified using ICD-9 codes. The effects of autoimmune disease on overall survival (OS) and cancer-specific survival (CSS) were estimated using multivariable Cox regression and Gray's method respectively controlling the effects of age, race and chronic kidney disease (CKD). The cumulative CSS was estimated taking death as a competing risk. **Results:** The overall prevalence of investigated autoimmune diseases among the 137,324 patients with breast cancer was 26.69%. The most common autoimmune diseases identified were RA (23.35%), psoriasis (2.41%) and SLE (1.12%). In stage IV breast cancer patients the OS and CSS were significantly higher in patients with autoimmune disease (p values < 0.0001), with a median OS of 36 months compared to 30 months in patients without autoimmune disease. After adjusting for the effects of age, race, and CKD, autoimmune disease was still predictive of higher OS (HR: 1.46, 95% CI: 1.37 – 1.57, $p < 0.0001$) and CSS (HR: 1.39, 95% CI: 1.29 – 1.5, $p < 0.0001$). Patients with autoimmune disease and stage I-III breast cancer, had lower OS ($p < 0.0001$, $p < 0.0001$, and $p = 0.026$ respectively) compared to patients without autoimmune disease. **Conclusions:** We found a higher prevalence of RA, Crohn disease, ulcerative colitis, and SLE in patients with breast cancer compared to cohorts of similar age ranges in the general population. History of autoimmune disease resulted in significantly improved OS and CSS in patients with stage IV breast cancer even when controlling for age, race and CKD, in this pre-immunotherapy cohort. These results suggest that that anti-tumor immunity plays an important role in late-stage breast cancer, and could be potentially exploited to improve the effectiveness of immunotherapy. Further research into the relationship between autoimmunity and breast cancer is warranted. Research Sponsor: Department of Hematology and Oncology at University Hospitals Cleveland Medical Center.

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A phase 1a/b trial of imlunestrant (LY3484356), an oral selective estrogen receptor degrader (SERD) in ER-positive (ER+) advanced breast cancer (aBC) and endometrial endometrioid cancer (EEC): Monotherapy results from EMBER.

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Background: Imlunestrant is a novel, orally bioavailable SERD with pure antagonistic properties that result in sustained inhibition of ER-dependent gene transcription and cell growth. In dose escalation, imlunestrant showed favorable safety, pharmacokinetics (PK) and preliminary efficacy in patients with ER+, HER2- aBC and ER+ EEC (Phase 1a EMBER, Jhaveri 2021). Here we present updated data from the dose escalation (Phase 1a) and dose expansion (Phase 1b) of imlunestrant monotherapy in EMBER (NCT04188548). **Methods:** Phase 1a/1b enrolled patients with ER+ aBC (prior ET sensitivity; ≤3 prior therapies for aBC in Phase 1a following protocol amendment and ≤2 in Phase 1b) and ER+ EEC (prior platinum therapy; no prior fulvestrant or aromatase inhibitor). Premenopausal women received a concomitant GnRH agonist. Serial plasma samples were obtained for PK and ctDNA analysis. Key endpoints included recommended phase 2 dose (RP2D) determination, safety and tolerability, PK, objective response rate per RECIST v1.1 (ORR: complete response [CR] or partial response [PR]) in patients with measurable disease and ≥1 post-baseline tumor assessment or discontinued prior to tumor assessment, and clinical benefit rate (CBR: CR or PR, or stable disease ≥24 weeks) in patients enrolled ≥24 weeks prior to data cut. **Results:** As of January 14, 2022, 138 patients (n = 114 aBC, n = 24 EEC) received imlunestrant monotherapy at doses ranging from 200-1200 mg QD. Median age was 62.0 years (range 32-95). Median number of prior therapies for aBC and EEC was 2 (range 0-8) and 1 (0-5), respectively. aBC patients had received a prior ET (94.7%), CDK4/6 inhibitor (92.1%), fulvestrant (50.9%) and chemotherapy (26.3%). No dose-limiting toxicities were observed. Most treatment-emergent adverse events (TEAEs) were grade 1. At the RP2D (400 mg QD, n= 69), the most common all grade TEAE's were nausea (33.3%), fatigue (27.5%), and diarrhea (23.2%). Across all doses, the incidence of treatment-related grade 3 AEs was low (3.6%). No patient discontinued due to a TEAE. In evaluable aBC patients, ORR was 8.0% (6/75) and CBR was 40.4% (42/104). In evaluable EEC patients, ORR was 5.0% (1/20 had a PR- ongoing pending confirmation) and CBR was 47.1% (8/17). Clinical benefit was observed regardless of baseline *ESR1* mutation status as determined by ctDNA sequencing. Additional biomarker analyses will be presented at the meeting. **Conclusions:** Imlunestrant continues to demonstrate a favorable side effect profile, with no cardiac or opthalmic safety signals, and has continued evidence of clinical activity in heavily pre-treated ER+ aBC and EEC patients. Clinical trial information: NCT04188548. Research Sponsor: Eli Lilly and Company.

1022 **Poster Discussion Session**

Open-label, phase 2, multicenter study of lasofoxifene (LAS) combined with abemaciclib (Abema) for treating pre- and postmenopausal women with locally advanced or metastatic ER+/HER2− breast cancer and an *ESR1* mutation after progression on prior therapies.

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Background: Resistance to endocrine therapy can develop when treating estrogen receptor positive (ER+), metastatic breast cancer (mBC). Treatment with aromatase inhibitors can lead to acquired mutations in the estrogen receptor 1 (*ESR1*), which can constitutively activate the ER, leading to endocrine resistance and worse disease prognosis. Treatment options for mBC patients with an *ESR1* mutation are limited. Further, data suggest that patients could derive clinical benefit from Abema after progression on prior cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). LAS, a third-generation selective estrogen receptor modulator, as monotherapy or combined with a CDK4/6i, was shown to have superior efficacy over fulvestrant (FVT) in preclinical breast cancer models expressing *ESR1* mutations. Based on these results, a phase 2 clinical trial of LAS combined with Abema was initiated in mBC patients with *ESR1* mutations. **Methods:** ELAINE 2 is an open-label, phase 2, multicenter trial evaluating the safety and efficacy of LAS combined with the CDK4/6i, Abema. Study participants were pre- and postmenopausal women with ER+/HER2- mBC with acquired *ESR1* mutation (identified by ctDNA testing), whose disease had progressed on one or two lines of hormonal therapy for metastatic disease with or without a CDK4/6i (including Abema). Patients took oral LAS 5 mg/day and Abema 150 mg BID. Treatment continued until evidence of disease progression, death, unacceptable toxicity, or withdrawal from the study. The primary endpoint was safety, and secondary endpoints were progression free survival (PFS), objective response rate (ORR), and clinical benefit rate (CBR). **Results:** 29 patients were enrolled at 16 US sites (Oct 2020 to June 2021). Mean age was 58.3 y (35-79 y); 86% were Caucasian. Most had progressed with at least 2 previous hormonal treatments (80%). All except 1 patient received a prior CDK4/6i and 72% had received prior FVT; 48% had chemotherapy in the metastatic setting. Four patients discontinued the trial due to adverse events (AEs, n = 2), consent withdrawal (n = 1), or investigator withdrawal (n = 1). No deaths occurred during the study and few Grade 3/4 AEs were observed. Most common AEs were diarrhea, nausea, and leukopenia. Five patients had an Abema dose reduction from 150 mg to 100 mg BID. To date, 11 patients have progressed and 14 continue treatment. The censored median PFS was 13.9 mos (95% CI, 8.0–NE), the ORR 33.3% (95% CI, 16.3–56.3) with 6 confirmed partial responses, and the CBR 62.1% (95% CI, 44.0–77.3). **Conclusions:** LAS combined with Abema in the ELAINE 2 trial was well tolerated and demonstrated robust and meaningful efficacy in women with ER+/HER2- mBC and an *ESR1* mutation who had progressed on previous CDK4/6i therapies. Clinical trial information: NCT04432454. Research Sponsor: Sermonix Pharmaceuticals.

1023 **Poster Discussion Session**

A phase 1b/2 study of the BET inhibitor ZEN-3694 in combination with talazoparib for treatment of patients with TNBC without gBRCA1/2 mutations.

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Background: Metastatic triple negative breast cancer (mTNBC) is an aggressive and heterogeneous cancer with limited therapeutic options. PARP inhibitors (PARPi), approved to treat patients with HER2- breast cancer with a germline BRCA1/2 (gBRCA1/2) mutation, have not shown efficacy in homologous recombination repair (HRR) proficient tumors. In pre-clinical models, the BET inhibitor (BETi) ZEN-3694 sensitizes wild-type (WT) BRCA1/2 tumors to PARPi through downregulation of HRR gene expression, providing a rationale for combination therapy. We previously reported results from the Ph 1b portion of the trial evaluating the combination of ZEN-3694 plus talazoparib, in TNBC patients without gBRCA1/2 mutations; here we present results from the completed Ph 1b/2 study. **Methods:** A Ph 1b dose finding portion (n = 15) was followed by a single arm Ph 2 Simon 2-stage portion (n = 17+20 (37)). The primary endpoint of the Ph 1b portion of the study was safety and recommended Ph 2 dose (RP2D). The secondary endpoints were pharmacokinetics (PK), pharmacodynamics (PD), and clinical benefit rate (CBR = confirmed objective response rate (ORR) + stable disease > 16 weeks). Ph 2 measured CBR as the primary endpoint, ORR and duration of response (DOR) as key secondary endpoints. Eligibility criteria for Ph 1b included TNBC (ER/PR < 10%, HER2-), WT gBRCA1/2, and > 1 prior cytotoxic regimen for mTNBC, and in the Ph2 portion ER/PR < 1% and < 2 prior cytotoxic regimens for mTNBC. Patients were dosed daily in continuous 28 day cycles until disease progression or unacceptable toxicity. Adverse events, PK, and PD in whole blood and tissue biopsies were assessed. Response endpoints were assessed per RECIST 1.1 every 2 cycles. **Results:** RP2D was determined to be 48mg qd ZEN-3694 plus 0.75mg qd talazoparib. The most common AE for the Ph 1b/2 study was thrombocytopenia (TCP) (55% any grade, 34% G3/4), which was managed with dose holds and reductions. Dose intensity analysis showed average daily doses of ZEN-3694 and talazoparib could be maintained above 40mg and 0.5mg, respectively, over 8 cycles. Robust target engagement was demonstrated using BET-dependent and HRR transcripts assessed in paired tumor biopsies. Ph 2 portion of the trial met its primary endpoint with a CBR of 30% (11/37). For the Ph 1b/2 trial, investgator assessed ORR was 22% (11/50), including 2 CR, CBR was 35% (18/51) and the median DOR was 24 weeks. For the subset of TNBC at diagnosis patients (no history of HR+ disease), ORR was 32% (11/34), and CBR was 44% (15/34). **Conclusions:** Combination of ZEN-3694 and talazoparib demonstrated anti-cancer activity in pretreated mTNBC WT gBRCA1/2 patients. All confirmed responses were observed in TNBC at diagnosis patients, whose tumors are expected to be more sensitive to the combination due to their basal-like properties. The trial is being expanded to Ph. 2b to accrue an additional 80 TNBC at diagnosis patients. Clinical trial information: NCT03901469. Research Sponsor: Zenith Epigenetics.

Results from plasmaMATCH trial cohort E: A phase II trial of olaparib and ceralasertib in patients with triple-negative advanced breast cancer (CRUK/15/010).

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Background: The plasmaMATCH trial was an open label platform trial, consisting of circulating tumour DNA (ctDNA) testing in ~1000 patients with advanced breast cancer (ABC) linked to parallel treatment cohorts with therapies matched to mutations identified in ctDNA. Cohorts A-D have already reported (Turner N et al, Lancet Oncol 2020). Cohort E recruited patients with triple negative breast cancer (TNBC) without a targetable mutation identified at ctDNA screening, treating with olaparib (PARP inhibitor) plus ceralasertib (ATR inhibitor). **Methods:** Patients with TNBC who had received 1 or 2 lines of chemotherapy for advanced disease or relapsed within 12 months of (neo)adjuvant chemotherapy were eligible. Treatment was olaparib 300mg b.i.d continuously and ceralasertib 160mg qd on days 1–7 on a 28 day cycle, until disease progression. The primary endpoint was confirmed objective response rate by RECIST v1.1. Secondary endpoints included clinical benefit rate, progression-free survival (PFS) and safety. Biomarker analysis included response according to *BRCA* and somatic DNA repair gene status and ATM loss. Using a two-stage design with a target response rate of 25%, unacceptable response rate of 10%, alpha=2% and power=90%, ≥13 responses out of 69 evaluable stage 2 patients were required to infer efficacy (5/37 stage 1). **Results:** Between 17/09/18 and 5/10/20 75 patients enrolled in Cohort E of whom 70 were evaluable for response. The median age was 55.6 years. 42 (56%) patients had 1 and 13 (17.3%) had 2 prior line(s) of chemotherapy for metastatic disease. Efficacy is shown in Table. The most common grade ≥3 adverse events were: hypertension 12 (17%) and anaemia 9 (13%). Dose reductions and interruptions occurred in 19 (26.4%) and 34 (47.2%) patients respectively. **Conclusions:** The response rate to olaparib and ceralasertib did not meet pre-specified criteria for efficacy in the overall evaluable population. Responses were observed in patients without germline or somatic BRCA1/2 mutations. Translational analyses are underway to identify potential biomarkers of response in this population and will be presented at the meeting. Clinical trial information: ISRCTN16945804. Research Sponsor: Cancer Research UK and Stand Up To Cancer, Pharmaceutical/Biotech Company.

Response rates and median PFS.

Population	N	Number of confirmed responses	Confirmed response rate, % (95%CI)	Median PFS (IQR), months
All evaluable patients	70	12	17.1 (9.2, 28.0)	4.3 (1.9, 10.0)
***BRCA1/2* germline mutation**	10	3	30 (6.7, 65.2)	8.4 (6.1, 25.4)
***BRCA1/2* germline or somatic mutation**	13	3	23.1 (5.0, 53.8)	7.3 (4.5, 25.4)
No germline or somatic *BRCA1/2* mutation^	55	9	16.4 (7.8, 28.8)	3.7 (1.9, 10.0)
ATM loss*	14	3	21.4 (4.7, 50.8)	3.4 (1.4, 10.2)
No ATM loss*	29	4	13.8 (3.9, 31.7)	2.5 (1.9, 10.0)

*ATM loss defined as H score ≤10. ATM loss subgroup analysis was restricted to those with no *BRCA1/2* germline or somatic mutation. 12 patients had either a missing or inadequate sample. ^2 patients did not have somatic BRCA testing.

1025 **Poster Session**

The mutational profile of ER-, PR+, HER2- metastatic breast cancer.

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Background: ER-PR+Her2- breast cancer is a rare subtype occurring at approximately 1% of all breast carcinomas. Most of these cancers behave in an aggressive fashion with limited benefit from anti estrogen therapy, similar to triple negative breast cancer (TNBC). Better characterization of these tumors is needed for predicting clinical behavior, response to endocrine therapy, and eligibility for clinical trials. Here we sought to evaluate the mutational profile of a well curated set of ER-PR+HER2- metastatic breast cancers and compare to other receptor phenotypes. **Methods:** 2049 consecutive breast cancers submitted to Foundation Medicine for comprehensive genomic profiling (CGP) were included. ER, PR and HER2 expression were abstracted from submitted pathology reports. Cases without complete ER, PR and HER2 information in pathology reports were excluded. CGP was performed as previously described (Frampton, 2013). **Results:** Patient ages were similar across subgroups. Generally, ER-PR+HER2- tumors were rare (n = 23, 1.1%) and most similar to TNBC in their genomic profiles. These tumors harbored high rates of *TP53* and *BRCA1* alterations and low rates of *PIK3CA, ESR1,* and *CDH1* alterations. Genomic loss of heterozygosity (gLOH) was similar in the ER-PR+HER2- and ER+PR+HER2-subtypes (8.18% and 8.66% respectively), and lower than TNBC (17.19%). Notably, a high rate of *RB1* alterations were identified in the ER-PR+HER2- patients (13%, 3/23), numerically higher than the other subtypes. *EGFR*, *MET*, *PTEN*, *CDKN2A* and *KRAS* alterations were also observed at a higher frequency in ER-PR+Her2- cancers (8.7, 4.2, 39.1, 13.0 and 13.0% respectively) relative to the other subtypes. IO drug biomarkers including MSI, TMB and PD-L1 IHC were similar among the groups. **Conclusions:** The mutational profile for ER-PR+Her2- metastatic breast cancer more closely resembles TNBC than ER+ breast cancer. These data suggest molecular profiling may be a useful adjunct to optimize treatment strategies for this rare subset of cancers. Based on molecular characteristics, we recommend including ER-PR+Her2- patients in clinical trials for TNBC. Finally, genes including RB1, *CKDN2A*, *PTEN*, *EGFR* and *MET* are mutated at higher frequency in ER-PR+Her2- cancers than other subsets, suggesting unique biology with potential therapeutic implications. Research Sponsor: None.

	Overall cohort	ER+ PR+ HER2-	ER+ PR- HER2-	ER- PR+ HER2-	HER2+	TNBC
Number of Cases (% cohort)	2049	906 (44.2%)	388 (18.9%)	23 (1.1%)	178 (8.7%)	554 (27.0%)
Median Age (range)	59 (24-89+)	60 (26-89+)	61 (24-89+)	54 (29-85)	54 (30-89)	56 (22-89+)
CDH1	14.32%	17.70%	23.50%	4.30%	4.80%	5.90%
TP53	51.53%	27.80%	43.10%	91.30%	72.50%	88.10%
RB1	4.06%	3.00%	5.90%	13.00%	3.00%	4.50%
PIK3CA	37.86%	48.60%	43.30%	21.70%	36.50%	17.70%
BRCA1	3.37%	1.30%	2.30%	8.70%	1.20%	8.00%
RAD21	21.91%	18.80%	16.80%	13.00%	35.30%	26.70%
ESR1	8.97%	14.40%	9.50%	4.30%	5.40%	1.10%

1026 **Poster Session**

A phase II, single-arm, open label, Simon two-stage study of pembrolizumab in patients with metastatic HER2-negative breast cancer: Evaluation of impact of germline variants in APOBEC3B (AUROR).

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Background: A germline deletion in the *APOBEC3B* cytosine deaminase gene [A3Bdel] occurs more frequently in Asian women (45% heterozygous deletion (hetD) and 15% homozygous deletion (homD)) compared to in Caucasian women (15% hetD and 4% homD). Carriers are more likely to develop breast cancer, and cancers in carriers are more likely to have a hypermutator phenotype (with C > T transitions) and to be immune-enriched. In this clinical trial, we aim to evaluate whether the immune activation increases response to checkpoint immunotherapy. **Methods:** In this open label, single arm Phase II study of single agent pembrolizumab in metastatic HER2-receptor negative breast cancer patients with germline deletion in A3B, 40 evaluable subjects who have received > = 1 but < = 3 lines of therapy in a metastatic setting will be enrolled and given pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 administrations (2 years), with Objective Response Rate (ORR) using RECIST 1.1 as the primary study endpoint. The study applies a Simon two-stage design, where if at least 3 out of 22 evaluable patients achieve CR/PR in stage I, the study will proceed to stage II. **Results:** To date, 84 breast cancer patients were screened for germline A3Bdel, of whom 46 (54.8%) were heterozygous carriers and 12 (14.3%) were homozygous carriers. The study enrolled 22 female A3Bdel carriers with a median age of 59.4 years (range: 32.1, 82.9 years) between September 2020 and September 2021 for stage I analysis. On average, patients received 2 prior lines of chemotherapy in a metastatic setting [6 with 1, 8 with 2 and 8 with 3 lines of prior chemotherapy]. Complete response (CR) was observed in one patient, while partial response (PR) was observed in 4 patients, with an ORR of 22.7% (5 over 22 subjects) in stage I, meeting the pre-defined criteria to proceed to stage II. Notably, the patient with complete response had received 2 prior lines of chemotherapy, whereas of the patients with partial response, 1 had received 1 prior line and 3 had received 3 prior lines of chemotherapy in a metastatic setting. As the observed ORR was greater than the value of r_1 (13.6%), the study has met the statistical criteria to proceed to the stage II enrolment with an additional 18 patients required to complete the entire study. **Conclusions:** Single agent pembrolizumab demonstrates promising efficacy in germline A3Bdel carriers, who constitute almost two-thirds of Asian patients. Clinical trial information: NCT03989089. Research Sponsor: Cancer Research Malaysia, Other Foundation.

1027 **Poster Session**

Targetable genomic mutations in young women with advanced breast cancer.

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Background: Advanced breast cancer in women < 40 years is more aggressive, with worse prognosis and disease-free survival, compared to older women with the disease. With increasing availability of targeted and immune therapies, we aimed to compare genomic alterations (GA) using comprehensive genomic profiling (CGP) of tumor tissue. **Methods:** We analyzed 2,049 breast cancers submitted to Foundation Medicine for CGP. Hybrid-capture based CGP was performed to evaluate all classes of GA. Tumor mutational burden (TMB) was determined on at least 0.8 Mbp of sequenced DNA and microsatellite instability was determined on at least 95 loci. Tumor cell PD-L1 expression (defined as tumor proportion score >/= 1) was determined by IHC (Dako 22C3). We identified 28 (1.37%) patients <30 years, 159 (7.76%) between 30-39 years, and 1862 (90.87%) >/= 40 years. Breast tissue was used for CGP in 69.5% of cases and remainder of specimens were lymph node, metastatic, or unspecified. **Results:** Breast tumors were less likely to be estrogen receptor positive in younger women (54% of those <30 years, 60% of those 30-39 years, 69.4% of those >/= 40 years) and more likely to be triple negative (43%, 33%, 26.1% in the same respective groups). There was no clear pattern in HER2+ status by age (0%, 15.1%, 7.2%). Younger women had higher rates of *BRCA1* (17.9%, 10.1%, 2.6%), *BRCA2* mutations (7.10%, 5.70%, 4.1%), and *RB1* mutations (14.3%, 9.4%, 6.1%), and lower rates of *CDH1* (7.1%, 5%, 15.4%) and *PIK3CA* mutations (17.9%, 17.6%, 40.0%). Younger women were more likely to have PD-L1 expression (55.6%, 54.4%, 51.5%) but had lower frequencies of TMB >10 (0.0%, 5.0%, 8.7%). Differences are statistically significant in *BRCA1*, *CDH1*, and *PIK3CA*. **Conclusions:** These findings confirm that young women with breast cancer have actionable GA. Different mutational profiles may support differential use of targeted and immune therapies. Statistically and clinically significant differences include higher *BRCA1* mutations which may lend to PARP inhibitor use and lower *PIK3CA* mutations which may reduce alpelisib use. Higher *RB1* mutations and immunotherapy biomarker differences were not statistically significant. However, these may clinically translate into CDK4/6 resistance and reduced immunotherapy options, respectively. Research Sponsor: None.

	All Cases All Ages (n = 2049)	<30 Years of Age (n = 28)	30-39 Years of Age (n = 159)	>/= 40 Years of Age (n = 1862)	<30 Comparison to >/= 40	30-39 Comparison to >/= 40
ER+ / PR+ Status by IHC	70.0% / 49.0%	54% / 57%	60% / 45%	69.4% / 49.3%	NS / NS	P<0.0001 / NS
HER2+ (ERBB2 Amplification by CGP)	8.7%	0%	15.10%	7.2%	NS	P=.0005
TNBC Status	27.0%	43%	33%	26.1%	NS (P=.052)	NS (P=.051)
BRCA1 / *BRCA2*	3.37% / 4.25%	17.90% / 7.10%	10.10% / 5.70%	2.6% / 4.1%	P=0.0009 / NS	P<.0001 / NS
RB1	6.9%	14.30%	9.40%	6.1%	NS	NS
CDH1	14.32%	7.10%	5.00%	15.4%	NS	P.0001
PIK3CA	37.86%	17.90%	17.60%	40.0%	P=.02	P<.0001
TMB > 10	8.60%	0.00%	5.00%	8.7%	NS	NS
PD-L1 Positive	51.10%	55.60%	54.40%	51.5%	NS	NS

Neratinib plus fulvestrant plus trastzuzumab (N+F+T) for hormone receptor-positive (HR+), HER2-negative, *HER2*-mutant metastatic breast cancer (MBC): Outcomes and biomarker analysis from the SUMMIT trial.

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Background: N is an oral, irreversible pan-HER TKI with activity against *HER2* mutations. Genomic analyses from the SUMMIT MBC cohort following N±F suggest that resistance to N may occur via mutant allele amplification or secondary *HER2* mutations. Adding T to N+F in SUMMIT showed encouraging durable responses in patients (pts) with HR+, *HER2*-mutant MBC and prior CDK4/6 inhibitors (CDK4/6i). **Methods:** SUMMIT (NCT01953926) enrolled pts with HR+, HER2-negative MBC with activating *HER2* mutation(s) and prior CDK4/6i. Pts received N+F+T (oral N 240 mg/d with loperamide prophylaxis, im F 500 mg d1&15 of cycle 1 then q4w, iv T 8 mg/kg initially then 6 mg/kg q3w). During the small, randomized portion of the trial, pts received N+F+T, F+T or F (1:1:1 ratio). Pts randomized to F+T or F could crossover to N+F+T at progression. Efficacy endpoints: investigator-assessed ORR and CBR (RECIST v1.1); DOR; best overall response. Pre-treatment tumor tissue was centrally assessed retrospectively by next-generation sequencing. ctDNA from patient samples was assessed by NGS. **Results:** SUMMIT has completed enrolment; we report efficacy from 45 pts in the N+F+T cohort, plus 10 pts who progressed on F (n=6) or F+T (n=4) and crossed over to N+F+T (Table). *HER2* allelic variants in the 45 N+F+T pts and ORR (%) (pts may have >1 mutation) were: V777L (n=6, 50%), L755S/P (n=15, 40%), S310F (n=4, 50%), exon 20 insertion (n=11, 36%), other KD missense (n=6, 33%), TMD missense (n=2, 0%), exon 19 deletion (n=1, 0%). **Conclusions:** N+F+T is a promising combination for HR+, *HER2*-mutated MBC with prior exposure to CDK4/6i, across a range of activating *HER2* mutations. Results from the upcoming Apr 2022 data cut, including biomarkers, safety, mechanisms of acquired resistance, and preclinical mechanism of N+T, will be presented. Clinical trial information: NCT01953926. Research Sponsor: Puma Biotechnology, Inc.

Efficacy findings: HR+, *HER2*-mutant MBC with prior CDK4/6i.

	All HR+ prior CDK4/6i (N+F+T) (n=45)	Randomized HR+ (F+T) (n=7)	F+Tcrossover to N+F+T (n=4)	Randomized HR+ (F) (n=7)	Fcrossover to N+F+T (n=6)
Objective response,[a] n (%) (95% CI)	17 (38) (24–54)	0 (0–41)	1 (25) (0.6–81)	0 (0–41)	2 (33) (4–78)
CR PR	1 (2)16 (36)	00	01 (25)	00	02 (33)
Median[b] DOR, months (95% CI)	14.4 (6.4–NE)	NE	NE	NE	6.3 (6.2–6.4)
Clinical benefit,[c] n (%) (95% CI)	21 (47) (32–62)	0 (0–41)	1 (25) (0.6–81)	0 (0–41)	5 (83) (36–100)
CR PR SD ≥ 24 weeks	1 (2)16 (36)4 (9)	000	01 (25)0	000	02 (33)3 (50)
Median PFS, months (95% CI)	8.2 (4.2–15.1)	3.9 (1.9–4.1)	NE	4.1 (1.6–4.1)	8.3 (3.9–10.3)

[a]CR or PR confirmed ≥ 4 weeks after response criteria met.[b]Kaplan-Meier analysis.[c]Confirmed CR or PR or SD for ≥ 24 weeks. Tumor response based on investigator assessment (RECIST v1.1).CI, confidence interval; CR, complete response; DOR, duration of response; F, fulvestrant; HR+, hormone receptor-positive; N, neratinib; NE, not evaluable; PR, partial response; SD, stable disease; T, trastuzumab.

1029 **Poster Session**

Detection of presumed germline pathogenic variants of hereditary breast cancer predisposition genes in circulating tumor DNA: SCRUM-Japan MONSTAR-SCREEN.

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Background: Approximately 5-10% of breast cancer are hereditary. Variant allele frequency (VAF) of hereditary breast cancer predisposition genes in circulating tumor DNA (ctDNA) may be useful for detecting presumed germline pathogenic variants. **Methods:** One hundred and sixty-eight patients with advanced breast cancer (ABC) who underwent ctDNA and tumor tissue sequencing analyses in the SCRUM-Japan MONSTAR-SCREEN, a cancer genome screening project in Japan, from December 2019 to November 2021 were included. The patients were tested and monitored for their genomic alterations by FoundationOne Liquid assay or FoundationOne Liquid CDx assay. The pathogenic variants (PV) of hereditary breast cancer predisposition genes with VAF of 30% or higher in ctDNA were defined as PGPV. The VAF of *BRCA1/2* on ctDNA analyses in *BRCA1/2* germline pathogenic variant (GPV) carriers and the prevalence of PGPV in five hereditary breast cancer predisposition genes, including *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*, were investigated. **Results:** From 168 patients with ABC, including 115 Luminal, 32 HER2-positive, and 21 triple negative breast cancer, with a median age of 58 years, 39 PVs in 5 genes were identified with a median VAF of 0.62% (range: 0.1-84.77). ctDNA identified GPV of known *BRCA1/2* GPV carriers (1 with *BRCA1* and 6 with *BRCA2*), with a median VAF of 51.4% (range: 48.2-77.5). The VAF of GPV on ctDNA were higher than 30% in subsequent consecutive samples. Among 161 patients with ABC, excluding 7 known *BRCA1/2* GPV carriers, 6 PGPV (1 with *BRCA1*, 3 with *BRCA2*, and 2 with *PALB2*) were detected, with a median VAF of 65.5% (range: 51.2-84.8). Subsequent confirmatory tests were performed for two PGPV, and the variants were confirmed to be of germline origin. **Conclusions:** VAF on ctDNA analysis can help to easily detect PGPV of hereditary breast cancer predisposition genes. The PGPV detected in ctDNA analysis should be validated by established germline tests, and the results could provide opportunities for targeted therapies, as well as cancer risk assessment of patients and their relatives. Research Sponsor: None.

Association of interleukin-enhanced factor 2 (ILF2) expression with prognosis and clinico-genomic features in breast cancer (BC).

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Background: Novel prognostic and predictive biomarkers beyond traditional histological subtypes are needed to better inform outcomes and enhance therapy guidance in breast cancer (BC). We have previously reported that ILF2 was overexpressed in TNBC cell lines and has a functional role in DNA and RNA metabolism, making it a promising biomarker for risk assessment and treatment decisions. Herein, we aim to leverage a large clinico-genomic dataset to further characterize ILF2 in BC patients (pts). **Methods:** A total of 9456 BC tissue samples underwent molecular profiling at Caris Life Sciences (Phoenix, AZ). Analyses included next generation sequencing of DNA (592 Gene Panel, or Whole Exome Sequencing), and RNA (Whole Transcriptome Sequencing), and immunohistochemistry (IHC). Wilcoxon and Fisher's exact were used to determine statistical significance. Overall survival (OS) was obtained from insurance claims and Kaplan-Meier estimates were calculated. Spearman correlation was used to identify highly correlated genes (ρ>0.6) with ILF2 and significant genes that were subsequently analyzed via pathway analysis using STRING. **Results:** BC pts were grouped into ILF2-High (H, top quartile) and ILF2-Low (L, bottom quartile) based on mRNA expression (TPM). ILF2-H pts were significantly younger (73 vs 80% for pts >50), enriched in ductal histology (90.9 vs 77.7%), TNBC subtype (48.9 vs 18.9%), and had a higher CNS metastases rate (4.3 vs 1.4%) compared to ILF2-L pts (all q<0.0001). ILF2 overexpression was associated with significantly inferior OS in all BC pts (HR 3.38, 95%CI: 2.97 – 3.84); when stratified into known BC hormonal receptor (HR) subtypes, ILF2 was prognostic in both HR+ BC (HR 1.7, 95 CI: 1.34-2.19) and TNBC (HR 3.8, 95 CI: 3.1-4.7), all p<0.0001. In TNBC (n=2468), ILF2-H was associated with a higher frequency of TP53 mutations(mt), lower rate of PIK3CA mt and higher amplification of CCNE1 and FGF23; in HR+/HER2- BC (n = 5071), an association with a higher rate of TP53 mt, PD-L1 expression, NOTCH2 and CCND2 amplification was seen (Table). No significant molecular correlation with ILF2 was seen in HR-/HER2+ BC (n=682). In TNBC, ILF2 expression was significantly correlated with genes involved in spliceosome, cell cycle and RNA transport pathways. In HR+/HER2- BC, ILF2-correlated genes were significantly enriched in mismatch repair and DNA replication pathways (p<0.05 for all factors individually). **Conclusions:** High expression of ILF2 is associated with a poorer prognosis independent of subtype in BC and our study warrants further investigation on ILF2 as a diagnostic and therapeutic target. Research Sponsor: None.

Fold change of ILF2 median in altered/WT tumors (>1, positive; <1, negative association, q <0.05).

Mt	TNBC	Mt	HR+/HER2-
TP53	1.4	TP53	1.2
PIK3CA	0.7	MAP2K4	0.8
ARID1A	0.7	IHC	
HRAS	0.5	IHC-PD-L1	1.2
KRAS	0.6	IHC-AR	0.7
TERT	0.6	Amp	
		NOTCH2	2.1
Amp		FGF23	2.3
FGF23	1.5	CCND2	2.3
CCNE1	1.4	CCNE1	1.6

1031 **Poster Session**

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

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Background: HER2-targeted agents have improved outcomes in HER2-positive breast cancer, but 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. In a Phase 1 trial (NCT02892123) zani was well tolerated and demonstrated preliminary antitumor activity as monotherapy/with chemotherapy in pts with pre-treated advanced HER2+ breast cancer. **Methods:** Cohort 1 of this ongoing open-label, Phase 1b/2 study (NCT04276493) is evaluating zani in combination with docetaxel as a 1L therapy in adult females with advanced HER2+ breast cancer who may have received prior neoadjuvant/adjuvant treatment. Cohort A pts received zani 30 mg/kg IV, Cohort B pts received zani 1800 mg IV, both with docetaxel 75 mg/m^2 IV Q3W. 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), disease control rate (DCR) and progression-free survival (PFS). **Results:** As of Nov 26, 2021, 25 pts with a median age of 57.0 years (range: 33.0–80.0) were assigned to Cohort A (n=11) or B (n=14). Median study follow-up was 7.0 months (range: 1.1–17.4) and the median number of treatment cycles was 10 (range: 2–20), 16 (64.0%) pts remained on treatment. Of the 22-efficacy evaluable (EE) pts, confirmed ORR was 86.4% (95% CI: 65.1, 97.1). The 6 months PFS rate was 90.9% (95% CI: 68.3, 97.7). Efficacy data are summarized in Table 1. All pts experienced ≥ 1 treatment emergent adverse event (TEAE) and 17 (68.0%) pts experienced ≥ Grade 3 TEAEs. In total, 23 (92.0%) pts experienced treatment related TEAEs (trTEAEs), and 17 (68.0%) pts experienced ≥ Grade 3 trTEAEs. The most common trTEAEs were diarrhea (56.0%) and decreased neutrophil count (52.0%). Serious trTEAEs occurred in two (8.0%) pts, trTEAEs leading to treatment discontinuation occurred in one (4.0%) pt and no trTEAEs led to death. **Conclusions:** Zani and docetaxel combination demonstrated antitumor activity in 1L therapy for advanced HER2+ breast cancer, with a manageable safety profile. Clinical trial information: NCT04276493. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Victoria Dagwell, MSc, of Ashfield MedComms, an Ashfield Health company, and funded by BeiGene, Ltd.

Summary of efficacy results (EE analysis set*).

	Cohort A (n=9)	Cohort B (n=13)	Total (n=22)
Confirmed best overall response, n (%)			
Complete response	1 (11.1)	0 (0)	1 (4.5)
Partial response	7 (77.8)	11 (84.6)	18 (81.8)
Stable disease	0 (0)	1 (7.7)	1 (4.5)
Progressive disease	1 (11.1)	1 (7.7)	2 (9.1)
Confirmed ORR, n (%) 95% CI	8 (88.9) 51.8, 99.7	11 (84.6) 54.6, 98.1	19 (86.4) 65.1, 97.1
Confirmed DCR, n (%) 95% CI	8 (88.9) 51.8, 99.7	12 (92.3) 64.0, 99.8	20 (90.9) 70.8, 98.9
Confirmed DoR, range	1.4–12.4	1.5–5.6	1.4–12.4

*Three pts without any post-baseline tumor assessments were excluded from EE analysis set.Data cut-off: Nov 26, 2021.

Serena-1: Updated analyses from a phase 1 study (parts C/D) of the next-generation oral SERD camizestrant (AZD9833) in combination with palbociclib, in women with ER-positive, HER2-negative advanced breast cancer.

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Background: SERENA-1 (NCT03616587) is a Phase 1, multi-part, open-label study of camizestrant in women with ER+, HER2– advanced breast cancer (ABC). Parts A/B (escalation/expansion) assessed camizestrant monotherapy and have been presented previously. Parts C/D examine camizestrant in combination with palbociclib; here we present mature data from camizestrant 75 mg in combination with palbociclib; 75 mg being the camizestrant dose currently under investigation in the Phase 3 studies SERENA-4 (NCT04711252) and SERENA-6 (NCT04964934). **Methods:** The primary objective was to determine the safety and tolerability of camizestrant once daily (QD) with palbociclib. Secondary objectives included anti-tumor response and pharmacokinetics (PK). Prior treatment with < 2 lines of chemotherapy in the advanced setting was permitted. There was no limit on the number of lines of prior endocrine treatment in the advanced setting; prior treatment with CDK4/6 inhibitors and fulvestrant (F) was permitted. **Results:** As of 9 September 2021, 25 patients had received camizestrant 75 mg QD in combination with palbociclib. Tolerability of the combination of camizestrant 75 mg and palbociclib was consistent with that of each drug individually. No patient required camizestrant dose interruption/reduction/discontinuation due to a camizestrant-related adverse event (AE); moreover, none experienced a Grade ≥3 camizestrant-related AE. All camizestrant-related heart rate reductions were Grade 1 (asymptomatic). All camizestrant-related visual effects were Grade 1 (mild), apart from one patient who experienced transient Grade 2 (moderate) visual effects that resolved to Grade 1 without dose modification. Camizestrant-related gastrointestinal disorders were all Grade 1, except one instance of Grade 2 nausea lasting one day. PK data for camizestrant 75 mg QD and palbociclib combined were broadly consistent with camizestrant as monotherapy and published palbociclib steady-state PK data, further supporting the use of camizestrant 75 mg QD (Phase 3 dose) in combination with the approved palbociclib doses. In these heavily pre-treated patients (48% prior chemotherapy, 80% prior CDK4/6i, 68% prior F; all in advanced disease setting) and of whom 60% had visceral metastases, the clinical benefit rate at 24 weeks was 7/25 (28%). **Conclusions:** The PK and safety profile of camizestrant 75 mg QD in combination with palbociclib is favorable in this mature Phase 1 dataset. Despite extensive pre-treatment - including chemotherapies, CDK4/6i, and F - camizestrant 75 mg QD in combination with palbociclib exhibits encouraging clinical activity. The results from the ongoing Phase 3 studies, SERENA-4 and SERENA-6, will further elucidate the role of this combination in the treatment of patients with HR+/HER2– ABC. Clinical trial information: NCT03616587. Research Sponsor: AstraZeneca.

1033 **Poster Session**

Pyrotinib in combination with metronomic oral vinorelbine in patients with HER2-positive advanced breast cancer who had failed prior trastuzumab-based therapy: A single-center, single-arm, prospective phase 2 study.

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Background: In 15% to 30% of breast cancers, human epidermal growth factor receptor 2 (HER2) is overexpressed, this is related to aggressive disease and poor prognosis. Although important clinical benefits for patients have been achieved by the use of the HER2 antibody trastuzumab, 50% to 74% of patients with metastatic disease have no response to treatment, and approximately 75% progress within one year. The purpose of this study was to evaluate the efficacy and safety of oral pyrotinib in combination with oral metronomic vinorelbine in patients with HER2-positive advanced breast cancer who had failed prior trastuzumab-based therapy. **Methods:** This prospective phase 2 study enrolled patients aged 18-75 years with HER2-positive advanced breast cancer who had failed prior trastuzumab-based therapy, and had an Eastern Cooperative Oncology Group performance score of 0-2. Patients received pyrotinib 400 mg once daily and vinorelbine 40 mg once on Monday, Wednesday, Friday of each week until disease progression or unacceptable toxicity. Both pyrotinib and vinorelbine were orally administered 30 min after meals. The primary endpoint was progression-free survival (PFS). The secondary endpoints were objective response rate (ORR), disease remission rate (DCR), overall survival (OS), quality of life (QoL) and safety (CTCAE 5.0). The follow-up of this study is ongoing, but enrolment is closed. This study is registered on Clinical Trials.gov, number NCT04903652. **Results:** Between Oct 21, 2019, and Jan 21, 2022, 36 patients were enrolled and all of them were included in the intent-to-treat (ITT) population. 20 of 36 patients had disease progress or death. Median follow-up was 16.23 months. The median PFS (mPFS) was 14.23 months (95% CI 8.13-20.33). The ORR and DCR were 38.9% and 83.3%, respectively. The median OS was not reached. Grade 3 adverse events (AEs) occurred in 17 of 36 patients, the most common were diarrhea 27.8% and stomachache 5.6%. No grade 4 AEs were observed. **Conclusions:** Pyrotinib combined with metronomic oral vinorelbine showed promising efficacy and manageable safety in patients with HER2-positive advanced breast cancer who had failed prior trastuzumab-based therapy. This study might represent a potential treatment option for these patients. Clinical trial information: NCT04903652. Research Sponsor: CSCO--Hengrui Cancer Research Fund (Y-HR2018-075).

1034 **Poster Session**

Pyrotinib monotherapy or pyrotinib in combination with capecitabine could significantly prolong progression-free survival and overall survival in patients with HER2-positive metastatic breast cancer.

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Background: In the NALA phase III trial, irreversible pan-ErbB tyrosine kinase inhibitor (TKI) neratinib plus capecitabine demonstrated significant improvement in the progression-free survival (PFS), but no significant benefit in overall survival (OS) compared to lapatinib plus capecitabine. However, another TKI pyrotinib plus capecitabine showed significant benefits in PFS and a trend of OS benefits in the PHOEBE phase III study. But in general, current data on survival of irreversible TKIs in patients with HER2-positive metastatic breast cancer (MBC) was limited. Thus, we performed a pooled analysis of individual patient data from the phase I to III trials in HER2-positive MBC patients receiving pyrotinib or pyrotinib combined with capecitabine, to provide a cumulative assessment on long-term outcomes of irreversible TKI. **Methods:** Individual patient data was collected and analyzed from the phase I trial for pyrotinib and pyrotinib plus capecitabine, the Pivotal phase II trial and the PHOEBE phase III trials that enrolled patients in China National Cancer Center. Next-generation sequencing was performed on circulating tumor DNA for predictive biomarkers in the phase I trial. **Results:** Between August 2013 and October 2018, a total of 120 patients were assigned to received pyrotinib (n = 38), pyrotinib plus capecitabine (n = 53) and lapatinib plus capecitabine (n = 29) across the above four trials. The median follow-up duration for OS was 73.6 months (95% CI:69.9-77.3 months). The estimated median PFS was 8.2 months (95% CI:5.6-10.9 months) in the pyrotinib monotherapy group and 22.0 months (95% CI:13.2-30.8 months) in the pyrotinib plus capecitabine group (P= 0.002), while the median OS was 27.1 months (95% CI: 21.6-32.5 months) in the pyrotinib monotherapy group and 44.5 months (95% CI: 30.8-58.1 months) in the pyrotinib plus capecitabine group (P= 0.065). In this pooled analysis, pyrotinib 400mg in combination with capecitabine, recommended for phase II and III trials, had significantly longer PFS (22.0 vs 6.9 months, $P < 0.001$) and OS (59.9 vs 31.2 months, P= 0.035) than lapatinib plus capecitabine. Analysis of all genetic alterations in baseline blood samples suggested that the patients harbored concomitant mutations in HER2-related signaling network (including HER2 bypass signaling pathway, PI3K/Akt/mTOR pathway and TP53) were observed with significantly poorer PFS and OS compared to none or one genetic alteration (median PFS, 7.3 vs. 26.1 months, P= 0.003; median OS, 25.1 vs. 48.0 months, P= 0.013). **Conclusions:** This pooled analysis based on phase I to III trials revealed promising PFS and OS was achieved in pyrotinib and pyrotinib plus capecitabine. Concomitant mutations in HER2-related signaling network may be a potential efficacy and prognosis biomarker for pyrotinib in HER2-positive MBC. Clinical trial information: NCT01937689,NCT02361112,NCT02422199,NCT03080805. Research Sponsor: National Nature Science Foundation of China(82103634).

1035 **Poster Session**

Pyrotinib plus nab-paclitaxel in patients with HER2-positive advanced or metastatic breast cancer: A multicenter, single-arm, open-label phase 2 trial.

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Background: For human epidermal growth factor receptor 2 (HER2) positive advanced or metastatic breast cancer, the standard therapeutic strategy is HER2-targeted agents combined with a taxane. This multicenter, single-arm phase 2 trial was designed to assess the efficacy and safety of pyrotinib (a brand-new generation, irreversible anti-HER2 tyrosine kinase inhibitor) plus nab-paclitaxel in patients with HER2-positive advanced or metastatic breast cancer. **Methods:** This was a multicenter, single-arm, open-label phase 2 trial conducted at seven centers in China (ChiCTR1900023653). Women aged 18-75 years, with histologically or cytologically confirmed HER-2 positive (immunohistochemistry [IHC] 3+ or positive confirmed by fluorescence in situ hybridization) advanced or metastatic breast cancer and with Eastern Cooperative Oncology Group performance score (ECOG PS) of 0-1 were enrolled. Patients with primary resistance to trastuzumab and bone-only metastases were excluded. Eligible patients received pyrotinib (400 mg, po, qd) plus nab-paclitaxel (125 mg/m^2, iv, day 1/8/15) for each 28-day cycle until disease progression, unacceptable toxicity, consent withdrawal or death. The primary endpoint was objective response rate (ORR), defined as the proportion of patients with complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary endpoints included progression-free survival (PFS), overall survival, safety and quality of life. **Results:** Between December 2019 and December 2021, 51 patients were enrolled. The median age was 55 years (range 35–72). Twenty-three patients (45.1%) had ECOG PS of 0. Ten patients (19.6%) with metastatic disease had previously received first-line treatment and 28 (54.9%) had received prior treatment with trastuzumab. More than half (29 of 51, 56.9%) had hormone receptor-positive disease. Visceral metastases occurred in 56.9% of the patients (29 of 51) and 26 patients (51.0%) were menopausal. The data cutoff for the present analysis was January 21, 2022. Among 38 evaluable patients, four patients (10.5%) had CR, 27 (71.1%) had PR, six (15.8%) had stable disease, and one (2.6%) had progressive disease. The confirmed ORR was 81.6% (95% CI 65.1-91.7%). The PFS data were still immature. The most common grade ≥3 treatment-emergent adverse events included neutropenia (14 of 51, 27.5%), diarrhea (10 of 51, 19.6%), fatigue (5 of 51, 9.8%) and peripheral neuropathy (4 of 51, 7.8%). **Conclusions:** Pyrotinib combined with nab-paclitaxel showed a promising antitumor activity with good tolerance in patients with HER2-positive advanced or metastatic breast cancer. Clinical trial information: ChiCTR1900023653. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

1036 **Poster Session**

Monitoring and management of interstitial lung disease/pneumonitis among patients with metastatic breast cancer treated with trastuzumab deruxtecan.

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Background: Trastuzumab Deruxtecan (T-DXd) was associated with an increased risk of interstitial lung disease (ILD)/pneumonitis (P) in metastatic breast cancer (mBC) patients (pts) in clinical trials, leading to ILD/P monitoring and management guidelines in the product label. This study aims to describe the monitoring and management of ILD/P during T-DXd therapy among US community oncology practices. **Methods:** Oncologists in the Cardinal Health Oncology Provider Extended Network (OPEN) participated in a cross-sectional survey on monitoring approaches for ILD/P among mBC pts. Participating physicians provided data from medical charts of up to 10 pts who were treated with T-DXd regarding presence of ILD/P symptoms, management, and outcomes of ILD/P symptoms. **Results:** Twenty-eight physicians from across the U.S participated and provided data on 149 T-DXd pts. Nearly all physicians reported they were monitoring ILD/P after T-DXd initiation by physical examination (n = 27), symptoms checklist (n = 25) and pulse oximetry (n = 23) at every visit, whereas fewer reported performing lung CT scan (n = 18), echocardiogram (n = 13), chest X-ray (n = 12), lung PET scan (n = 10), pulmonary function tests (n = 8) and diffusion testing (n = 7) on a less frequent basis. Among 149 T-DXd pts, 4 pts were diagnosed with ILD/P over an average T-DXd treatment duration of 5.5 months. All 4 cases initiated T-DXd treatment at 5.4mg/kg every 3 weeks, experienced ILD/P within the first 5 cycles of T-DXd, were diagnosed with lung CT scan and initially presented with Grade 2 symptomology (2 cases progressed to Grade 3). For both cases that remained as Grade 2, ILD/P completely resolved within 23 days. One case received IV methylprednisolone (1000mg daily; duration of therapy (DOT): 3 days) during hospitalization, oxygen therapy and T-DXd was permanently discontinued; whereas the other one received oral prednisone (started at 40mg daily and tapered to 5mg daily; DOT: 7 days) and T-DXd dose was held. For the two grade 3 cases, one received IV methylprednisolone (125mg daily; DOT: 7 days) during hospitalization, T-DXd dose was held, and ILD/P completely resolved within 11 days; whereas the other case received oral prednisone (started at 80mg daily and tapered to 5mg daily; DOT: 63 days), oxygen therapy, T-DXd was permanently discontinued, and ILD/P resolved with sequela within 46 days. **Conclusions:** ILD/P incidence in this small study sample of patients receiving T-DXd treatment was 2.7%. Although general awareness of ILD and routine screening by pulse oximetry and physical exam were common, management approaches for ILD/P were not always consistent with T-DXd prescribing information. Further physician education may be needed to improve appropriate management of ILD/P and outcomes for T-DXd pts. Research Sponsor: Daiichi Sankyo.

1037 **Poster Session**

Updated results and biomarker analyses from the phase I trial of A166 in patients with HER2-expressing locally advanced or metastatic solid tumors.

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Background: A166, an antibody-drug conjugate, with an anti-HER2 antibody site-specifically conjugated to Duo-5 (anti-microtubule agent), via a stable protease-cleavable valine citrulline linker, has proved its safety and efficacy in patients with HER2 positive breast cancer (Xichun Hu et al. ASCO 2021). Here, we report updated data and biomarker analyses from this single-arm, multi-center, open-label, phase I trial (CTR20181301). **Methods:** This study has two parts: dose escalation and dose expansion. In the expansion part, dose cohorts were expanded at 4.8 and 6.0 mg/kg Q3W, and the primary endpoint was ORR, as assessed according to the RECIST 1.1. Next-generation sequencing was performed on tissue-derived DNA and blood-derived circulating tumor DNA (ctDNA). **Results:** As of Dec 10, 2021, in total 58 female pts were enrolled in the expansion dose cohorts. Median age was 53.5 years (range 26-71), 58 pts (100%) had prior HER2-targeted therapy with the median lines of 4, including 100% received trastuzumab ± pertuzumab, 94.8% received anti-HER2 TKIs, and 20.7% received anti-HER2 ADCs in the metastatic setting. Any grade treatment-related AEs (TRAEs) were documented in 100.0% (58/58) of pts. Common TRAEs were corneal epitheliopathy (98.3%), blurred vision (89.7%), peripheral sensory neuropathy (67.2%), muscular weakness (36.2%) and dry eyes (32.8%). Most common grade ≥3 TRAEs were corneal epitheliopathy (34.5%), blurred vision (22.4%) and ulcerative keratitis (10.3%). 7 pts had serious AEs, 3 of whom were possibly related to the study drug, including thrombosis, peripheral motor neuropathy and muscular weakness. TRAEs led to 39.7% (23/58) dose reduction and 1.7% (1/58) treatment discontinuation. All patients were evaluable for efficacy with the best ORR being 73.91% (17/23; 95% CI, 51.59 to 89.77) and 68.57% (24/35; 95% CI, 50.71 to 83.15), mPFS being 12.30 months (95% CI, 6.00 to not reached) and 9.40 months (95% CI, 4.00 to 10.40) in 4.8 and 6.0 mg/kg cohort, respectively. Of 23 pts treated at 4.8 mg/kg dose level, one had a confirmed and sustained complete response lasting 7+ months. At the time of the data cutoff, 24 pts (41.4%) continued to receive A166 treatment.NGS of 520 genes was performed on tissue-derived DNA and ctDNA of baseline tumor tissue samples (n = 42) and blood samples (n = 53), respectively, and post-treatment blood samples (n = 8). Univariate and multivariate analysis showed that baseline PIK3CA/PTEN status had no influence on the PFS, and gave an idea of FGFR1 amplification as a potential negative predictor of A166 efficacy in HER2-positive breast cancer. **Conclusions:** The previously demonstrated preliminary clinical benefit of A166-ADC was maintained with no new safety signals, which demonstrated manageable toxicity and encouraging antitumor activity in heavily pretreated HER2-positive metastatic breast cancer patients. Clinical trial information: CTR20181301. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

1038 **Poster Session**

Early clinical safety and pharmacokinetics data of DZD1516, an BBB-penetrant selective HER2 inhibitor for the treatment of HER2-positive metastatic breast cancer.

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Background: Patients with HER2+ metastatic breast cancer (MBC) are at high risk of developing central nervous system metastases. DZD1516 is a reversible HER2-specific tyrosine kinase inhibitor (TKI) with full blood-brain barrier (BBB) penetration. Here we report the preliminary safety and PK data from the ongoing phase 1 study (NCT04509596) in patients with HER2+ MBC who relapsed from multiple prior treatments. **Methods:** Eligible patients received single oral dosing of DZD1516 on C0D1 and then twice daily (BID) oral dosing from C1D1 in a continuous 21-day cycle until disease progression, unacceptable toxicity or withdrawal of consent. The primary objective is to investigate the safety and PK of DZD1516 as a single agent. **Results:** As of 17 January 2022, DZD1516 was explored in 21 HER2+ MBC patients from the USA and China. DZD1516 was well tolerated at doses < 300 mg, BID. Two DLT events were reported in the 300 mg cohort. In all cohorts, 20 (95.2%) patients reported treatment-emergent adverse events (TEAEs), and 3 (14.3%) patients reported grade 3 drug-related TEAE. Two patients had dose interruption and one patient had dose reduction due to TEAE, all in the 300 mg cohort. Majority of TEAEs were reversible. The longest treatment duration was > 3 months. In all cohorts, the most common (> 20%) TEAEs included headache (42.9%), vomiting (38.1%), nausea (23.8%) and hemoglobin decreased (23.8%). At doses < 300 mg, there is no diarrhea or rash reported. PK data showed that combined exposure of DZD1516 and its active metabolite DZ2678 increased in a dose-proportional manner across the dose ranges. Elimination half-life was about 15-19 hrs. About 2-fold accumulation of DZD1516 in AUC was observed on multiple doses. *In vitro*, both DZD1516 and DZ2678 showed good permeability, and were not substrates of P-gp and BCRP. In patients, $K_{puu,CSF}$ of DZD1516 and DZ2678 was around 2.13 and 0.66, respectively, suggesting good CNS penetration. At the time of data cutoff, 16 patients had at least one post treatment anti-tumor assessment. With a median of 7 lines of prior treatment, the best anti-tumor response was stable disease. **Conclusions:** Preliminary clinical data showed that DZD1516 is a full BBB-penetrant HER2 TKI, with good safety profile. Consistent with its high selectivity, no wide type EGFR related AEs have been reported. Further evaluation of its safety and efficacy is ongoing. Clinical trial information: NCT04509596. Research Sponsor: Dizal Pharmaceutical.

Demographics	25 mg (N = 1)	50 mg (N = 4)	100 mg (N = 4)	200 mg (N = 5)	250 mg (N = 3)	300 mg (N = 4)	Total (N = 21)
Median age	64	57.5	50	61	47	42	57
Race, n							
Asian	1	3	2	5	3	3	17
White	0	0	2	0	0	0	2
Other	0	1	0	0	0	1	2
Patient type, n	1	4	4	5	3	4	21
Brain mets	0	4	3	2	2	2	13
Leptomeningeal mets	0	0	1	0	0	0	1
Without CNS mets	1	0	0	3	1	2	7
Median line of prior systemic therapy	7	9	4.5	10	9	5.5	7
Therapy Class, n							
HER2 antibody and/or ADC	1	4	4	5	3	4	21
HER2 TKI	0	3	3	5	3	4	18
Chemo	1	4	4	5	3	4	21
Others	0	2	0	3	3	2	10

1039 **Poster Session**

Survival of elderly patients with HER2+/HR- metastatic breast cancer in clinical practice: SEER-Medicare data 2012-2016.

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Background: Older patients with human epidermal growth factor 2-positive (HER2+) metastatic breast cancer(mBC) are underrepresented in clinical trials. We aim to assess the overall survival (OS) and breast cancer-specific survival of elderly women with de novo HER2+/hormone receptor-negative (HR-) mBC in a real-world setting. **Methods:** Elderly women with HER2+/HR- mBC treated with chemotherapy and/or HER2-targeted agents and with continuous Medicare Part A, B, and D coverage 1-year before diagnosis were identified from the SEER-MEDICARE database 2012-2016. Patients were retrospectively followed from metastatic diagnosis until death, disenrollment from Medicare A, B, or D, or end of the observation period. Patients' year and month of diagnosis and death were retrieved from SEER. Death dates were verified with Medicare records reported by the Social Security Administration (SSA). For all-cause deaths, Kaplan-Meier analysis was used to estimate overall survival. The cumulative incidence competing risk (CICR) method based on cumulative incidence function (CIF) was used to estimate breast cancer-specific death incidence. **Results:** Seventy-three patients (mean age at diagnosis, 75.0±7.7 years) met the inclusion criteria. Among them, 56 were treated with trastuzumab ± pertuzumab /chemotherapy as first-line treatment, and 17 were treated with chemotherapy only. The median time to initiate trastuzumab-based treatment from diagnosis was 2.5 months, and the longest trastuzumab treatment length was over 44 months. The median follow-up for OS was 13 months. One patient developed stomach cancer 6 months after breast cancer diagnosis. In Kaplan-Meier analysis, censoring or not censoring this patient after second cancer development resulted in a median OS of 19 months (95% CI, 9-24 months) and 18 months (95% CI, 9-22 months). The OS at the end of 46 months was approximately 25%. Five patients died from other causes, including lung cancer, cerebrovascular diseases, aortic aneurysm and dissection, pneumonia and influenza, and heart diseases during treatment. Considering these competing risks, 50% (95% CI, 36%-64%) of patients specifically died from breast cancer between 21 and 22 months, estimated by the CICR method. **Conclusions:** Our study observed a shorter OS among HER2+/HR- mBC elderly patients in clinical practice than the OS of 40.8 and 56.5 months among younger patients in the CLEOPATRA trial, suggesting that age is an important prognostic factor for breast cancer survival. The presence of second cancer and other competing risks led to overestimating the probabilities of breast cancer-specific death and resulted in a shorter OS using the Kaplan-Meier method. The CICR method is more relevant to estimate the breast-cancer-specific death incidence. Research Sponsor: None.

1040 **Poster Session**

Pyrotinib-based therapy for patients with HER2-positive breast cancer: A multicenter, real-world study.

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Background: Pyrotinib, an irreversible pan-ErbB inhibitor, has been approved for the treatment of HER2-positive advanced breast cancer in China. Real-world data is instructive for effect evaluation and application of the drug in clinical practice. Herein, this study was conducted to evaluate the effectiveness and safety of pyrotinib-based therapy in patients with HER2-positive breast cancer in the real-world setting. **Methods:** In this retrospective, multicenter, real-world study, data of patients with HER2-positive breast cancer who received pyrotinib-based therapy from 19 sites were reviewed. Disease characteristics, prior therapies, and treatment patterns were summarized. Progression-free survival (PFS) and the incidence of diarrhea were analyzed. **Results:** Between September 2018 and June 2021, a total of 378 patients with HER2-positive advanced breast cancer were included. Of 378 patients, 47.4% had hormone receptor (HR)-positive disease, 41.3% had HR-negative disease, and 11.4% had unknown HR status. Brain, lung, liver, and bone metastases were found in 24.9%, 35.7%, 31.7%, and 33.1% of all cases, respectively. Most of patients (83.1%) were trastuzumab-exposed, 12.7% were pertuzumab-exposed, and 8.2% had been treated with lapatinib or neratinib before receiving pyrotinib. Pyrotinib plus chemotherapy (211 [55.8%]) was the most commonly used regimen, followed by pyrotinib monotherapy (115 [30.4%]), pyrotinib plus trastuzumab and chemotherapy (29 [7.7%]), other regimens (18 [4.8%]), and unknown regimen (5 [1.3%]). Standard dose (400 mg once daily) was used in 256 (67.7%) patients. With a median follow-up duration of 20.5 months, the median PFS was 13.0 months (95%CI, 12.0-14.0). Further analyses showed that the median PFS did not differ in subgroups by age (≥65 or < 65 years), HR status (positive or negative), brain metastasis (yes or no), lung metastasis (yes or no), liver metastasis (yes or no), bone metastasis (yes or no), prior exposure to trastuzumab (yes or no), treatment regimen (pyrotinib monotherapy or combination therapy). Significant variance was discovered between sufficient dosage group and non-sufficient group (13.2 months vs 10.93 months, $p = 0.028$). The survival advantage of sufficient dosage was also evident in brain metastasis cases (14.4 months vs 8.3 months, $p = 0.043$).The most common adverse event was diarrhea (85.7%), and grade ≥3 diarrhea occurred in 18.5% of patients. Diarrhea was the leading cause for does reduction of pyrotinib. **Conclusions:** The PFS data in our study was similar to previous clinical trials referring to HER2-positive advanced breast cancer treated with pyrotinib. Cases with brain metastasis also displayed a satisfactory survival result. Sufficient dosage is of great importance for prolonged survival, prevention of diarrhea may efficiently avoid does reduction and guarantee the drug efficacy. Research Sponsor: None.

1041 **Poster Session**

HER2 alterations and prognostic implications in all subtypes of breast cancer.

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Background: Amplification or overexpression of human epidermal growth factor receptor 2 (HER2) oncogene is present in about 15-20% of breast cancers & is a prognostic & predictive biomarker. Additional *ERBB2*/HER2 alterations have become apparent on tumor next generation sequencing (NGS), including activating kinase domain mutations & fusions. **Methods:** DNA NGS (592 gene panel or whole exome) data from 12,153 breast samples retrospectively reviewed for *ERBB2* alterations with RNA whole-transcriptome sequencing (WTS) data available for 7289 (60%) samples. Gene fusions detected using the ArcherDx fusion assay or WTS. Clinicopathologic features were described including breast cancer subtype, age, & biopsy site. HER2 status determined according to 2018 ASCO-CAP guideline. Overall survival obtained from insurance claims & Kaplan-Meier estimates were calculated for defined patient (pt) cohorts. Statistical significance was determined using Chi-square & Wilcoxon rank sum tests. **Results:** ERBB2 mutations (*ERBB2mts*) were identified in 3.2% (n = 388) of tumors overall & most common in liver metastases (113/1972, 5.7%). *ERBB2mts* were found more in breast lobular tumors compared to ductal tumors (10 vs 2.1%, $p < 0.001$). HER2+ tumors had higher frequency of *ERBB2mts* compared to HER2- (4.3 vs 3%, $p = 0.028$). Tumors with score of 0 by immunohistochemistry demonstrated lower rate of *ERBB2mts* (0+ 2.2%, 1+ 3.5%, 2+ 4.5%, 3+ 3.45%, $p < 0.05$). Among HER2- tumors, *ERBB2mts* were present in 3.6% of hormone receptor (HR)+/HER2- & 1.9% of TNBC. Metastatic tumors had a higher rate of *ERBB2mts* compared to locoregional breast tumors (3.8 vs 2%, $p < 0.001$), with increased rates of activating mutations S310F (0.1 vs 0.0%, $p < 0.05$) & D769H (0.3 vs 0.1%, $p < 0.05$), & the resistance mutation L755S (1.2 vs 0.6%, $p < 0.01$). Compared to *ERBB2*-WT, *ERRB2mts* were associated with decreased *ERBB2* transcripts levels in HER2+ samples (222 vs 441 transcripts per million [TPM], $p < 0.001$) & increased levels in HER2- samples (73 vs 35 TPM, $p < 0.001$). High tumor mutational burden (≥ 10 mut/Mb) & *ERBB3* mutations were more common in *ERBB2mts* compared to *ERRB2*-WT (16.7 vs 7.7%, $p < 0.001$; 10.6 vs 0.8%, $p < 0.001$). *ERBB2* fusions were rare (0.49%) with 97% occurring in HER2+ tumors. Of 8358 pts with outcome data, prognosis (HR 1.2, $P = 0.06$) & response to chemotherapy (HR 1.1, $P = 0.42$) was similar between pts with HER2- *ERBB2mt* & *ERBB2*-WT. **Conclusions:** *ERBB2mts* & fusions were observed in all breast cancer subtypes - more commonly in HER2+, metastatic, & lobular histology tumors - & did not influence prognosis. These alterations may reflect response to treatment pressures in HER2+ disease to reactivate HER2-mediated growth pathways following anti-HER2 therapy & may represent a targetable upregulated oncogenic pathway in HER2- disease. Ongoing identification of *ERBB2* alterations may augment treatment options for breast cancer pts & clinical outcomes from this approach are under investigation. Research Sponsor: Caris Life Sciences.

1042 **Poster Session**

Matched FES and FDG PET imaging in patients with hormone receptor-positive, HER2+ advanced breast cancer.

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Background: The recently FDA approved ^{18}F-Fluoroestradiol (FES) is a PET imaging tracer for characterizing disease in patients with ER+ breast cancer. As FES PET enters clinical practice it will be important to establish its utility in the full population of hormone-receptor positive patients, including those with HER2+ tumors. Historically the consensus around ER+/HER+ disease has been that these tumors are primarily driven by HER2, with therapies focused on targeting this pathway. Emerging research suggests that ER+ and HER2+ tumors represent a distinct phenotype, with bidirectional crosstalk between ER and HER2 pathways contributing to resistance to therapies targeting these critical pathways. **Methods:** Our cross-sectional database of patients with one or more FES scans stretches back to 1996. We selected all patients with HER2+ advanced breast cancer to determine whether ER is functional in the ER+/HER2+ subset. We examined paired FDG and FES scans and recorded SUVmax in matched lesions between the FDG and FES scans. We also looked at a subset of patients who underwent scans at more than one time-points and examined the clinical characteristics of these cases over time. **Results:** 36 patients with metastatic ER+, HER2+ breast cancer underwent concurrent FDG and FES PET scans between 1996 and 2013. 34 subjects (94%) were female; 32 (89%) were Caucasian, and 4 (11%) were Asian. Eight patients underwent serial scans. A total of 200 metastatic sites were recorded with the majority (67%) being bony lesions. No difference in quantitative FES avidity was observed between soft tissue and osseous sites. Six patients (16%) had negative FES scans despite displaying FDG avid lesions; three patients had at least one negative FES scan on serial scans, and two demonstrated FES-avid lesions with no FDG activity. Average FES SUVmax for positive scans was 3.5, with a range of 0.8 to 10.7. Among eight patients with multiple scans, half had 2 scans, three had 3 scans, and one had 4 scans. In 7/8 patients (88%) FES avidity increased over time even as FDG decreased or stayed stable with treatment; in one, both FES and FDG decreased on follow up scan. **Conclusions:** In a cohort of ER+, HER2+ patients undergoing FDG and FES PET scans, robust concordance between FDG and FES uptake was observed. FES avidity increased in patients with multiple scans, suggesting that the ER pathway remained active during treatment. The strong FES positivity in many HER2+ patients in this cohort suggests that FES PET could be used to guide patient selection for trials examining deescalated regimens employing a non-chemotherapy partner for HER2-directed therapy or emphasizing more ER-directed therapies such as CDK4/6 inhibitors, which are not currently approved in this population. With the ongoing development of HER2- PET imaging, combination scans could carry the potential for discrimination between sites, possibly serving as a tool to guide biopsy. Research Sponsor: U.S. National Institutes of Health.

1043 **Poster Session**

Treatment patterns and their impact on the outcome of patients with HR+/HER2+ metastatic breast cancer in a large real-world cohort.

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Background: The place of endocrine therapy (ET) in the treatment of hormone receptor-positive (HR+), HER2+ metastatic breast cancer (MBC) is still not clearly defined. Data suggest that blocking both HR and HER2 signaling pathways could be an efficacious strategy to overcome secondary resistance. **Methods:** We aimed to retrospectively evaluate the impact of first line (L1) therapy for HR+/HER2+ MBC patients (pts) included between 2008- 2017 in the French real-world ESME MBC database (NCT03275311). Our primary endpoints were median overall survival (mOS) and median first progression-free survival (mPFS1). We used descriptive statistics and the Kaplan-Meier method to report patient characteristics and outcomes. Cox proportional hazards models and a propensity score were constructed to report and adjust for prognostic factors. **Results:** From the 23,501 female pts in the ESME MBC cohort, 1,790 pts had HR+/HER2+ MBC treated with Trastuzumab (T, n=1,089) or Trastuzumab-Pertuzumab (TP, n=701) during L1. Among them, 1,584 pts received antiHER2 therapy+CT+/-ET and 206 pts, antiHER2+ET only. Pts with antiHER2+CT+/-ET had more often ECOG performance status 0 (29.5% vs 15.8%, $p<0.001$), grade III tumors (36.6% vs 25.6%, $p=0.007$), time to MBC < 6 mo (51.6% vs 29.1%, $p<0.001$), TP as antiHER2 therapy (43.2% vs 9.4%, $p<0.001$), ≥3 metastatic sites (23.2% vs 14.8%, $p=0.007$), visceral metastasis (56.5% vs 42.4%, $p<0.001$), and less often bone-only disease (18.4% vs 35%, $p<0.001$) than pts with antiHER2+ET. In multivariable analysis, antiHER2+CT+/-ET was not superior to antiHER2+ET (Table), while TP was superior to Trastuzumab, and this result was confirmed by matching pts using a propensity score ($p=0.76$ for mOS and $p=0.85$ for mPFS1). Using the time-dependent ET variable among pts with antiHER2+CT, pts with maintenance ET had significantly better PFS1 and OS than those without (adjusted HR for PFS1=0.70 [95%CI 0.60-0.82], adjusted HR for OS=0.47 [95%CI 0.39-0.57], $p<0.001$). **Conclusions:** These data suggest that endocrine therapy could be an interesting less toxic alternative to chemotherapy in combination with antiHER2 therapy as first line treatment for HR+/HER2+ MBC pts. Research Sponsor: Roche, Pfizer, AstraZeneca, MSD, Eisai, Daiichi Sankyo.

Univariate and multivariable analysis for OS and PFS1 for pts treated with T or TP.

Univariate	N	OS			PFS1		
		median	95% CI	*p* value	median	95% CI	*p* value
Trastuzumab							
antiHER2+CT+/-ET	902	58.6	54.9-63.3	0.13	13.8	12.6-15.5	0.05
antiHER2+ET	187	48.7	42.9-63.9		10.1	8.5-14.1	
TP							
antiHER2+CT+/-ET	682	88.9	78.0-NR	0.93	23.1	21.0-27.1	0.69
antiHER2+ET	19	NR	37.8-NR		18.6	9.9-NR	
Multivariable analysis*		**HR**			**HR**		
AntiHER2 therapy							
TP	675	1		<0.001	1		<0.001
Trastuzumab	1,048	1.66	1.38-1.99		1.44	1.28-1.63	
Treatment group							
antiHER2+ET	203	1		0.8	1		1
antiHER2+CT+/-ET	1,520	1.03	0.82-1.28		1	0.84-1.19	

*The multivariable analysis also included: tumor grade, age at MBC, time to MBC, no of metastatic sites, type of metastases, ECOG performance status.

1044 **Poster Session**

Prognostic implications of HER2Neu-low in metastatic breast cancer.

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Background: HER2-Low (or HER2-equivocal, FISH negative) breast cancer has historically been treated as HER2-negative; however, recent evidence suggests that there may be prognostic and/or predictive differences between the two. We explore demographic characteristics and clinical outcomes of HER2-negative and HER2-low metastatic breast cancer (MBC) patients using real world data. **Methods:** We queried the National Cancer Database to identify MBC patients that were HER2 0, HER2 1+, or HER2 2+ per immunohistochemical staining, with the latter two defined as HER2-low and the former HER2-negative. A multivariable binomial regression analysis identified demographic and clinical correlates of each subtype. A Cox multivariable regression analysis (MVA), propensity matched to HER2 status, was performed to identify correlates of survival. **Results:** After excluding missing data, 24,636 MBC patients diagnosed between 2008-2015 were identified, 6,865 (27.9%) of whom were HER2-negative and 17,771(72.1%) of whom were HER2-low. There were no differences between the two groups with respect to age, race, year treated, location, income, insurance status, Charles Deyo comorbidity score, laterality, T stage, N stage, or use of systemic therapy. HER2-low tumors were half as likely to have concomitant hormone receptor-negative status (OR = 0.49, 95% CI 0.46-0.53). The 3-year survival rate among hormone receptor-negative patients was 33.8% for HER2-low and 32.2% for HER2-negative, and 60.9% and 55.6% in HER2-low and HER2-negative cases among hormone receptor-positive patients, respectively. HER2-low cases were associated with better survival on MVA (HR = 0.91, 95% CI 0.87-0.95), and remained superior with propensity-matching (HR = 0.92, 95% CI 0.89-0.96). In a subset analysis isolated to hormone receptor-positive cases, HER2-low remained correlated with improved survival (HR = 0.93, 95% CI 0.89-0.98) with propensity-matched MVA. Correlates of worse survival include older age as a continuous variable (HR = 1.02), Black race (HR = 1.13), uninsured (HR = 1.18), comorbidity score > 0 (HR = 1.28), higher T stage (HR = 1.17 to 2.34), node positivity (HR = 1.17) and, as the most influential, hormone receptor-negative status (HR = 1.94) [all $P < 0.01$]. **Conclusions:** Consistent with recent data in non-MBC, our study demonstrates a small but statistically significant association with improved survival for HER2-low tumors compared to HER2-negative tumors in MBC. Randomized data are necessary to further validate this discrepancy and determine if different management is warranted for each subtype. Research Sponsor: None.

1045 **Poster Session**

Brain metastasis as first and only metastatic relapse site portends poor outcomes in patients with advanced HER2+ breast cancer.

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Background: In patients (pts) with stable or no extracranial disease (ECD) presenting with breast cancer brain metastases (BCBrMs), current guidelines recommend pts receive local therapy with radiation +/- surgery, without changing systemic therapy. However, preliminary studies suggest that pts with isolated HER2+ BCBrM without ECD have inferior overall survival (OS) compared to pts with concurrent ECD. Our study further explores the implications of ECD status on intracranial progression free survival (iPFS) and OS. **Methods:** Retrospective analysis was performed on data from 153 pts diagnosed with initial HER2+ BCBrM who received CNS radiation at Duke between 2008 and 2020. Demographics, dates of metastatic and BCBrM diagnosis, ECD status at first CNS event, systemic therapy, and outcomes were collected. The primary endpoint was iPFS defined as the time from first CNS radiation to the subsequent documentation of intracranial progression (RANO-BM). OS was defined as time from first CNS radiation and first metastatic disease to date of death or last known contact. ECD status was defined by RECIST1.1 from systemic staging scans within 30 days of first CNS event. **Results:** In this cohort of 153 pts with HER2+ BCBrMs undergoing CNS radiation, > 70% of pts with known ECD status had controlled systemic disease: either no ECD (27%) or stable/responding disease (44%). 64% of pts' tumors were ER+. Median age was 50 years (range 24 – 75). Most pts (59%) developed first CNS event during adjuvant or $1^{st}/2^{nd}$ line metastatic therapy. CNS radiation treatment included 48% of pts receiving SRS only, 9% WBRT only, and 43% SRS and WBRT. All pts with no ECD presented with isolated BCBrMs as first metastatic disease. Among pts with known ECD status, OS from initial metastatic disease to death was markedly worse for pts with isolated brain metastases or no ECD (median = 28.4m, 95% CI: 18.1 to not reached) compared to those with progressive or stable/responding ECD (48.8m, 95% CI: 40.5 to 65.0; and 68.1m, 95% CI: 55.2 to 85.7, respectively; log-rank p = 0.004). OS from first CNS involvement to death was significantly worse for pts with progressive ECD (17.8m, 95% CI: 13.7 to 28.8) versus stable/responding (36.6m, 95% CI: 29.7 to 45.2) or no ECD (28.4m, 95% CI: 18.1 to not reached; log-rank p = 0.008). iPFS did not differ statistically among subgroups of pts with known ECD status: progressive ECD (median = 7.7m), no ECD (8.3m), or stable/responding ECD (11.2m) (log-rank p = 0.15). **Conclusions:** Overall survival in pts with HER2+ isolated BCBrM was markedly inferior to that of pts with progressive or stable/responding ECD. Studies investigating initiation of brain penetrable HER2-targeted therapies earlier in the disease course of isolated HER2+ BCBrMs pts are warranted. Research Sponsor: None.

1046 **Poster Session**

Dynamic circulating tumor DNA (ctDNA) in monitoring trastuzumab deruxtecan (TDXd) activity for patients (pts) with advanced breast cancer: Preliminary results of a feasibility study.

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Background: Trastuzumab Deruxtecan (TDXd), a novel antibody-drug conjugate (ADC) that combines trastuzumab with a topoisomerase I inhibitor, has recently demonstrated high efficacy in HER2-overexpressing breast cancer after trastuzumab failure. Resistance to TDM1 have recently suggested to be dynamically associated with distinct circulating ctDNA species (*Allegretti et al, Mol Cancer 2021*). A prospective study aiming to evaluate the feasibility of Liquid Biobsy (LB) in monitoring ctDNA in pts receiving TDXd in the national Expanded Access Program was conducted. **Methods:** In this prospective study, LB for ctDNA analysis (evaluating '*per pt*' ctDNA species and Variant Allelic Frequencies, VAF) was performed using 52-gene targeted NGS panel, in patients who progressed after two or more prior anti-HER2-based regimens and candidates to TDXd (3-weekly 5.4 mg/kg). This preliminary analysis reports data referring to Time-0 (T0) and T6 (cycle 6) assays. **Results:** From April 2021, LBs were collected for 14 pts and to date 8 are evaluable for LB. Median pts' age was 59 yrs (range 38-72) and median number of previous anti-HER2 lines was 6 (2-11); 4 pts had Pertuzumab/Trastuzumab plus taxane as first-line and all pts received TDM-1. Median cycles of TDXd administered was 7.5 (1-10). At T0, 5/8 pts had at least one detectable ctDNA specie, and the remaining 3 developed at least one ctDNA at T6. ctDNA species and VAFs ranged from 1 to 5, and A0.1% to 68.94%, respectively. Decreases and increases were observed simultaneously in the same pt. The former varied from marginal to drastic, whereas the latter were invariably below 0.5% in VAFs. ctDNA monitoring was possible in 8/8 pts and at T6 ctDNA progression was detectable in 5/8 pts. Two pts displayed multiple HER2 copy number variations. **Conclusions:** The early results of this study suggest that considerable ctDNA burden, marked clonal complexity, and variable clonal response to TDXd can be found in pretreated HER2 positive patients, who progressed after antiHER2 therapies. Although the very small sample, this complex tumor evolution is surprising in light of the bystander payload effect of TDXd. Research Sponsor: None.

1047 **Poster Session**

Factors associated with short- and long-term survival in metastatic HER2+ breast cancer.

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Background: There have been significant therapeutic advances for HER2+ metastatic breast cancer (MBC) over the past decade. The aim of this study was to evaluate prognostic factors in metastatic HER2+ disease and their relationship with short- and long-term overall survival (OS) in the modern era. **Methods:** We evaluated patients (pts) with de novo metastatic HER2+ breast cancer diagnosed between years (y) 2010 and 2018, reported in SEER. Univariate analyses were performed to determine the effect of each variable on OS. Significant variables were included in a multivariate Cox model for OS that evaluated all pts diagnosed 2010 – 2018. Univariate and multivariate logistic regression was used to evaluate the association of each variable with short (< 2 y) and long (≥ 5 y) term OS. To allow sufficient follow up, only pts diagnosed 2010 – 2016 were included in the logistic regression for OS < 2 y, and only those diagnosed 2010 – 2014 were included for OS ≥ 5 y. **Results:** We included 5,576 pts with a median follow up of 48 months (IQR 25 – 73 months). Median OS was 41 months. The proportion alive at 2 y, 5 y, and 8 y, was 63.3% (95% CI 62.0% - 64.7%), 37.8% (95% CI 36.2% - 39.4%) and 26.8% (95% CI 24.8% - 28.9%), respectively. In multivariate analysis for OS, older vs younger age (HR 2.5), black vs white pts (HR 1.4), non-ductal non-lobular vs ductal (HR 2.7), bone metastases vs not (HR 1.2), brain metastases vs not (HR 1.8), liver metastases vs not (HR 1.6), lung metastases vs not (HR 1.3), 6 metastatic organ sites vs 1 (HR 3.6), ER/PR- vs + (HR 1.3), < $35k income vs ≥ $75k (HR 1.8), and being diagnosed in earlier years (HR 1.06 per each prior year) had significantly worse OS (all p≤0.044). Similar results were seen for breast cancer-specific survival. Factors associated with < 2 y OS in adjusted models were older age (OR 3.8), black race (OR 1.5), non-ductal non-lobular (OR 4.6), brain metastases (OR 3.0), liver metastases (OR 2.0), lung metastases (OR 1.6), ER/PR- (OR 1.7) and lower income (OR 1.6), all p < 0.04. Number of metastatic organ sites was not significant in this model. Factors associated with ≥ 5 y OS in adjusted models were younger age (OR 2.9), white vs black race (OR 1.7), fewer metastatic organ sites (OR 2.6), ER/PR+ (OR 1.3), and higher income (OR 3.3), all p < 0.02. Specific organ sites (bone, brain, liver and lung) were not significant in this model. **Conclusions:** In this cohort of pts with de novo HER2+ MBC, OS improved significantly over the study period, and a considerable proportion of pts were still alive at 8 y. Factors associated with shorter survival included older age, black race, lower income, and the presence of visceral or brain metastases. Long-term (≥ 5 y) survival was associated with both demographic (younger age, white race, higher income) and tumor-related (fewer metastatic sites, ER/PR positivity) factors. Research Sponsor: None.

HER2-targeted immunoconjugates for breast cancer: Ancestry and dose adjustment for thrombocytopenia.

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Background: Thrombocytopenia (TCP) is a common toxicity of HER2-targeted agents, trastuzumab emtansine (TDM1) and trastuzumab deruxtecan (TDXd). A high incidence of this toxicity was observed in pivotal trials that led to approval of these agents. We investigated whether Asian ancestry increases risk of dose adjustment for TCP on TDM1/TDXd and its impact on dosing in the real-world setting. **Methods:** Females with HER2+ breast cancer who initiated TDM1/TDXd between 1/16/17-10/26/21 were identified by retrospective review. Primary endpoint was number of chemotherapy cycles until adjustment of TDM1/TDXd dose for TCP; competing endpoints included discontinuation for other toxicity, disease progression, and completion of treatment. Individuals who were switched from TDM1 to TDXd contributed an additional observation post-switch. Recurrent events analysis evaluated Asian ancestry ($p<0.05$) using a proportional means model, with robust sandwich estimate recognizing correlation between repeated observations per individual. Covariates (age, metastatic disease, drug, prior adjustment) were retained if they improved the model. **Results:** The study excluded individuals who declined to self-identify (n=23), self-identified as other than Asian or White (n=28), and/or dissented to research (n=24). The study included n=181 individuals (mean age 55.1+12.8 years), of whom n=48 (26.5%) identified as Asian and n=124 (68.5%) had metastatic disease. Overall, 33 individuals received TDXd exclusively, leaving 148 (81.8%) individuals who received TDM1, including 45 individuals who later switched to TDXd after development of TCP while on TDM1 (n=9) or other toxicity (n=36) on TDM1. For n=226 observations (total 2551 cycles), the endpoint was dose adjustment for TCP (n=32), discontinuation for other toxicity or disease progression (n=112), completion of treatment (n=27), or censoring (n=55). Taking into account history of switching drug for TCP, Asian ancestry was associated with increased risk of dose adjustment for TCP (Table). Neither age, metastatic disease, nor specific drug improved the model (data not shown). **Conclusions:** Among individuals taking TDM1 and/or TDXd for HER2+ breast cancer, we observed that those with Asian ancestry are at greater risk of dose reduction for TCP than their non-Asian counterparts. Upon confirmation in additional individuals with HER2+ cancers of the breast and other sites, this heightened susceptibility to TCP among Asian individuals should be further investigated to elucidate the underlying mechanism and optimize clinical guidelines for prevention and management. Research Sponsor: None.

Predictors of dose adjustment for thrombocytopenia among individuals with breast cancer on HER2-targeted agents.

Independent Risk Factors	Hazards Ratio (95% Confidence Interval)	p
Asian Ancestry	2.84 (1.39-5.82)	0.0044
Prior Discontinuation for Thrombocytopenia	6.96 (2.80-17.30)	<0.0001

Post-recurrence survival in asymptomatic compared with symptomatic metastatic breast cancer: A multicenter retrospective study.

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Background: Asymptomatic metastatic breast cancer (mBC) is often detected using tumor marker or imaging tests in Japan. At the ASCO 2019, we reported on mBC detection, the distribution of symptomatic and asymptomatic disease by subtype (abstract e12568). We aimed to determine whether there are differences in post-recurrence survival (PRS), and treatment between asymptomatic and symptomatic MBCs, and identify factors associated with PRS. **Methods:** We performed a multicenter, retrospective analysis of patients with mBC treated in our hospitals from 2008 to 2018. Patients were divided into asymptomatic and symptomatic MBCs to compare their prognosis by breast cancer (BC) subtypes: luminal (hormone receptor positive/human epidermal growth factor 2 [HER2] negative), HER2 (any hormone receptor/HER2 positive), and triple-negative (TN) (hormone receptor negative/HER2 negative). **Results:** Of 204 patients with mBC (114 asymptomatic, 90 symptomatic), PRS was longer in asymptomatic mBC than in symptomatic mBC (median survival: 55 months vs. 29 months; $p < 0.001$) and tended to have longer overall survival (OS) (110 months vs 72 months, respectively; $p = 0.09$). In multivariate analysis, TN, recurrence-free survival (RFS), multiple metastasis sites, and symptomatic disease were independently predictive of PRS (Table). In luminal and HER2, PRS trended higher in the asymptomatic group than in the symptomatic group (luminal: 54 months vs. 41 months; $p = 0.08$, HER2: 71 months vs. 27 months; $p = 0.09$), but without significant difference in OS (luminal: 112 months vs. 124 months; $p = 0.91$, HER2: 113 months vs. 72 months; $p = 0.40$). In the luminal group, 13 patients (11%) were treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors. The median PRS was 80 months for luminal patients with three factors — longer than 4 years of RFS, a single metastasis site, and asymptomatic disease. The duration of endocrine therapy did not differ between groups; however, the patients with luminal BC in the asymptomatic group had longer chemotherapy than those in the symptomatic group. In TN, PRS was very short (asymptomatic, 28 months; symptomatic, 10.5 months; p = 0.01). **Conclusions:** We demonstrated that asymptomatic MBC and symptomatic MBC differed in terms of subtypes, prognosis, and duration of chemotherapy in the luminal group. Therefore, unique treatment strategy for asymptomatic or symptomatic MBC should be developed. Research Sponsor: None.

Variable	HR	95% CI	*p* Value
TN vs no-TN	2.56	1.69 to 3.90	<0.001
RFS, year	0.91	0.87 to 0.96	<0.001
Multiple sites of metastasis vs single sites of metastasis	1.86	1.32 to 2.61	<0.001
Symptomatic vs asymptomatic	1.76	1.26 to 2.45	<0.001

HR = hazard ratio; CI = confidence interval; TN = triple-negative; RFS = recurrence-free survival.

1050 **Poster Session**

Chemotherapy shows better efficacy than endocrine therapy in patients with metastatic breast cancer with heterogeneous estrogen receptor expression.

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Background: Heterogeneity of estrogen receptor (ER) expression has long been challenges for diagnosis and treatment strategy of metastatic breast cancer (MBC). A novel convenient way of ER detection using ^{18}F-fluoroestradiol positron emission tomography/computed tomography (^{18}F-FES PET/CT) offers a chance to screen and analyze MBC patients with ER uncertainty. **Methods:** MBC patients who received ^{18}F-FES PET/CT were screened and patients with both FES positive (FES+) and negative (FES-) lesions were enrolled in this study. Progression-free survival (PFS) was estimated by Kaplan-Meier method and compared by log-rank test. **Results:** A total of 635 patients were screened and 75 of 635 (11.8%) patients showed ER uncertainty. 51 patients received further treatment and were enrolled in this study. Among them, 20 (39.2%) patients received chemotherapy (CT), 21 (41.2%) patients received endocrine-based therapy (ET) and 10 (19.6%) patients received combined therapy (CT+ET). CT showed better progression-free survival (PFS) compared to ET (mPFS 7.1 vs 4.6 months, HR 0.44, 95% CI 0.20-0.93, P = 0.03). CT+ET did not improve PFS compared to either CT or ET alone (mPFS 4.4 months, P > 0.2). **Conclusions:** ^{18}F-FES PET/CT could identify patients with ER heterogeneity. Patients with ER uncertainty showed better sensitivity to CT rather than ET. Combined therapy of CT+ET did not improve treatment outcome. Research Sponsor: None.

1051 **Poster Session**

Aromatase inhibitors for breast cancer therapy: Analysis of real-world FAERS data.

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Background: Aromatase inhibitors (AIs) are extremely effective adjuvant treatment in postmenopausal women with hormone receptor-positive breast cancer (HRPBC). We utilized the Food and Drug Administration Adverse Event Reporting System (FAERS) database to evaluate the musculoskeletal (MSK), fractures, and ischemic heart disease (IHD) adverse events (AEs) caused by AIs. **Methods:** We conducted a retrospective FAERS public database review to assess the MSK, fracture, and IHD AEs for the three AIs (anastrozole, letrozole, and exemestane) from 2001 through 2021. Chi-square was used to compare categorical variables. **Results:** A total of 31,683 AEs reports were identified, out of which, 15,140 (47.8%) were MSK, 13,311 (42.0%) were fracture, and 3,232 (10.2%) were IHD. The differences in AEs distributions among the three drug classes were statistically significant for MSK and fracture AEs ($P < 0.001$) but not reached statistical significance for IHD AEs ($P = 0.140$). MSK AEs were mostly reported with anastrozole, followed by exemestane, and letrozole in 35.23%, 33.97%, and 32.06%, respectively ($P < 0.001$). Compared to older individuals, younger adults (≤65 years) had higher rates of MSK AEs—mostly with anastrozole (38.43%, $P < 0.001$), followed by exemestane (36.37%, $P = 0.006$) and letrozole (34.28%, $P < 0.001$). Fracture AEs were mostly reported, in descending order, with letrozole, exemestane, and anastrozole in 12.07%, 11.41%, and 9.34% respectively ($P < 0.001$). Older adults (> 65 years) had higher rates of fracture AEs with letrozole (16.77%, $P < 0.001$) and anastrozole (10.37%, $P < 0.001$), while unable to demonstrate statistical significance with exemestane (13.48%, $P = 0.108$). Among older adults (> 65 years), IHD AEs were significantly reported with anastrozole (21.56%, $P < 0.001$) and exemestane (14.18%, $P = 0.016$) but no statistical significance reached for letrozole (14.12%, $P = 0.528$). **Conclusions:** The findings in this study highlight trends for selected AEs with various AI regimens, provide further insights, and help guide therapeutic decisions for patients with HRPBC. Research Sponsor: None.

1052 **Poster Session**

Long-term safety of inavolisib (GDC-0077) in an ongoing phase 1/1b study evaluating monotherapy and in combination (combo) with palbociclib and/or endocrine therapy in patients (pts) with *PIK3CA*-mutated, hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer (BC).

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Background: Dysregulating mutations in *PIK3CA*, encoding the PI3K p110α subunit, occur in ~40% of HR+/HER2– BCs. Inavolisib is a PI3Kα-specific inhibitor that also promotes degradation of mutant p110α. It has demonstrated encouraging preliminary antitumor activity in pts with *PIK3CA*-mutated HR+ BC as a monotherapy, and in combo with other anticancer agents. **Methods:** We included pts from NCT03006172 on treatment ≥1 year with inavolisib alone (Arm A), or in combo with palbo + letrozole (letro) (B), letro (C), fulvestrant (fulv) (D), or palbo + fulv (E; + metformin in Arm F for pts with body mass index ≥30 and/or HbA1c ≥5.7%). Inavolisib was administered orally daily (PO QD) at 3, 6, 9, or 12 mg (3+3 dose-escalation design); letro at 2.5 mg PO QD; palbo at 125 mg PO QD for 21/28 days; and fulv at 500 mg intramuscularly every 4 weeks, in 28-day cycles until intolerable toxicity/disease progression. Safety was assessed by NCI-CTCAE v4. **Results:** 57 female pts were included (cutoff 07/26/21; N = 1, 18, 6, 12, 15, 5 in Arms A–F); median age: 57 years (range 33–80); median lines of prior therapy: 2 (1–7). All but 2 pts, both in Arm B (3 mg), were assigned the 9 mg inavolisib recommended phase 3 dose. Overall median treatment duration: 19 months (range 12–45); median inavolisib cumulative dose intensity, 95%. The most frequent treatment-related adverse events (AEs; in ≥20 pts/35%) were hyperglycemia (68%), stomatitis (68%; grouped terms), neutropenia (58%), diarrhea (51%), nausea (39%), alopecia (35%), and rash (35%; grouped terms). The most frequent treatment-related Grade (G) 3–4 AEs (≥2 pts/4%) were neutropenia (47%), hyperglycemia (16%), leukopenia (9%), thrombocytopenia (9%), lymphopenia (7%), weight decreased, and hypokalemia (4% each). G3–4 neutropenia, leukopenia, thrombocytopenia, and lymphopenia were all reported in palbo arms. One G5 AE of pleural effusion was reported (disease progression-related). 39 pts (68%) had ≥1 AE resulting in study treatment modification (drug interruption/dose reduction/treatment withdrawal); 11 (19%) had an inavolisib dose reduction and 2 (4%) discontinued treatment due to an AE (1 related G2 diarrhea, 1 unrelated G3 cerebrovascular disorder). AEs typically occurred during the first 6 months and tended to be less frequent in later cycles. No new safety signals were observed with long-term inavolisib use. **Conclusions:** These data indicate acceptable long-term tolerability. The safety profile of pts on study treatment with inavolisib alone or in combo with endocrine-based anticancer therapies for ≥1 year was similar to that reported for the overall study population. Updated data will be presented. A phase 3 study of inavolisib + palbo + fulv is enrolling (NCT04191499; INAVO120). Clinical trial information: NCT03006172. Research Sponsor: Genentech, Inc.

1053 **Poster Session**

Phase I study combining pembrolizumab and aromatase inhibitor in patients with metastatic hormone receptor–positive breast cancer.

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Background: Aromatase inhibitor (AI) is standard of care for patients with hormone receptor positive (HR^+) human epidermal growth factor receptor 2-negative ($HER2^-$) metastatic breast cancer (MBC). The current phase I trial was designed to test the safety and efficacy of AI and the immune checkpoint inhibitor pembrolizumab (NCT 02648477). **Methods:** Key eligibility criteria were HR^+ $HER2^-$ MBC per ASCO/CAP; RECIST 1.1 measurable disease; adequate organ function; and ECOG 0-1. Eligible patients received 200 mg pembrolizumab IV every 3 weeks plus AI until progression or unacceptable toxicity. Primary objectives were to evaluate the safety and efficacy of this combination. This study employed a 3-at-risk design with a lead-in at the standard dosing of both AI and pembrolizumab with a targeted accrual of 20 patients. **Results:** A total of 20 patients were accrued between March 2016 and April 2017. Median age was 62 (range 34-79), with 75% white, 15% Asian and 10% unknown. Median lines of therapy were 3 (0, 9). All but one patient received aromatase inhibitor and/or fulvestrant prior to enrollment. The combination was well tolerated, and the most common adverse events were grade 2 fatigue (35%), rash (15%), and hot flashes (10%). Grade 3 adverse events were elevated AST/ALT (5%), rash (5%), and lymphopenia (5%). Responses were 10% partial response and 15% stable disease, resulting in a clinical benefit rate (CBR) of 20% at 6 months. Median follow-up time was 40.1 months (range 31.3 – 46.8 months). Median progression free survival was 1.8 months (95% CI 1.6, 2.6) and median overall survival was 17.2 months (95% CI 9.4, NA). 14 tumor specimens had programmed death ligand 1–positive (PD-L1) by 22C3 testing, including 3 PD-L1-positive and 11 PD-L1 negative. No association between PD-L1 and response was found. **Conclusions:** The combination of pembrolizumab and AI is well tolerated in patients with HR^+ $HER2^-$ MBC who were not pre-selected for PD-L1. There was minimal overall clinical activity observed beyond what was to be expected with AI alone in this group of patients. Clinical trial information: NCT 02648477. Research Sponsor: Merck.

Molecular alterations associated with rapid progression following CDK4/6 inhibitors (CDKi) in metastatic hormone receptor–positive breast cancer (mHRBC).

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Background: Combination of CDKi with endocrine therapy is a key treatment for mHRBC due to survival benefit and favorable safety profile. However, progressive disease inevitably develops and outcomes after CDKi discontinuation (dc) are not well-described. Within our institution, we previously reported clinical characteristics and outcomes for a cohort of 140 mHRBC patients who received CDKi therapy. Median progression-free survival (PFS) and overall survival (OS) post-CDKi dc were 7.0 and 15.4 months, respectively. However, 29% experienced rapid progression or death within 4 months following CDKi dc. Molecular predictors of rapid progression after CDKi are unknown and may help define therapies to improve outcomes. In this study, we sought to identify molecular predictors for rapid disease progression after CDKi dc in mHRBC. **Methods:** We identified within our cohort 34 patients with mHRBC who progressed on CDKi with next-generation sequencing (NGS) performed on pre-CDKi tissue samples. PFS and OS, measured from CDKi dc, were analyzed with the Kaplan-Meier estimator and log-rank test. Rapid progression was analyzed with logistic regression and Fisher's exact test to evaluate association between pre-CDKi tumor mutation and rapid progression post-CDKi. **Results:** NGS of pre-CDKi tumor biopsies found 12 genes (*FGF3, FGF4, FGFR, PIK3CA, PTEN, AKT, RB1, CDKN2A, MYC, CCND1, ESR1, TP53*) that were altered in ≥3 of the 34 patients. The six patients (18%) with a *PTEN mutation (mut)* had a median PFS of 3 months and median OS of 4 mo. In comparison, median PFS and OS of *PTEN wild-type (wt)* patients were 7 mo. (log-rank p=0.008) and 21 mo. (log-rank p<0.001), respectively. Moreover, those with *PTENmut* tumors were more likely to experience rapid progression compared to *PTENwt* (odds ratio = 7.0, 95% CI: 1.1 – 60.5, p=0.048). Notably, in the 10 rapid progression patients with pre-CDKi NGS results, alterations to PI3K pathway constituents were prevalent: *PTENmut* (40%), *FGFRmut* (50%), *AKTmut (*20%) and *PIK3CAmut* (40%). **Conclusions:** PI3K pathway alterations are prevalent in mHRBC patients who develop rapid progression post-CDKi dc, with *PTENmut* being the most significant predictor. These hypothesis-generating findings provide the basis for ongoing investigations to find clinical and molecular biomarkers that can help improve outcomes for mHRBC at risk of rapid progression post-CDKi therapy. Research Sponsor: None.

Relationship of *PTENmut* and other PI3K pathway mutations on post-CDKi outcomes.

Impact of pre-CDKi *PTENmut* on post-CDKi dc outcomes *PTENmut*	*PTENwt*	log-rank p-value	
mPFS	3 mo	7 mo	0.008
mOS	4 mo	21 mo	<0.001
Association of pre-CDKi PI3K pathway mutations with rapid progression post-CDKi dc			
	Rapid progression	No rapid progression	Fisher's p-value
PTENmut (n=6)	66.7%	33.3%	0.053
AKTmut (n=3)	66.7%	33.3%	0.212
FGFRmut (n=12)	41.7%	58.3%	0.433
PIK3CAmut (n=14)	28.6%	64.3%	1.000

1055 **Poster Session**

Clinical outcomes with alpelisib (ALP) plus fulvestrant (FUL) after prior treatment (tx) with FUL in patients (pts) with advanced breast cancer (ABC): A real-world (RW) analysis.

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Background: ALP (α-selective PI3K inhibitor and degrader) + FUL was FDA approved and reflected in the NCCN guidelines in 2019 for pts with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) ABC with *PIK3CA* mutations following progression on or after endocrine-based therapy (ET). The Phase III SOLAR-1 trial excluded prior FUL, and data on ALP + FUL after FUL are limited. As cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) + ET (including FUL) is the standard in the first line (1L) or second line (2L) for pts with HR+/HER2– ABC, more data on ALP + FUL post-FUL are needed. Here we report patterns and clinical outcomes on RW use of ALP + FUL in pts with HR+/HER2– ABC with prior FUL exposure. **Methods:** This retrospective study used de-identified electronic health record data from the ConcertAI Patient360 Breast Cancer data product sourced from US oncology centers. Adults with HR+/HER2– ABC treated with ALP + FUL (index tx) who received prior FUL (monotherapy or in combination) in the metastatic setting were included; pts with a *PIK3CA* negative test on or prior to the index were excluded. Pts were followed until date of death or last activity. RW progression-free survival (rwPFS), defined as first documented progression/death from ALP + FUL start date, was assessed. **Results:** This analysis included 157 pts (median age, 63 y [57-71 y]) who received ALP + FUL from 2019 to 2021, with 11.5% pts in 1L, 17.8% in 2L, 26.8% in third line (3L), and 43.9% in fourth line and beyond (4L+). Prior FUL tx included CDK4/6i + FUL (74.5%), FUL alone (33.8%), and non-CDK4/6i + FUL (21.0%). In pts who received ALP + FUL in 1L (n = 18), prior FUL exposure was in the same line without documented progression. In the metastatic setting, 28.0% of pts received > 1 FUL-containing regimen and/or 72.0% received prior chemotherapy (CT). At the median duration of follow-up (8.7 mo [4.1-12.5 mo]), the median rwPFS was 5.7 mo (4.0-7.3 mo) in the overall population. The median rwPFS was also analyzed by line of therapy (Table). In pts with CDK4/6i + FUL as immediate prior therapy (n = 39), the median rwPFS was 6.2 mo (3.0-9.1 mo); 79.5% of these pts received ALP in ≤ 3L. At the time of analysis, 107 pts (68.2%) had discontinued ALP + FUL; the median time to discontinuation was 4.7 mo (3.7-6.1 mo). Following discontinuation of ALP + FUL, CT was the most common subsequent therapy (33.8%). **Conclusions:** This analysis on RW data from early years of ALP access in the US shows clinical benefit of ALP + FUL in pts with HR+/HER2– ABC with *PIK3CA* mutation even when exposed to prior FUL, confirming the oncogenic dependence of the tumor on the *PIK3CA* mutation. Research Sponsor: Novartis Pharmaceuticals.

Line of therapy	1L	2L	3L	4L+
n	18	28	42	69
rwPFS, median, mo	11.9 (1.1-NR)	6.2 (2.5-9.1)	4.0 (2.7-7.5)	4.8 (3.8-7.3)

NR, not reached.

1056 **Poster Session**

CDK4/6 inhibitors outcomes in patients with advanced breast cancer based on HER2-low expression.

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Background: HER2-low expression, defined as HER2 immunohistochemistry (IHC) score of 1+ or 2+ with negative in situ hybridization assay (FISH), accounts for 50% of breast cancers. There is limited and conflicting evidence regarding the efficacy of cyclin-dependent kinase (CDK) 4 and 6 inhibitors in patients with ER+ and HER2-low tumors. This study aimed to investigate the prognostic value of HER2-low expression in patients with ER+/HER2-negative advanced breast cancer treated with CDK 4/6 inhibitors. **Methods:** We retrospectively selected consecutive patients with ER+/HER2-negative advanced breast cancer treated with CDK 4/6 inhibitors plus endocrine therapy in our institution from May 2015 to Feb 2020. Two cohorts were compared, including HER2-0 (IHC score) and HER2-low (HER2 IHC score 1+ and 2+ [negative FISH]) tumors. Comparisons in progression-free survival (PFS) and overall survival (OS) were performed using a log-rank test. The prognostic value of HER2-low was investigated by the Cox regression model. **Results:** Among the 186 patients included, median age at treatment was 55 (r 27-84), and majority had ECOG 0 (126, 67.8%). Progesterone receptor was positive in 155 (83.3%) tumors. Of note, most patients received CDK4/6 inhibitors and endocrine therapy as first-line setting (131, 70.4%). Mostly received palbociclib (161, 86.6%), while ribociclib and abemaciclib were used in 23 (12.4%) and 2 (1.08%) patients, respectively. Overall, 27 patients (14.5%) had de novo metastatic disease, 68 (36.6%) had only bone metastases, and 69 (37.1%) had visceral disease. Of the total population, 64 (34.4%) tumors were HER2-low (43 [23.1%] HER2-1+, and 21 [11.3%] HER2-2+), and 122 (65.6%) were HER2-0. Median PFS among patients with HER2-0 and HER-low were 19 mo. (95% CI, 13.9-24.1), and 15.6 mo. (95% CI, 11.1-20.0), p = 0.074, respectively. In patients treated with CDK 4/6 in the first-line setting, no statistically significant differences were observed in terms of PFS and OS between HER2-0 and HER2-low (PFS HR 0.73 [95% CI, 0.47-1.13; p = 0.160], and OS HR 1.04 [95% CI, 0.51-2.14; p = 0.909]). **Conclusions:** In our study, HER2-low expression did not show a statistically significant impact on patients with ER+/HER2-negative advanced breast cancer treated with CDK 4/6 inhibitors. Our study supports the necessity of real-world evidence and the design of pooled analysis to understand the real implication of this biomarker in patients with ER+/HER2-negative tumors. Research Sponsor: None.

1057 **Poster Session**

ESR1 mutations in circulating tumor DNA (ctDNA) are associated with CTCs and increased hormone receptors in metastatic tumor tissues of patients with metastatic breast cancer (MBC).

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Background: The monitoring of ctDNA and circulating tumor cells (CTCs) in patients with MBC predicts metastasis and prognosis. We previously reported that HER2 and *ESR1* alterations in ctDNA were associated with predicted metastasis in MBC (2019 ASCO#1036). Furthermore, ctDNA can be used to evaluate tumor heterogeneity (2020 ASCO #1028). Here, we report that baseline ctDNA *ESR1* mutation is a key point associated with tumor tissue characteristics and CTCs, which may help to elucidate disease resistance in MBC. **Methods:** This study included 288 hormone receptors positive MBC patients who received systemic treatment under an IRB-approved clinical trial (NU16B06) at NU Lurie Cancer Center (2016-2021). Baseline plasma ctDNA was analyzed by Guardant360 NGS for ESR1 mutations. CTC enumerations were performed by using 7.5ml blood in CELLTRACKS (Menarini). Estrogen receptor (ER), progesterone receptor (PR), HER2 and Ki67 in each patient's biopsy tumor tissue before surgery, surgical tumor tissue and metastatic tumor tissue were evaluated by NU PathCore. Kruskal-Wallis was used for statistics. **Results:** Of the 288 patients, *ESR1* mutations were found in 18 hotspots from 38 patients ($ESR1^{Mut}$, 13.19%) and there were 250 patients without any mutation ($ESR1^{WT}$, 86.81%). Median of Total CTCs (/7.5ml) and $HER2^{+}$ CTCs (/7.5ml) were significantly increased in $ESR1^{Mut}$ group compared to $ESR1^{WT}$ group, total CTCs were 8.0 vs 1.0 (P=0.006) and $HER2^{+}$ CTCs were 1.5 vs 0 (P=0.014), respectively. There were significant differences on hormone receptors expression (positive cells %) in tumor tissues between $ESR1^{Mut}$ group and $ESR1^{WT}$ group: 1) $ESR1^{Mut}$ group has significant higher expression in ER and PR in biopsy tumor tissues. The mean of ER in $ESR1^{+}$group was 90.48% vs 48.18% in $ESR1^{WT}$ group ($p<0.001$). The mean of PR in $ESR1^{Mut}$ group was 40.86% vs 25.60% in $ESR1^{WT}$ group ($p<0.001$). Meanwhile, there is not significant difference on HER2 expression in $ESR1^{Mut}$ group compared $ESR1^{WT}$group; 2) In the surgical tumor tissues, the mean ER was 97.64% in $ESR1^{Mut}$ group which was significantly higher than 47.90% in $ESR1^{WT}$ group ($p<0.001$), while the PR was 45.33% and 24.32%, respectively; 3) In metastatic tumor tissues, the mean of ER in $ESR1^{Mut}$ group was 84.75% vs 34.89% in $ESR1^{WT}$group ($p<0.001$) and the mean of PR in $ESR1^{Mut}$ group was 32.25% vs 9.33% in $ESR1^{WT}$ group ($p<0.001$). Furthermore, median of Ki67 in $ESR1^{Mut}$ group is 28.33% which was significantly higher than 18.75% in $ESR1^{WT}$ group ($p<0.01$). **Conclusions:** Baseline ctDNA ESR1 mutations not only had higher total CTCs and $HER2^{+}$ CTCs but also significantly correlated with high hormone receptors and proliferation in tumor metastatic tumor tissues. The synergy of ctDNA *ESR1* mutation and tissue pathological characteristics expands the early predictive role of ctDNA monitoring metastatic prognosis for clinical decision-making. Research Sponsor: U.S. National Institutes of Health.

1058 **Poster Session**

Longitudinal circulating tumor DNA (ctDNA) whole-exome sequencing (WES) in the phase Ib/II trial of palbociclib and bazedoxifene reveals genomic dynamics and clonal evolution with the acquisition of treatment resistance in hormone receptor-positive, HER2-negative (HR+ HER2-), advanced breast cancer (ABC).

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Background: Patients (pts) with HR+ HER2- ABC ultimately develop endocrine resistance. To gain insights into the genetic mechanisms of resistance we performed WES on serial plasma samples from endocrine resistant pts treated on a clinical trial (NCT02448771). **Methods:** Plasma samples were collected at baseline (n=36), day 1 of cycle 2 (n=33), and at the end of treatment (EOT, n=33). Samples were subjected to ultra-low passage (ULP, 0.19-0.57X) WGS to determine ctDNA tumor fraction (TF) for the selection of samples (TF>0.03) for subsequent WES (193X). Somatic single nucleotide variations, somatic copy number alteration (SCNA), phylogeny, tumor mutational burden, mutational signatures, and germline analyses were performed. **Results:** All 102 samples underwent successful ULP and 68 WES. Overall, most frequent pathogenic mutations were in *ESR1* and *PIK3CA*. At baseline, 32% of pts had *ESR1* mutation and 21% *PIK3CA* mutation. There was no association between *ESR1* mutations and PFS. In contrast, baseline *PIK3CA* mutations were detected only in pts who did not have a clinical benefit, and were associated with worse PFS compared to pts with wild-type *PIK3CA* (1.8 vs. 3.9 months, respectively, HR=0.2, 95% CI 0.06-0.6, *P=0.0019*, log-rank test). Additionally, pts with a baseline truncating mutation, mostly in tumor suppressor genes (*TP53, MEN1, RB1, CDKN1B, NF1, TP53BP1, TP63, SMAD2/4, ARID1A, KMT2C*), also had a significantly worse PFS (1.7 vs 3.8 months, HR=0.3, 95% CI 0.1-0.7, *P=0.006*, log-rank test). At EOT, 20% (4/20) of pts with matched baseline samples had newly acquired mutations that are suggestive of mechanisms of acquired resistance and offer potential therapeutic targets (e.g. *ERBB2, PIK3CA)*. SCNA analysis showed that in all pts there were at least 2 SCNAs in cancer-related driver genes, most common in *CCND1* and *ELF3*. Moreover, in all samples we identified at least 1 SCNA related to a potential mechanism of resistance. To better understand tumor heterogeneity and sub-clonal architecture we performed an evolutionary analysis (sufficient TF≥0.15, available in n=7). Phylogenetic analysis revealed sub-clonal dynamics that could explain the acquisition of resistance in at least three pts (3/7), and identified novel genes which might have role in endocrine resistance (e.g. *DCAF13, ZFHX3*). **Conclusions:** Our results demonstrate the feasibility and utility of serial WES in a clinical trial. Serial ctDNA WES and evolutionary studies enabled us to discover novel potential genomic mechanisms of tumor progression, and identified *PIK3CA* mutations as a candidate biomarker of resistance to the combination of palbociclib and bazedoxifene, which may apply to other next generation endocrine treatments. Clinical trial information: NCT02448771. Research Sponsor: Pfizer.

1059 **Poster Session**

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

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Background: Hyperactivation of the PI3K pathway in breast cancer is implicated in malignant transformation, cancer progression, and resistance to endocrine therapy. Salt Inducible Kinase- 3 (SIK3) is highly expressed in breast cancer and elevated SIK3 expressions are shown to contribute to tumorigenesis. Tenalisib (RP6530), a highly selective PI3K δ/γ and SIK3 inhibitor has been evaluated in > 150 patients with haematological malignancies and demonstrated encouraging activity in T-cell lymphoma with a differentiated safety profile. Tenalisib has a major metabolite (IN0385) which shows potent SIK3 inhibition. Preclinical studies in breast cancer cell lines have demonstrated that Tenalisib potentiated the activity of taxol 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 (MBC). **Methods:** This randomized, open-label study was designed to evaluate two doses (800 mg BID and 1200 mg BID) of Tenalisib in HR+/HER2- locally advanced or MBC patients including TNBC patients whose disease had progressed following at least one line of therapy. Tenalisib was given orally in a 28-days cycle until disease progression. Forty pts (20 pts at each dose level) were planned to be enrolled with the primary outcome being the percentage of pts without disease progression at the end of 6 months. The investigator-assessed ORR, PFS, and Clinical Benefit Rate (CBR = CR+PR+SD), using RECIST v1.1 were secondary outcomes. **Results:** All forty pts have been enrolled in the study. Pts had a median of 3 (range 1-7) lines of prior therapy; of these, 87% pts had prior endocrine therapy, and 40% and 30% pts had aromatase inhibitor or fulvestrant as their last prior therapy respectively. The median age was 63.8 (31-71) years, 52.5% of pts had PS 1, 77.5% had visceral disease, and 95.0% had ≥ 2 metastatic lesions at the time of enrollment. As of 07-Feb 2022, twenty-eight pts were efficacy evaluable. Of the 28, 2 pts had a PR (7%), 17 pts had SD (61%) and 6 pts had PD (21%) at the first efficacy assessment after completion of 2 cycles. Three pts discontinued from the study due to adverse events (11%) before the first efficacy assessment. The CBR was 68%. On safety, the most common TEAEs (≥5%) of any grade were transaminitis (All: 22%, ≥G3: 10%), GGT elevation (All: 7%, ≥G3: 5%), fatigue (All: 7%, ≥G3: 0%), rash (All: 7%, ≥G3: 2.5%). Discontinuations due to related TEAEs were infrequent (7%). There were no unexpected TEAEs. Two pts were discontinued due to related TEAEs (rash and GGT elevation). **Conclusions:** Based on the data from the ongoing study, Tenalisib showed encouraging preliminary efficacy as a single agent in patients with advanced MBC. Updated efficacy and tolerability data will be provided at the time of presentation. Clinical trial information: NCT05021900. Research Sponsor: None.

1060 **Poster Session**

Predicting hyperglycemia among patients receiving alpelisib plus fulvestrant for metastatic breast cancer.

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Background: Although hyperglycemia is recognized as a common adverse event (AE) on alpelisib (ALP), this AE has been little studied outside clinical trials. We report the frequency of ALP-associated hyperglycemia in a real-world setting and evaluate proposed risk factors. **Methods:** We retrospectively identified patients with PIK3CA-mutated, hormone receptor-positive, metastatic breast cancer who initiated treatment with ALP+fulvestrant (FUL) between August 2019 and December 2021. Five primary characteristics (diabetes, prediabetes, body mass index (BMI), age, Asian ancestry) were evaluated as independent risk factors for ALP-associated hyperglycemia using ordinal logistic regression that considered 3 glycemic levels: normoglycemia, grade 2, and grade 3-4 hyperglycemia. Overall risk of error from multiple hypothesis testing was kept below 5% using the False Discovery Rate method. **Results:** The study included n = 92 subjects, all but 1 female, mean age 59.9 (+11.9) years, 13.0% with Asian ancestry. One third (33.7%) of patients had pre-existing diabetes, another 9.8% had pre-diabetes only. One third (32.6%) were obese, another third (31.5%) were overweight. Hypertension and hyperlipidemia were present in 53.3% and 41.3%, respectively. On ALP+FUL, 59 (64.1%) current subjects developed hyperglycemia of grade 1-4, a rate no different than the 181/284 (63.7%) reported in the ALP+FUL arm of the SOLAR-1 trial. Among our subjects, risk of grade 2-4 hyperglycemia was independently increased by 4 of 5 hypothesized risk factors, specifically pre-existing diabetes (Odds Ratio 3.75, 95% Confidence Interval: 1.40-10.01), pre-diabetes (6.22, 1.12-34.47), Asian ancestry (7.10, 1.75-28.84), each unit of BMI above 20 (1.17, 1.07-1.28), but not by additional year of age (1.01, 0.97-1.05). Exploratory analysis detected no association with pre-existing hypertension or hyperlipidemia. **Conclusions:** These findings suggest that Asian ancestry merits further study as a predisposing factor for ALP-associated hyperglycemia. Our study of this AE also demonstrates that pre-existing hyperglycemia and greater BMI are independent risk factors; diabetes and pre-diabetes confer similar degrees of risk; risk from BMI begins after BMI 20 and rises incrementally; and age is not a contributing factor. Research Sponsor: U.S. National Institutes of Health.

1061 **Poster Session**

Utility of liquid biopsy for identifying emerging mutations (mut) and novel treatment options in luminal metastatic breast cancer (LMBC).

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Background: Molecular characterization of LMBC for the choice of therapy and inclusion in clinical trials is frequently performed in archival biopsies procured several years before. Emerging mut secondary to therapeutic pressure are hence frequently missed but could be detected by real-time analysis of circulating tumor DNA. Aim: 1) To assess the emergence of *ERBB2* and other mut upon therapeutic pressure; 2) To compare the concordance of mut in tumor and plasma samples between patients (pts) with metachronous and synchronous sample acquisition. **Methods:** Pts with LMBC and available tumor biopsy and plasma samples were identified and divided in two groups: 1) Cohort 1 (metachronous) if the time between tissue and plasma acquisition was > 3 months and systemic treatment was given between the sampling; 2) Cohort 2 (synchronous) if sampling occurred with < 3 months interval in the absence of systemic treatment. Tumor and plasma were analyzed using MiSeq Amplicon-based NGS (custom panel of 60 cancer-related genes). The emergent mut in plasma in Cohort 1 and the concordance of ESCAT Tier I and II mut (*PIK3CA, AKT1, ERBB2, ESR1, PTEN*) in both Cohorts were determined and correlated with clinical features. **Results:** 176 pts were included, 112 in Cohort 1 and 64 in Cohort 2. In Cohort 1, emerging mut in *PIK3CA* were identified in 5 cases (14% of total cases with *PIK3CA* mut), *ESR1* in 22 cases (85% of cases with *ESR1* mut) and *PTEN* in 3 cases (43% of cases with *PTEN* mut). No emerging *ERBB2* or *AKT1* mut were seen in plasma. In Cohort 1 *ERBB2* mut were identified in 10 pts (8.9%), 5 both in plasma and tissue and 5 only in tissue. Concordance between tumor and plasma was 53% in Cohort 1 and 66% in Cohort 2 (95% CI of the difference -2% to 38%, P =.09). In Cohort 1, concordance was not associated with (neo)adjuvant treatment, number of lines for MBC, presence of visceral metastasis, location of biopsy (primary tumor or metastasis), interval between sampling (range 3.6 – 288 months) or type of systemic treatment before plasma sampling. In Cohort 2, higher concordance associated with shorter interval between primary diagnosis and sampling (p = 0.02). *PI3KCA* and *ESR1* were the two genes most frequently altered in both cohorts. *PI3KCA* mut had the highest degree of concordance in both groups (70% in Cohort 1 and 76% in Cohort 2). Concordance for *ESR1* mut was low in both cohorts (20% and 48%, respectively). **Conclusions:** A significant number of *ESR1* mut emerged upon therapeutic pressure in LMBC. Plasma analysis could also detect the emergence of *PIK3CA* and *PTEN*, but not *ERBB2* mut. The trend towards lower concordance between metachronous and synchronous tumor and plasma sampling is probably due to increased tumor heterogeneity and clonal diversity secondary to systemic treatment. Our findings confirm that liquid biopsies provide complementary information respect to tumor tissue that may be potentially useful for clinical decisions. Research Sponsor: Puma Biotechnology.

1062 **Poster Session**

Clinical value of next-generation sequencing in endocrine therapy for advanced hormone receptor–positive/HER2-negative breast cancer.

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Background: Acquired gene mutation is a major mechanism of resistance to endocrine therapy in hormone receptor (HR)-positive advanced breast cancer. Circulating tumor DNA (ctDNA) facilitates the current assessment of the genomic profile in patients with advanced cancer. We performed this clinical trial to determine the landscape of gene mutation before endocrine therapy, to search for molecular markers of endocrine therapy efficacy, and to explore the clinical value of ctDNA to guide precise endocrine therapy in patients with advanced breast cancer. **Methods:** We conducted an open-label, single-center, multicohort, prospective study. Patients were women with pathologically and immunohistochemically confirmed HR-positive/HER-2-negative patients with advanced breast cancer. Patients relapsed during or after adjuvant endocrine therapy or progressed after completing at least one previous line of treatment for advanced breast cancer. Patients were assigned to four parallel treatment cohorts-matched to mutations identified in ctDNA: 1) cohort A comprised patients with abnormal activation of PI3K/Akt/mTOR pathway signal, preferred mTOR inhibitor combined with endocrine therapy; 2) cohort B comprised patients with ESR1 mutation and who did not use fulvestrant before, preferred fulvestrant; 3) cohort C comprised patients with HER2 mutations, preferred pyrotinib combined with endocrine therapy; 4) cohort D comprised patients with no significant gene mutation, making treatment plan according to the actual clinical situation. If more than one mutation was identified, the priority of entry is cohorts C, cohorts A and cohort B. In the A-D cohort, patients who obey the treatment plan are the compliance group, and patients who do not obey the treatment plan are the violation group. The primary endpoints were progression-free survival (PFS), and the secondary endpoints included overall survival time (OS). **Results:** A total of 113 patients underwent NGS detection of ctDNA, and 84 patients were enrolled in the study. In all cohorts, combined median PFS was 4.9 months, and the median PFS in the compliance group was 3.0 months longer than in the violation group (6.03 vs 3.03 months, p = 0.0222, HR = 0.5743, 95%CI 0.3273-1.007). In cohort C, the median PFS was 11.1 months in the compliance group and 2.22 months in the violation group (p = 0.0067, HR = 0.1980, 95%CI 0.032-1.22). There was no significant difference in the median PFS between patients with and without compliance with the treatment protocol in cohort A and cohort B (p = 0.5054 and 0.7325, respectively). **Conclusions:** The study suggested that ctDNA detection may guide the optimal endocrine therapy strategy for patients with advanced breast cancer and achieve the benefit of progression free survival. NGS detection might distinguish patients with HER2 mutation and provide new treatment strategies. Clinical trial information: NCT03786575. Research Sponsor: None.

1063 **Poster Session**

Ribociclib-induced acute kidney injury: Uncover the MONALEESA's dark face.

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Background: The phase-3 MONALEESA-2,-3 and -7 randomized trials showed improved progression-free survival (PFS) and overall survival (OS) with the addition of cyclin D-cyclin-dependent kinase 4/6 (CDK4/6) inhibitor ribociclib to endocrine therapy in women with advanced-stage breast cancer. However, ribociclib induced acute renal injury is not recognized in these studies. In this report, we explore ribociclib-induced acute kidney injury (AKI) in breast cancer patients receiving ribociclib. **Methods:** We performed a retrospective chart review of all breast cancer patients who received ribociclib at our institution between April 2019 and September 2021. Patients and disease characteristics were collected, details of creatinine kinetics in relation to administration of ribociclib and other nephrotoxic drugs were obtained. Acute kidney injury grades (AKI-KDIGO classification) were captured. **Results:** 145 females, median age 60.0 years, all with advanced-stage breast cancer treated with aromatase inhibitors (AI) or fulvestrant plus ribociclib were reviewed. A total of 26 (17.9%) patients developed AKI; 3 were grade-I, 21 grade-II and 2 were grade-III. Rate of AKI was significantly higher (n = 15, 48.4%) among 31 patients on other concomitant nephrotoxic drugs, compared to 11 (9.6%) of 114 other patients, p = 0.001. Nephrotoxic drugs include non-steroidal anti-inflammatory (38%), metformin (30%), angiotensin-II receptor blockers (26%), and angiotensin-converting enzyme inhibitors (11%). Median time to develop AKI was 54 (range, 21-168) days, while the median time for creatinine recovery was 5 (range, 4-7) days after holding the drugs. Average creatinine increment for affected patients was 2.28 times the baseline level. Time to AKI was shorter, but not statistically significant, among patients on nephrotoxic drugs and recovery was faster after stopping these drugs (Table). **Conclusions:** Ribociclib-induced AKI is not uncommon and not adequately addressed. Though reversable in majority of patients, some patients may develop grade-III AKI or require treatment interruption. Nephrotoxic medications seem to significantly enhance ribociclib-associated renal injury. Withhold these medications with periodical assessment by nephrologist is strongly recommended in these patients. Larger studies are warranted to validate our findings. Research Sponsor: None.

	Without other nephrotoxic drugs	With Other nephrotoxic drugs	P-Value
Total number of patients (n)	114	31	
Patient with AKI, n (%)	11 (9.6%)	15 (48.4%)	0.001
Time to AKI (mean; range), days	66 (28-98)	52 (21-168)	0.14
Grade-11/III AKI, n (%)	10 (2.6%)	13 (3.38%)	0.88
Time to recovery (mean; range), days	6 (4-10)	5.4 (4-7)	0.12

1064 **Poster Session**

Identifying genetic factors of response and resistance to CDK4/6 inhibitors in metastatic HR+/HER2-breast cancer using real-world data.

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Background: CDK4/6 inhibitors plus endocrine therapy are approved for treatment of HR+/HER2- metastatic breast cancer (MBC) and have shown to provide a significant progression free survival benefit over endocrine therapy alone. But not all patients benefit from this treatment and some develop resistance over time. The molecular mechanisms governing this resistance are poorly understood. We have developed a real world dataset that includes data elements from structured EMR tables as well as deeply curated unstructured data from BC patients (ConcertAI Genome360 BC Dataset) who have been treated with CDK4/6 inhibitors and have undergone DNA sequencing to identify somatic mutations. We have leveraged this linked clinical-genomics dataset to identify genetic drivers of resistance and response to CDK4/6 inhibitors. **Methods:** This retrospective study uses the Genome360 BC Dataset (N = 1249). The patient's eligibility to be included in this study (N = 456) was HR+/HER2- MBC patients with age > 18 years treated with at least one of the CDK4/6 inhibitors and have response data based on RECIST criteria (responders = 231, non-responders = 225). For each patient in both cohorts, all pathogenic gene mutations and copy number changes were identified and enrichment analysis was performed. Biomarkers with Z value > 1.96 (p value < 0.05) were considered for further analysis. Pathway analysis was performed using these biomarkers and the CDK4/6 pathway to identify pathways and genes that can potentially be targeted to overcome resistance based on the mutational landscape of the patients receiving therapy. **Results:** We identified 7 potential segments (similar groups of genes) which predicted response or resistance to CDK4/6 inhibitors. Here we present data on 3 such segments which are closely related. Loss of function mutations in RB1 were enriched in the non-responder population (Z value = 2.33; p value = 0.026; N = 31). This is consistent with previously reported findings. In addition, amplifications and gain of function mutations in MYC and associated genes were also significantly enriched in the non-responder population (Z value = 2.71; P value = 0.01; N = 44). Interestingly, loss of function mutations in TSC1/2 genes which are downstream of MYC were predictors of good response to CDK4/6 inhibitors (Z value = 2.19; P value = 0.036; N = 30), strengthening the role of the parallel MYC signaling pathway in resistance to CDK4/6 inhibitors. **Conclusions:** Using our Genome360 BC Dataset, we have identified genetic markers affecting response to CDK4/6 inhibitors. In addition to the known role of RB1 in resistance to CDK4/6 inhibitors, the MYC signaling pathway emerged as a strong candidate. Based on these results, patients with mutations in these pathways may benefit from addition of mTOR or PKL1 inhibitors to CDK4/6 inhibitors to overcome resistance and prolong their effect. Research Sponsor: None.

1065 **Poster Session**

Real-world efficacy of ribociclib (RIB) plus aromatase inhibitor (AI)/fulvestrant (FUL), or endocrine monotherapy (ET), or chemotherapy (CT) as first-line (1L) treatment (tx) in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC): Results of fourth interim analysis (IA) from RIBANNA.

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Background: RIBANNA is a real-world, noninterventional study conducted in Germany evaluating efficacy, safety, and tolerability of RIB in combination with AI/FUL aiming to gain insights into routine clinical practice for pts with HR+, HER2– ABC. Here, we present results of the fourth IA from RIBANNA. **Methods:** Pre-, peri- and postmenopausal pts who received 1L tx with RIB+AI/FUL, or ET or CT for HR+, HER2– ABC were included in accordance with the German tx guideline. The effect of baseline demographic characteristics, including histological grade, age, previous adjuvant tx, Eastern Cooperative Oncology Group-performance score (ECOG-PS), and metastatic sites on progression-free survival was evaluated using Cox regression model. **Results:** At data cutoff October 11, 2021, 2598 pts were enrolled in the study (RIB+AI/FUL, n = 2177; ET, n = 239; CT, n = 182). Data from 1L tx were available for 2492 pts (95.9%), second-line tx for 689 pts (26.5%), third-line tx for 263 pts (10.1%), and fourth-line tx for 94 pts (3.6%). Significant differences were observed in baseline mean age and metastatic sites for pts in RIB+AI/FUL cohort vs ET and CT cohorts (both < 0.001). At baseline, the mean (SD) ages of pts were 65.5 (11.6), 70.7 (11.5) and 61.6 (11.6) years in RIB+AI/FUL, ET, and CT cohorts, respectively. While comparing the performance status, 44.2% of pts in RIB+AI/FUL, 34.7% of pts in ET and 42.1% of pts in CT cohort were fully active with ECOG-PS = 0. CNS, liver, or lung metastases were recorded in 42.6% of pts in RIB+AI/FUL, 26.8% of pts in ET and 67.1% of pts in CT cohort. Bone only metastases were reported in 30.8%, 47.9% and 15.0% of pts in RIB+AI/FUL, ET, and CT cohorts, respectively. Overall, 32.1%, 37.7%, and 52.7% of pts discontinued the study in RIB+AI/FUL, ET, and CT cohorts, respectively, the most common reasons being deaths (16.1%,17.2%, and 31.9%, respectively) and lost to follow-up (5.9%, 8.8%, and 9.3%, respectively). The most common tx-emergent adverse event (grade 3 or 4) observed in RIB+AI/FUL cohort was neutropenia (14.8%), while 6.6% and 6.9% of pts in ET and CT cohorts, respectively, experienced neutropenia. The efficacy results from all 3 cohorts, including Kaplan-Meier curves, will be presented during ASCO 2022. **Conclusions:** RIBANNA study showed diverse population characteristics among pts who received RIB tx in a real-world setting. Overall higher number of pts were treated in 1L with RIB+AI/FUL followed by ET and CT. The differences in baseline characteristics on metastatic pattern, age, and ECOG-PS reflect different selection strategies for 1L tx decision. No new safety signals were identified. Clinical trial information: CLEE011ADE03. Research Sponsor: Novartis Pharma GmbH, Germany.

Dalpiciclib in combination with letrozole/anastrozole or fulvestrant in HR+/HER2- advanced breast cancer: A phase Ib study.

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Background: Dalpiciclib (Dalp; SHR6390) is a novel cyclin-dependent kinase 4/6 inhibitor which showed tolerability and preliminary clinical activity as monotherapy for pretreated advanced breast cancer (ABC). Here we conducted a multicenter, phase 1b trial to further assess the safety, pharmacokinetics and efficacy of Dalp in combination with endocrine therapy (ET) in HR+/HER2- ABC. **Methods:** 5 cohorts of patients with HR+/HER2- locally recurrent or metastatic BC and any menopausal status were enrolled (~15 patients/combination regimen). Patients without prior treatment for ABC (cohort1/ 2) were given Dalp (125 or 150 mg po qd, d1-21, q4w) plus letrozole (LTZ; 2.5 mg po qd) or anastrozole (ATZ; 1 mg po qd); patients who progressed after ET (cohort 3-5) were given Dalp (125, 150, or 175 mg po qd, d1-21, q4w) plus fulvestrant (Fulv; 500 mg im, cycle 1 d1, d15, then d1 q4w). The primary endpoint was safety. The data cutoff date was Sep. 20, 2021. **Results:** 58 patients received Dalp plus LTZ/ATZ and 46 received Dalp plus Fulv. No maximum tolerated dose of Dalp was reached with LTZ/ATZ or Fulv. Across all cohorts, 75.0%-93.8% of patients had a grade ≥3 treatment-related adverse event (TRAE), with the most common being neutropenia (grade 3, 40.0%-87.5%; grade 4, 4.2%-46.7%) and leukopenia (grade 3, 33.3%-80.0%; grade 4, 0%; Table). Treatment-related serious AEs occurred in 2 (3.4%) patients with Dalp plus LTZ/ATZ and none with Dalp plus Fulv. At the tested dose levels, steady-state areas under the concentration curve and peak concentration of Dalp increased with dose in combination with LTZ/ATZ or Fulv. Dalp 150 mg was associated with a numerically higher objective response rate in both ET-untreated (67.6%, 95% CI 49.5-82.6) and ET-pretreated (53.3%, 95% CI 26.6-78.7) patients per investigator. The median progression-free survival with Dalp 150 mg was 20.3 mo (95% CI 16.9-not reached [NR]) and 16.7 mo (95% CI 1.9-24.1) in ET-untreated and ET-pretreated patients respectively. **Conclusions:** Dalpiciclib plus letrozole/anastrozole or fulvestrant showed an acceptable safety profile, with hematological toxicities as the most common TRAEs. The recommended phase 3 dose of dalpiciclib was 150 mg. Together with the promising antitumor activity observed with the combination therapy in HR+/HER2- ABC, further trials are warranted. Clinical trial information: NCT03481998. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co. LTD.

Grade ≥3 TRAEs occurring in ≥10% of patients in any cohort.

		Dalp 125 mg +LTZ/ATZ (n=24)	Dalp 150 mg +LTZ/ATZ (n=34)	Dalp 125 mg +Fulv (n=16)	Dalp 150 mg +Fulv (n=15)	Dalp 175 mg +Fulv (n=15)
Neutropenia	Grade ≥3	18 (75.0)	28 (82.4)	15 (93.8)	12 (80.0)	13 (86.7)
	Grade 3	17 (70.8)	21 (61.8)	14 (87.5)	10 (66.7)	6 (40.0)
	Grade 4	1 (4.2)	7 (20.6)	1 (6.3)	2 (13.3)	7 (46.7)
Leukopenia	Grade ≥3	11(45.8)	18 (52.9)	8 (50.0)	5 (33.3)	12 (80.0)
	Grade 3	11(45.8)	18 (52.9)	8 (50.0)	5 (33.3)	12 (80.0)
	Grade 4	0	0	0	0	0

Data are n (%).

1067 **Poster Session**

Survival outcomes in metastatic HR-positive, HER2-negative invasive ductal carcinoma compared to invasive lobular carcinoma and mixed ductal/lobular treated with endocrine therapy in combination with CDK4/6 inhibitors, mTOR inhibitor, or PI3K inhibitor.

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Background: The majority of invasive lobular breast cancers (ILC) are hormone receptor (HR)-positive, HER2-negative and are clinically treated similarly to HR+ HER2-negative invasive ductal cancers (IDC). However, ILC differs distinctly from IDC in its clinicopathologic characteristics and molecular alterations. ILC also differs in response to systemic therapy, with studies showing ILC as less sensitive to chemotherapy. It is currently unknown if patients with ILC or mixed ductal/lobular (MDL) histologies derive similar benefits as IDC from endocrine therapy (ET) in combination with cyclin-dependent kinase 4/6 inhibitors (CDK4/6is), mTOR inhibitor everolimus or PI3K inhibitor alpelisib. **Methods:** We retrospectively searched for patients treated at MD Anderson Cancer Center with a diagnosis of HR+, HER2-negative metastatic breast cancer (MBC) with ET in combination with CDK4/6is, everolimus or alpelisib. Patients were divided into 3 groups based on their histology: ILC, IDC and mixed. We obtained data on demographics, estrogen (ER) and progesterone (PR) receptor status, menopausal status, treatment duration and survival status. The Kaplan-Meier product-limit method was used to compare progression-free survival (PFS) and overall survival (OS) between the three different groups stratified by the treatment received. **Results:** We identified 2,971 patients (2,432 IDC [82%], 427 ILC [14%], 112 Mixed [4%]) with HR+ HER2-negative MBC treated with ET in combination with CDK4/6is, everolimus and/or alpelisib between 2010 and 2021. Median age was around 50 years in all groups. Around 80% of patients were white, 10% Hispanic and 5% black. Around 55% of patients were post-menopausal, 99% had ER+ and 88% PR+ tumors; 1,895 patients (81% IDC, 15% ILC, 4% mixed) received CDK4/6is, 1,027 (82% IDC, 14% ILC, 4% mixed) received everolimus and 49 (81% IDC, 19% ILC) received alpelisib. PFS and OS were not statistically different between the 3 groups (Table). **Conclusions:** HR+ HER2-negative MBC patients with IDC, ILC and MDL benefited from ET in combination with CDK4/6is, everolimus or alpelisib similarly with no significant differences in PFS and OS. Research Sponsor: None.

	CDK4/6i + ET N = 1,895			Everolimus + ET N = 1,027			Alpelisib + ET N = 49	
	IDC N = 1,549 (81%)	ILC N = 277 (15%)	Mixed N = 69 (4%)	IDC N = 843 (82%)	ILC N = 141 (14%)	Mixed N = 43 (4%)	IDC N = 40 (81%)	ILC N = 9 (19%)
Median PFS (months)	11.7	14.5	14.8	6.3	6.7	6.0	5.2	3.0
		P = 0.54			P = 0.48		P = 0.63	
Median OS (months)	34.2	34.6	26.5	23.6	19.0	24	13.6	16.4
		P = 0.26			P = 0.89		P = 0.67	

1068 **Poster Session**

Hormone therapy (HT) or capecitabine (CAP) as maintenance therapy following the first-line chemotherapy in HR+/HER2-ABC/MBC: Secondary endpoint adverse effects (AEs) and toxicity report of OVERSTEP Trial (ZJCH15001/CBCSG 035).

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Background: OVERSTEP (NCT02597868) is a multicenter, randomized clinical trial of capecitabine (CAP) versus endocrine therapy (HT) as maintenance therapy after 1st-line CAP-based combination chemotherapy in HR+/HER2- ABC/MBC. At 2020 SABCS conference, we reported the primary endpoint (progression-free survival, PFS) at follow-up of 24.3 months, at 2021 SABCS, repoted the PFS and OS at follow-up of 41.4 months. Here, we reported the secondary endpoint Adverse effects (AEs). **Methods:** Total of 181 patients with HR+ and HER2- MBC were enrolled in this study from Jun, 2013 to Jan, 2019. All the patients received at least 4 cycles of CAP-based combination regimen as 1st-line salvage chemotherapy. The patients who achieved CR, PR or durable SD by RECIST criteria entered into the maintenance therapy setting (MT), and randomly (1:1 ratio) assigned to either CAP single or HT group. Randomization was done centrally with stratification by endocrine sensitive or resistance and visceral or non-visceral metastasis. After combined chemotherapy, 75.14% (n=136) cases entered into the maintenance therapy setting, and 24.86% case were disease progressed (PD) during combined chemotherapy. After a median follow-up of 41.4 months (IQR 21.57-79.23), we reported the secondary endpoint Adverse effects (AEs). **Results:** In PPS, hematologic toxicities in ET group and CT group were as follows, anemia (69.6% vs 64.2%), leukopenia (60.8% vs 50.8%), neutropenia (66.7% vs 31.2%), thrombocytopenia (26.1% vs 26.9%). The non-hematologic toxicities were hand-foot syndrome (HFS) (33.3 vs 41.8%), increased ALT (50.7 % vs 37.3%), increased AST (53.6% vs 37.3%), hyperbilirubinemia (32.2% vs 25.4%), fatigue (14.5% vs 10.4%), hypokalemia (5.8% vs 4.5%), pneumonia (0.0% vs 6.0%), peripheral neuropathy (4.8% vs 0.0%),etc. Duration of maintenance, the AEs in the ET group were significantly lighter, just like anemia (0.0% vs 28.4%), leukopenia (5.8% vs 17.8%), neutropenia (5.8% vs 16.4%), thrombocytopenia (2.9% vs 22.4%) et al., the non-hematologic toxicities were HFS (0.0% vs 23.9%), increased ALT (4.3% vs 16.4%), increased AST (5.8% vs 16.4%), increased bilirubin (0.0% vs 10.4%), peripheral neuropathy (5.8% vs 0.0%). Moreover, the toxicities of grade 3/4 were in the CT maintenance group, anemia was 1 case (1.5%), neutropenia 2 cases (2.99%), HFS 5 Case (7.5%) and increased AST in 1 case (1.5%). The ET maintenance group had not any grade 3/4 AEs. **Conclusions:** For HR+ and HER2- MBC, after 1st-line salvage combined chemotherapy, HT maintenance therapy is superior to chemotherapy (capecitabine) maintenance in terms of efficacy and safety. But, if toxicity is well managed, the safety is still tolerated during chemotherapy maintenance. Therefore, in the post-CDK4/6 period, chemotherapy is still an option. Clinical trial information: NCT02597868. Research Sponsor: China breast cancer clinical research collaboration group.

1069 **Poster Session**

A novel analysis of data from the PALOMA-3 trial confirms the efficacy of palbociclib and provides an option for efficacy assessments that could accelerate drug approvals.

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Background: Advances in breast cancer (BC) therapy the past few decades have led to higher survival rates. Beginning with palbociclib, cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have emerged as a treatment option for BC. We analyzed data from PALOMA 3 that could release a biomarker of OS in patients that receive palbociclib. **Methods:** We estimated concurrent rates of growth (*g*) and regression (*d*) from the 393 women with advanced BC enrolled in PALOMA-3 who had radiographic tumor measurement data including 261 treated with fulvestrant + palbociclib, and 132 with fulvestrant + placebo. We analyzed data using a model defined as SLD (t) = exp (–*d* x t) + exp (*g* x t) – 1, where SLD = sum of longest diameters and t = time. We examined the relationship between *g* and overall survival (OS) and compared the median growth rates (*g*) of various cohorts. **Results:** *g* values associate highly with OS (p<0.0001). Emulating results in the clinical trial, palbociclib slowed the median *g* values of the entire population and those with sensitivity to previous endocrine therapy but not those deemed resistant. Further cohort analyses found greater benefit with palbociclib in those with visceral metastases, and longer disease-free interval, and benefit independent of ECOG PS, menopausal status, prior lines of therapy, and age. With only the baseline and two additional scans obtained, the median *g* values of the palbociclib and placebo arms were statistically different: p=0.038 after 28 (19/9) patients and p=0.0043 after 40 (26/14) patients. **Conclusions:** Estimates of palbociclib's impact on tumor growth rates (*g)* confirm its efficacy in PALOMA 3. Our ability to discern differences in *g*, a value associated with OS, after only two follow up scans in as few as 28 patients merits considering *g* an early biomarker of OS benefit that could bring effective drugs to patients as rapidly as possible. Research Sponsor: Pfizer Inc.

		g values x10^{-4}/day					
		Placebo		Placebo		Placebo	
	Cohorts	All	PAL	Resistant	PAL	Sensitive	PAL
All	*g*	28	12	24	15	34	11
	p	<0.0001		NS		<0.0001	
Non-visceral	*g*	12	10	14	15	12	9
	p	NS		NS		NS	
Visceral	*g*	34	14	26	16	41	13
	p	<0.0001		NS		<0.0001	
<65y	*g*	25	13	24	15	29	12
	p	0.0025		NS		0.0082	
>=65y	*g*	37	10	1	17	37	9
	p	0.0005		—		0.0002	
Disease-free interval*	cohorts	All		DFI ≤24 mos		DFI >24	
	g	28	12	26	13	30	12
	p	<0.0001		NS		0.0016	
ECOG	cohorts	All		ECOG 1		ECOG 0	
	g	28	12	27	13	30	12
	p	<0.0001		0.0026		0.0023	
Menopausal status	cohorts	All		Pre/Peri		Post	
	g	28	12	27	13	30	12
	p	<0.0001		0.0026		0.0023	
# Prior therapies	cohorts	0		1		3	
	g	22	10	28	14	62	14
	p	0.0374		0.0042		0.0388	
***g* estimated using only first 3 scans**	cohorts	All		Res		Sens	
	g	34	27	31	30	36	26
	p	0.0009		0.4387		0.0005	

*Disease-free interval was defined as the time from diagnosis of primary breast cancer to first relapse in patients who received adjuvant therapy

1070 **Poster Session**

The safety, tolerability, and preliminary antitumor activity of sitravatinib plus tislelizumab in patients with locally recurrent or metastatic triple-negative breast cancer.

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Background: Anti-PD-1 antibody plus chemotherapy has been demonstrated promising anti-tumor activity in patients with locally recurrent or metastatic triple negative breast cancer (TNBC). However, this regime only limited to TNBC patients with PD-L1 positive. As antiangiogenic agents could enhance the response to immune checkpoint inhibitors, we conducted this phase 2 study to assess the efficacy and safety of novel chemotherapy-free regimen of sitravatinib (targets receptor TKI against TYRO3, AXL, MERTK and VEGF family of receptors) in combination with tislelizumab (anti-PD-1 antibody) in patients with locally recurrent or metastatic TNBC regardless of PD-L1 status. **Methods:** Patients with locally recurrent or metastatic TNBC were included and divided into two cohorts. Patients received 70 mg (cohort A) or 100 mg (cohort B) sitravatinib QD PO and 200 mg tislelizumab IV Q3W until disease progression or intolerable toxicity. The primary endpoints included overall response rate (ORR) (cohort A and B) and rate of grade ≥3 treatment-related adverse events (AEs) (cohort B). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), duration of response (DOR), 1-year overall survival rate and safety/tolerability. In cohort A, the first statistical analysis would be performed when 12 patients were enrolled; if ≥1 of 12 patients were with confirmed response during the first stage, additional 9 patients would be enrolled to the second stage based on Simon's two-stage design. We would deem cohort A to be statistically superior to a historical control of 8% under the settings if > 3 of 21 patients responded (one-sided a = 0.1 and power of 80%). Patients' recruitment in cohort B would begin after completing the recruitment in cohort A. **Results:** Herein we reported the preliminary results in cohort A. Four patients were with confirmed response during the first stage, and additional nine patients were enrolled to the second stage. A total of 21 patients with 0-3 lines of prior chemotherapy were included from April 2021 to September 2021. The median age was 51 (32-66) years and 20 (95%) patients had ECOG PS 0. At data cut off 13 Jan 2022, 19 patients were alive, 11 are still on treatment. The confirmed ORR was 38.1% (95% CI, 18.1%-61.6%) based on current 21 efficacy evaluable patients. DCR was 95.2% (95% CI, 76.2%-99.9%), and median PFS was 7.0 (95% CI, 3.7 - not reached) months. 4/21 (19%) of patients experienced grade 3 treatment-related AEs. Grade 3 AEs reported in ≥5% of patients were aspartate aminotransferase increased (9.5%) and palmar-plantar erythrodysaesthesia syndrome (9.5%). No patients experienced grade 4 AEs. **Conclusions:** Sitravatinib combined with tislelizumab demonstrated clinically meaningful anti-tumor activity and had a manageable safety profile. Clinical trial information: NCT04734262. Research Sponsor: BeiGene (Beijing) Co., Ltd.

1071 **Poster Session**

Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated, metastatic triple-negative breast cancer (mTNBC): Final results from the phase 3 ASCENT study.

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Background: Treatment goals for pts with metastatic breast cancer include extended survival and improved quality of life (QoL). SG is an antibody-drug conjugate composed of an anti–Trop-2 antibody coupled to the cytotoxic SN-38 payload via a proprietary, hydrolyzable linker. SG received FDA approval for pts with mTNBC who received ≥2 prior chemotherapies (at least 1 in the metastatic setting). In the pivotal phase 3 ASCENT study (NCT02574455), SG demonstrated a significant survival benefit over single-agent chemotherapy TPC in the primary analysis population of pts with second line or greater (2L+) mTNBC without known brain metastases at baseline (Bardia A et al. *NEJM* 2021) and QoL (Loibl S. et al. ESMO 2021). With additional follow up, we present the final data on efficacy, including overall survival (OS), safety, and QoL. **Methods:** Pts with mTNBC refractory or relapsing after ≥2 prior chemotherapies with at least 1 in the metastatic setting were randomized 1:1 to receive SG (10 mg/kg IV on days 1 and 8, every 21 days) or TPC (capecitabine, eribulin, vinorelbine, or gemcitabine) until disease progression or unacceptable toxicity. Primary endpoint was progression-free survival (PFS) per RECIST 1.1 by independent review in pts without known brain metastases at baseline. Key secondary endpoints included OS, safety, and health-related QoL. Safety was analyzed in pts who received ≥1 dose of study drug. **Results:** Of 529 pts enrolled, 468 did not have known brain metastases at baseline (median age: 54 y [range, 27-82]; median prior lines: 4 [range, 2-17]). As of Feb 25, 2021 (final database lock), SG (n = 235) vs TPC (n = 233) significantly improved median PFS (5.6 vs 1.7 mo; HR: 0.39; $P < 0.0001$) and median OS (12.1 vs 6.7 mo; HR: 0.48; $P < 0.0001$). The OS rate at 24 months was 22.4% (95% CI, 16.8-28.5) in the SG arm and 5.2% (95% CI, 2.5-9.4) in the TPC arm. In the safety population (n = 482), key treatment-related grade ≥3 adverse events with SG (n = 258) vs TPC (n = 224) were diarrhea (11% vs 0.4%), neutropenia (52% vs 33%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%). There was no grade ≥3 neuropathy and 1 case of grade 3 interstitial lung disease reported with SG. No patient experienced a treatment-related death with SG, and there was 1 treatment-related death with TPC due to neutropenic sepsis. Treatment discontinuations due to AEs were ≤3% in both arms. SG arm showed clinically meaningful and statistically significant improvements than the TPC arm in scores for all five primary focus health-related QoL domains. **Conclusions:** The analysis based on the final database lock of ASCENT confirms the superior survival outcomes of SG over single-agent chemotherapy, with a manageable safety profile and improvement in QoL for pts with mTNBC in the 2L+ setting. These findings reinforce SG as an effective treatment option for this pt population. Clinical trial information: NCT02574455. Research Sponsor: Gilead Sciences, Inc.

1072 **Poster Session**

Apatinib combined with chemotherapy versus single chemotherapy in HER-2 negative advanced breast cancer: A randomized, controlled, open-label phase II study.

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Background: Apatinib is an oral, highly potent tyrosine-kinase inhibitor targeting VEGFR2. A series of clinical studies have shown that anti-angiogenic drugs combined with chemotherapy enable to improve the efficacy of HER2-negative advanced/metastatic breast cancer(MBC). **Methods:** Patients with HER2-negative MBC with less than two lines of systemic therapy were enrolled in this open-label, controlled, phase II trial. Patients with measurable disease were randomly assigned, in a 1:1 ratio, to receive oral apatinib (250 mg once daily) combined with chemotherapy(A+CT) or chemotherapy(CT) alone (the physician's choice) until disease progression or intolerable toxicity. The primary end point was progression-free survival(PFS), which was assessed by investigator and was analyzed on an intention-to-treat basis. **Results:** Between August 2017 and January 2021, of the 80 patients who underwent randomization, 40 were assigned to receive apatinib plus chemotherapy(A+CT) and 40 were assigned to receive standard therapy(CT). As of January 2022, 10 patient had not undergone response evaluation or dropout, 70 patients(36 patients in A+CT, 34 patients in CT were finally included with PFS events and 72 patients were included in safety set. Median PFS was significantly longer in A+CT than in CT (182 days vs 63 days; P = 0.043);The median PFS of TNBC subgroup (11 in A+CT group, 14 in CT) was longer in the aptinib group than in CT group (167 days vs 63 days; P = 0.637);The median PFS of HR+ subgroup(25 in apatinib group, 20 in chemotherapy group) was longer in the aptinib group than in CT group (259 days vs 56 days; P = 0.054);The median PFS of patients with liver metastases(19 in apatinib group, 17 in chemotherapy group) was longer in the aptinib group than in the CT group (151 days vs 54 days; P = 0.191); The severe adverse reactions (grade 3/4) were neutropenia(22.2% vs 13.9%), hypertension(11.1% vs 0.0%), leukopenia(8.3% vs 8,3%), hypokalemia(8.3% vs 2.8%), anemia(5.6% vs 11.1%), ALT(2.8% vs 8.3%), AST(0.0% vs 5.6%) in the apatinib group and the CT, respectively. Proteinuria did not occur in both groups. Treatment delay or dose reduction owing to adverse event was 16.7% and 11.1%, respectively. Treatment discontinuation owing to adverse event was 23.5% and 8.8%, respectively. **Conclusions:** Apatinib combined with chemotherapy showed a significant improvements in PFS and a manageable safety profile in HER2 negative MBC. Research Sponsor: None.

1073 **Poster Session**

Leveraging patient engagement to optimize a phase 3 clinical trial design, study participation and recruitment for women diagnosed with triple-negative breast cancer (TNBC).

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Background: The importance of Patient Engagement (PE) on clinical trial design is well established. PE in oncology medicines development can serve many purposes including obtaining input on trial design/procedures, identifying recruitment challenges and barriers to participation, and understanding retention strategies. Designing a clinical trial with procedures that have been confirmed as acceptable to participants is also likely to improve patient adherence to treatments. Triple-Negative Breast Cancer (TNBC) is a virulent subtype associated with early onset and increased risk of early recurrence and accounts for 15% to 20% of breast cancers. In addition, a higher risk exists in premenopausal and Black women. Chemotherapy is the mainstay of curative therapy recommended by guidelines. The aim was to obtain insights from patients to inform key aspects of a clinical study design including choice of chemotherapy regimen, study feasibility and recruitment strategies. **Methods:** Two groups of US women (N = 20) ages 28-54; (race 55% Caucasian, 30% African American, 10% Hispanic, 5% Native American) diagnosed with Stage IIb-IV TNBC and in active or completed treatment were recruited to participate in two in person IRB approved sessions. Trained 3rd party facilitators used qualitative methods to elicit patient feedback. Preliminary research included interviews with key stakeholders, including TNBC advocacy group leaders and a review of online patient communities. Patients reviewed a study design with an investigational agent every 3 weeks plus chemotherapy (nab-paclitaxel; paclitaxel) or placebo plus chemotherapy. **Results:** Patient reaction to the choice of taxane chemotherapy in the standard of care arm was neutral to negative. Approximately 50% of the patients identified taxane treatment as a barrier to participation. All patients requested flexibility in treatment choices, clear information about required tests and visits, and more diversity in recruitment materials. Black and Hispanic women impacted by TNBC did not feel they had equal access to clinical trials due to race, rural location, and other factors. Patient insights reinforced the decision to add another standard-of-care option (carboplatin plus gemcitabine) as a treatment arm to the trial design and was confirmed with investigators. Patient feedback was incorporated into the trial along with additional strategies to support recruitment of diverse patients in the clinical study. **Conclusions:** On November 13, 2020 the FDA approved this regimen in the label for pembrolizumab in combination with chemotherapy, as the 1st line treatment in women with locally recurrent or metastatic TNBC. Both patients and physicians perceived that a flexible chemotherapy backbone was a benefit. Research Sponsor: Merck & Co., Inc.

1074 **Poster Session**

Real-world outcomes of Black women versus non-Hispanic White women with advanced triple-negative breast cancer treated with immune checkpoint inhibitors at an urban cancer center.

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Background: Black women (BW) are disproportionately diagnosed with metastatic triple negative breast cancer (mTNBC) compared to Non-Hispanic White women (NHW). Median overall survival (OS) in mTNBC remains poor at 12-18 months. While immune checkpoint inhibitors (ICIs) are a promising treatment strategy, BW were significantly underrepresented in pivotal clinical trials that led to the approval of ICIs in mTNBC. Therefore, the efficacy, safety, and optimal biomarkers of ICI response in BW remain unknown. We sought to compare baseline characteristics and outcomes between BW and NHW with mTNBC treated with an ICI and chemotherapy at an urban tertiary care institution. **Methods:** BW and NHW with advanced unresectable or mTNBC treated with an ICI plus chemotherapy at Emory University between 2019 and 2021 were retrospectively evaluated. Baseline characteristics, including next generation sequencing (NGS), as well as clinical outcomes between BW and NHW were compared using Kruskal-Wallis tests and Fisher's exact tests. Progression free survival (PFS) and OS were analyzed with the Kaplan-Meir method. **Results:** Forty-one women with PDL-1 positive mTNBC treated with an ICI and chemotherapy were identified [BW, n = 26 (63%) and NHW, n = 15 (37%)]. A majority of patients had relapsed disease (73%); however BW were more likely to have de novo metastatic disease compared to NHW (38% vs 7%, p = 0.03). Twenty-seven (66%) patients received atezolizumab and 14 (34%) were treated with pembrolizumab. Of the 23 (56%) patients with NGS testing, alterations in TP53, PIK3CA, and BRCA were seen in 23 (100%), 5 (31%), and 1 (6%) patient, respectively. Median tumor mutational burden was similar between BW and NHW (5 vs 7, p = 0.8). BW had numerically lower median PDL-1 (SP142) compared to NHW (1% vs 2%, p = 0.5). Rates of immune and dose-limiting chemotherapy-related adverse events were similar between BW and NHW (Table). There were no differences in ICI response between groups, though BW had fewer complete responses and a shorter median PFS compared to NHW. Median OS was 12 months in BW compared to 28 months in NHW (p = 0.1). **Conclusions:** Our experience with real-world use of this regimen showed that BW had fewer complete responses and a trend towards worse OS compared to NHW. BW had numerically lower median PDL-1 expression compared to NHW, suggesting further investigation of biomarkers, potentially by Race, are needed to better identify responders to ICI in mTNBC. Research Sponsor: None.

Characteristics N(%)/months [95% CI]	BW (N = 26)	NHW (N = 15)	*P* value
Immune-related adverse events	3 (12)	4 (27)	0.4
Chemotherapy-related adverse events	9 (35)	3 (20)	0.5
Response	16 (64)	11 (73)	0.7
Partial	14 (88)	5 (45)	
Complete	2 (13)	6 (55)	
Progressive or stable disease	9 (36)	4 (27)	0.7
Median PFS	4 [2, 7]	8 [2, not reached]	0.2
Median OS	12 [8, 27]	28 [4, not reached]	0.1

1075 **Poster Session**

Real-world treatment patterns and outcomes among patients (pts) with second-line (2L) and third-line (3L) metastatic triple-negative breast cancer (mTNBC) in England using the Cancer Analysis System (CAS).

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Background: TNBC is the most aggressive type of breast cancer due to rapid growth, metastasis, and recurrence post-treatment. This study aimed to assess real-world treatment patterns and survival of pts with mTNBC who received 2L and 3L therapy in England and report OS and PFS of pts receiving 2L therapies stratified by treatment-free interval from the curative setting. **Methods:** This retrospective study using the CAS database, included pts with mTNBC who received at least three systemic treatments (at least two in metastatic setting) for TNBC during the years 2012 to 2020. $Cohort_{2L}$ included pts with initial early-stage BC diagnosis and treatment (at least two systemic treatments prior to 2L). $Cohort_{3L}$ included pts initially diagnosed with either early-stage TNBC, or de novo advanced TNBC (at least two systemic treatments prior to 3L). The two cohorts are not mutually exclusive. The study outcomes were stratified by cohort ($Cohort_{2L}$ and $Cohort_{3L}$) and treatment-free interval (<12 m versus ≥12 m from end of curative treatment to start of 1L treatment, $Cohort_{2L}$ only). Kaplan-Meier methods estimated progression-free survival (PFS) and overall survival (OS). PFS was proxied by 'Time to treatment discontinuation or death' (TTDD). Log-rank tests compared the distribution of OS and PFS for 2L stratified by treatment-free interval (<12 m versus ≥12 m). **Results:** $Cohort_{2L}$ included 606 pts and $Cohort_{3L}$ included 374 pts. Tumor morphology was similar across Cohorts. Pts at 3L had worse ECOG performance score compared to 2L, and more pts with de novo advanced TNBC had brain metastasis at any point after diagnosis than pts diagnosed with early-stage TNBC. Regimens at 2L for $Cohort_{2L}$ included capecitabine (32%), eribulin (16%), carboplatin and gemcitabine in combination (12%), and paclitaxel (10%). A similar distribution was seen for $Cohort_{3L}$. Regimens at 3L ($Cohort_{3L}$ only), included eribulin (38%), capecitabine (16%), and paclitaxel (13%). Stratifying $Cohort_{2L}$ by treatment-free interval did not exhibit significant differences in PFS nor OS by log rank tests (Table). **Conclusions:** This nationwide study, in England, accentuates the significant unmet need in 2L and 3L therapy for mTNBC highlighted by the poor prognosis. The stratification by prior treatment-free interval from curative setting did not show a difference in OS or PFS for patients receiving 2L treatment. Research Sponsor: Gilead Sciences.

mTNBC PFS and OS from commencement of treatment line.

Survival outcome	Median PFS_{TTDD} (*in months*)	Median OS (*in months*)
By cohort:		
$Cohort_{2L}$ (n=606)	2.53 (2.30–2.76)	6.70 (6.14-7.62)
$Cohort_{3L}$ (n=374)	2.43 (2.20–2.76)	5.54 (4.90-6.14)
By treatment-free interval ($Cohort_{2L}$):		
<12m (n=255)	2.30 (2.07-2.76)	5.72 (5.06-6.64)
≥12m (n=351)	2.76 (2.46-2.96)	7.49 (6.74-8.31)
	PFS distribution	**OS distribution**
Log rank test, P-value	0.31	0.10

1076 **Poster Session**

Exposure-response analyses of sacituzumab govitecan (SG) efficacy and safety in patients (pts) with metastatic triple-negative breast cancer (mTNBC).

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Background: SG is an antibody-drug conjugate composed of an anti–Trop-2 antibody coupled to the cytotoxic SN-38 payload via a proprietary, hydrolyzable linker. SG is approved for pts with mTNBC who received ≥2 prior chemotherapies (> 1 in the metastatic setting). The relationships between exposure of SG, free SN-38, and total antibody (tAB) following SG administration and its efficacy and safety outcomes were evaluated in pts with mTNBC. **Methods:** Available exposure efficacy and safety outcomes from the mTNBC cohort of the phase 1/2 IMMU-132-01 study (relapsed/refractory pts; n = 24) and mTNBC pts from the phase 3 ASCENT study who had received ≥2 prior therapies (> 1 in the metastatic setting; n = 253) were analyzed. Pts in IMMU-132-01 received 8 or 10 mg/kg SG and pts in ASCENT received 10 mg/kg SG on d1 and d8, of every 21d cycle. Effect of exposure on CR, ORR and the evaluated adverse events (AEs) of vomiting, diarrhea, hypersensitivity reactions, nausea, and neutropenia were analyzed using logistic (CR, ORR) or ordinal logistic (AE) regression models while OS, PFS, time to first dose reduction and time to first dose delay were analyzed using Cox PH models. Several exposure metrics related to the PK of SG, free SN-38, and tAB were evaluated as predictors of SG efficacy and safety and the most statistically significant exposure metric was retained in the model; effect of other covariates was characterized within the modeling framework. **Results:** Higher values of the average exposure over the treatment duration (CAVG) for SG ($CAVG_{SG}$) were significantly associated with an increase in the probability of CR and ORR and higher CAVG values for tAB ($CAVG_{tAB}$) were significantly associated with longer OS and PFS. The probability of Grade ≥1 evaluated AEs, the risk of dose reductions and dose delays were found to increase significantly with increasing $CAVG_{SG}$. Neutropenia was the only AE where the effect of exposure was significantly associated with the probability of Grade ≥3 evaluated AEs. No statistically significant associations between exposure and the probability of Grade 4 AEs were observed for any of the evaluated endpoints. The developed models were used to estimate the efficacy and safety outcomes for the 8 mg/kg vs 10 mg/kg SG dose levels and the results indicated a more favorable risk/benefit profile for the 10 mg/kg dose level driven by the higher estimated efficacy. Baseline Trop-2 expression level was not statistically correlated with magnitude of clinical response based on the limited available Trop-2 data. **Conclusions:** Exposure-response relationships were observed for all evaluated efficacy and safety endpoints for SG in patients with mTNBC, and the higher efficacy (as assessed by CR, ORR, OS and PFS) achieved with the exposures associated with the 10 mg/kg SG dose regimen and its manageable safety profile support the appropriateness of the approved regimen of SG. Clinical trial information: NCT02574455, NCT01631552. Research Sponsor: Gilead Sciences, Inc.

1077 **Poster Session**

A phase 3, multicenter, open, randomized controlled clinical study of gemcitabine plus capecitabine versus gemcitabine plus carboplatin in the first-line treatment for advanced triple-negative breast cancer.

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Background: Gemcitabine plus capecitabine (GX) regimen is still lack of phase III clinical trial evidence for the first-line treatment of advanced triple-negative breast cancer (TNBC). We designed this phase III trial to compare the efficacy and safety of GX with gemcitabine plus carboplatin (GC) in patients with advanced TNBC. We also explored the correlation between tumor infiltrating lymphocytes (TILs) and the prognosis in TNBC treated with different chemotherapy regimen. **Methods:** Patients with advanced TNBC were randomly assigned to receive gemcitabine (1,000 mg/m^2) on days 1 and 8 plus oral capecitabine (1,000 mg/m^2 twice a day) on days 1 through14; or, to receive gemcitabine (1,000 mg/m^2) on days 1 and 8 plus carboplatin (AUC = 2) on days 1 and 8. The primary end point was progression free survival (PFS), and secondary end points were objective response rate (ORR), clinical benefit rate (CBR), overall survival (OS) and safety. Immunohistochemistry was performed with antibodies against CD3, CD4, CD8, and CD 19 antigens on tissue sections of 52 TNBC patients. The margin used to establish non-inferiority was 1.2. This study is registered on Clinical Trials.gov, number NCT02207335. **Results:** From Jan 2014, to Dec 2020, 187 patients underwent eligibility assessment and were randomly assigned (93 in GX and 94 in GC). The ORRs in GX arm and GC arm were 37.6%, and 39.4%, respectively (P = 0.808). The CBRs in GX arm and GC arm were 78.5% and 79.8%, respectively (P = 0.828). Median PFS was 6.1 months for GX arm compared with 6.3months for GC arm (log-rank P = 0.348; HR = 1.148, 95% CI: 0.856 to 1.539, P = 0.357). The median OS in GX arm and GC arm was 21.0 months and 21.5 months, respectively (log-rank P = 0.992; HR = 1.002, 95% CI: 0.717 to 1.400, P = 0.992). Hematologic adverse events (AEs) were commonly observed in both arms, especially in GC arm. Non-hematological AEs such as hand-foot syndrome, diarrhea, and peripheral sensory neuropathy were more common observed in GX arm, while alopecia, nausea, vomiting, fatigue, decreased appetite, infusion related reaction, and hyperglycemia were more common in GC arm. Patients with high CD8$^+$ TILs had a significantly longer PFS (HR = 0.559; 95% CI: 0.314 to 0.993, P = 0.047) and OS (HR = 0.436; 95% CI: 0.226 to 0.843, P = 0.014) compared with patients with low CD8$^+$ TILs. In the high CD8$^+$ group , patients treated with GC had prolonged PFS (HR = 0.322; 95% CI: 0.127 to 0.816, P = 0.017) and OS (HR = 0.300; 95% CI: 0.094 to 0.957, P = 0.042) compared with GX. **Conclusions:** The trial did not meet the prespecified criteria for the primary end point of PFS in the ITT population. Compared with GC, GX demonstrated lower toxicity. Compared to patients with low CD8$^+$ TILs, patients with high CD8$^+$ TILs showed better outcomes, and in these patients, GC regimen could improve survival compared with GX regimen. Clinical trial information: NCT02207335. Research Sponsor: Tianjin Key Medical Discipline (Specialty) Construction Project, Other Foundation, the Key Task Project of Tianjin Health anTianjin Medical University Cancer Hospital “14th Five- Year” Peak Discipline Support Program Project.

1078 **Poster Session**

Mechanisms of action and acquired resistance to atezolizumab plus *nab*-paclitaxel in metastatic triple-negative breast cancer (mTNBC).

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Background: In the IMpassion130 study (NCT02425891) first-line atezolizumab plus *nab*-paclitaxel (A+nP) provided clinical benefit compared with placebo plus nP (P+nP) in patients with mTNBC whose tumors were PD-L1+ (Schmid NEJM 2018). However, in many patients, disease that was initially controlled eventually progressed. The mechanism of action of A+nP and nP in the mTNBC tumor microenvironment (TME) and the biological changes associated with tumor progression with these therapies remain largely unknown. The goal of the current study was to evaluate biological changes in the TME induced by atezolizumab and nP early on treatment (OT) and at the time of progressive disease (PD) in IMpassion130. **Methods:** Paired tumor biopsies from IMpassion130 collected pre-treatment at baseline (BL), after 4 weeks OT, and at clinical PD were evaluated histologically for PD-L1 expression, CD8 content, stromal tumor infiltrating lymphocytes and immune phenotypes. RNA sequencing was also used to evaluate TNBC molecular subtypes and gene expression (hallmark gene sets, and immune cell and stromal gene signatures). Matched tumor pair samples from BL and PD were further analyzed by next-generation sequencing for genomic changes using the FoundationOne gene panel. Wilcoxon, Fisher, and McNemar's tests were used for statistical analysis. **Results:** OT A+nP (n = 24 pairs), but not P+nP (n = 18 pairs) increased PD-L1 in both tumor-infiltrating immune cells and tumor cells, and increased frequency of immune-inflamed tumors. RNA-based signatures for A+nP showed an increase in lymphocytes (T-, B-, and NK cell), as well as IFN-α and IFN-γ responses, driven mainly by responders. While P+nP increased RNA-based stromal signatures (cancer-associated fibroblasts, pericytes, and angiogenesis) and epithelial mesenchymal transition, these changes were not observed with A+nP. OT A+nP and P+nP both reduced cell proliferation but only A+nP reduced metabolic pathways. At PD there was a significant reduction of RNA-based immune and stromal signatures in both A+nP (n = 59) and P+nP (n = 55) arms. Cell proliferation and DNA repair signatures were increased with A+nP but not P+nP. Evaluation of genomic changes suggested that both A+nP and P+nP increased tumor mutational burden (TMB), but only A+nP increased genomic scarring. At PD, the tumor immune phenotypes changed at PD with no directionality, while TNBC subtypes remained stable. **Conclusions:** A+nP boosted tumor immune inflammation and decreased tumor cell proliferation and metabolism in mTNBC patients, particularly in responders. Addition of atezolizumab prevented early stromal recruitment induced by nP. While decreased immune and stromal components and increased TMB were observed with both nP and A+nP, A+nP tumor escape was characterized by increased cell proliferation and DNA scarring. Clinical trial information: NCT02425891. Research Sponsor: F. Hoffmann-La Roche Ltd.

1079 **Poster Session**

Comprehensive immune profiling unravels evolution of spatial distribution and immune repertoire in tumor microenvironment from primary to metastatic triple-negative breast cancer.

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Background: Immune checkpoint inhibitors (ICI) have improved PFS and OS in metastatic triple-negative breast cancer (mTNBC), but benefit is limited to PD-L1 positive tumors. Metastatic tumors are notorious for deficient immune cell infiltration and immunosuppressive features that may limit responses to ICI in mTNBC. However, the underlying mechanisms for the weak immunogenicity of the metastatic tumor immune microenvironment (TIME) and related poor ICI responses are still not well understood. The current study was designed to investigate the evolution of the TIME between paired primary and metastatic TNBCs. **Methods:** Spatial distribution of 37 key immune regulators using the NanoString digital spatial profiling (DSP) platform was analyzed. 452 regions of interests (ROIs) from 33 primary tumors (PT) and 29 metastatic tumors (MT) including 28 paired specimens, were selected based on CD45+ immune hotspots, and the protein expression levels of the key immune regulators were quantified within pan-cytokeratin (panCK) and CD45 masked regions, respectively. In parallel, we examined the clonality of tumor infiltrating B cell receptors by reconstructing the immune repertoire from bulk RNA-seq data. **Results:** Using the DSP platform, we confirmed reduced immune infiltration (e.g., CD3 and CD20) in both panCK and CD45 masked regions of MT, while CD8A and CD11c ($p_{adj} = 2.8\times10^{-7}$ and 2.1×10^{-6}) expression was only observed in panCK masked regions of MT compared with PT. A significant shift in myeloid composition between PT and MT as evidenced by increased CD68 signal ($p_{adj} = 5.8\times10^{-4}$) in CD45 masked regions of MT was identified. Within MT, PD-L1 signal was substantially higher ($p_{adj} = 0.030$) in CD45 masked regions only, while PD1 counts were lower ($p_{adj} = 0.035$) in panCK masked regions. This suggests the limited responses to ICI for MT may stem from relatively low expression of activated and targetable T cell subsets in MT islands. In support of the lower CD20 counts in MT, immune repertoire analysis revealed B cell receptor (BCR) repertoire diversity (represented by Gini index) was substantially lower in MT than PT ($p = 0.041$) suggesting that the ability of B cells to recognize a wide variety of tumor antigens in MT is greatly reduced in contrast to PT. **Conclusions:** Through comprehensive analysis of the TIME spatial organization within paired PT and MT, a significant reduction in dendritic cell/macrophage ratios (CD11c/CD68), reduced tumor localized T cell activation (CD8, PD1, PD-L1), and reduced B cell diversity (BCR clonality) are key features of the reduced immunogenicity of the metastatic TIME in TNBC. Further work to understand key mechanistic features driving the evolution of these differences in TIME between primary and metastatic tumors are ongoing. Research Sponsor: Genentech.

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Genomic landscape and peripheral blood biomarkers of advanced triple-negative breast cancer treated with immune checkpoint blockade: An exploratory analysis of the TQB2450-Ib-07 trial.

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Background: Immune checkpoint inhibitor (ICI) has emerged as a novel therapeutic option for advanced triple-negative breast cancer (aTNBC). However, no robust biomarker indicative of clinical outcomes has been identified. Herein, we portraited the genomic landscape and explored the biomarkers for patients with aTNBC receiving ICI-based therapy. **Methods:** This is a prospective, multicenter, phase 1b clinical trial (NCT03855358) to assess the efficacy and safety profiles of TQB2450, a humanized monoclonal PD-L1 antibody, plus anlotinib in pretreated TNBC. Eligible patients undergo liquid biopsy at baseline and the timepoint of disease progression. NGS-based assay was performed based on circulating tumor DNA (ctDNA) in the bloodstream. Meanwhile, results of laboratory blood tests were dynamically collected and blood markers, including neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to lymphocyte ratio (PLR), were successively evaluated. The primary endpoints were progression-free survival (PFS) and clinical efficacy assigned via guidelines for response criteria for use in trials testing immunotherapies (iRECIST). **Results:** Between May 29, 2019, and December 31, 2020, 34 patients with aTNBC were enrolled. Gene alternations primarily comprised mutation, amplification, or deletion of *TP53*, *MLL3*, *DNMT3A*, *PI3KCA*, *EP300*, *PTEN*, *LRP1B*, *MDM2*, and *NCOR1*. The median maximum somatic allele frequency (MSAF) was 9.97% significantly indicative of PFS, which was 3.58 months for the MSAF-high group and 13.34 months for the MSAF-low group (P = 3e-04), respectively. Else, a strong association was also signified between MSAF and tumor shrinkage (CR/PR vs. SD/PD, P = 0.012). For blood tumor mutation burden (bTMB), the median was 6.72 muts/Mb, which the bTMB-low group was suggestive of a better PFS (11.09 months vs. 5.52 months, P = 0.007), yet no obvious association existing in terms of clinical response. Dynamic analysis revealed that a decline in MSAF was significantly associated with a better PFS (7.10 months vs. 2.74 months, P = 0.018), while no correlations were detected between bTMB and PFS. Based on NLR week 2/0 of 0.95, PFS was significantly worse in the NLR-low group (11.0 months vs. 3.5 months, P = 0.006) and likely distinguished the clinical response (CR/PR vs. SD vs. PD, P = 0.049; non-PD vs. PD, P = 0.022). Moreover, NLR week 2/0 could notably foretell the clinical response for patients with aTNBC with the AUC of 0.82 (0.61-1.00). No comparable utilities were identified regarding LMR and PLR. **Conclusions:** For aTNBC treated with ICI, MSAF tended to be a robust indicator for both PFS and clinical response. NLR week 2/0 presented a favorable profile indicative of PFS as well as a strong predictor for clinical responsiveness of patients with aTNBC receiving immune checkpoint blockade. Clinical trial information: NCT03855358. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Phase 1b/2 study of GX-I7 plus pembrolizumab in patients with refractory or recurrent (R/R) metastatic triple-negative breast cancer (mTNBC): The KEYNOTE-899 Study.

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Background: GX-I7 (efineptakin alfa) is a hybrid Fc-fused long-acting recombinant human IL-7 which plays an essential role in the development and homeostasis of T-cells. GX-I7 can potentially enhance the anti-tumor effect of pembrolizumab via induction of T-cell activity. Here, we report results of phase 1b/2 study of GX-I7 plus pembrolizumab in patients with R/R mTNBC. **Methods**: Eligible patients had R/R mTNBC that failed up to 3rd lines of chemotherapy in the metastatic setting. Phase 1b patients received GX-I7 in 5 dose levels ranging from 360 μg/kg to 1,440 μg/kg every 9 (Q9W) or 12 (Q12W) weeks plus pembrolizumab 200 mg Q3W (n=51). Phase 2 is an expansion cohort where 33 patients were treated with the recommended phase 2 dose (RP2D). The primary objective was to determine the RP2D for phase 1b and to assess the objective response rate (ORR) for phase 2. **Results**: The study included 84 patients (phase 1b, n=51; phase 2, n=33) and 53.6% (45/84) of patients have received 2nd to 3rd lines of previous therapy. In phase 1b, one dose-limiting toxicity (DLT; grade 3 skin rash) was reported in the 1,440 μg/kg cohort and GX-I7 1,200 μg/kg Q9W was selected as RP2D. The ORRs were 15.7% [95% confidence interval (CI): 7.0 – 28.6] for phase 1b (n=51) and 21.2% [95% CI: 9.0 – 38.9] for phase 2 (n=33). Median PFS was 2.4 months (95% CI: 2.1 – 2.7) at the median follow-up of 10.4 months for all patients combined (n=84). GX-I7 induced up to 3.6-fold (range 1.2 – 8.1) increase in absolute lymphocyte counts (including CD4+ and CD8+ T cell) in all dose levels. The most common treatment-related adverse events (AEs) of any grade were injection site reaction (50.0%), ALT increased (39.3%), pyrexia (38.1%) and rash (35.7%). The additional correlative study data will be presented. **Conclusions**: GX-I7 in combination with pembrolizumab demonstrated a manageable safety profile with promising anti-tumor activity in patients with R/R metastatic TNBC. Clinical trial information: NCT03752723. Research Sponsor: Korea Drug Development Fund.

Baseline characteristics.

N(%)		Total N=84	Phase 1b N=51	Phase 2 N=33
Age, median(range)	-	50.0 (29.0-75.0)	49.0 (29.0–75.0)	51.0 (29.0–67.0)
ECOG PS	1	38 (45.2)	26 (51.0)	12 (36.4)
No. of metastatic organ sites	1	18 (21.4)	13 (25.5)	5 (15.2)
	2	29 (34.5)	17 (33.3)	12 (36.4)
	3	26 (31.0)	17 (33.3)	9 (27.3)
	≥4	11 (13.1)	4 (7.8)	7 (21.2)
Visceral metastasis	-	77(91.7)	45(88.2)	32(97.0)
PD-L1 (CPS Score)	<10	12 (70.6)	NA	12 (70.6)
	≥10	5 (29.4)		5 (29.4)
ALCs, median(range)	-	1175 (591–600)	1328 (591–4812)	1120 (631–2005)
Lymphopenia (≤1,000 cells/mm^3)		26 (31.0)	12 (23.5)	14 (42.4)
No. of previous lines of therapy	1	39 (46.4)	20 (39.2)	19 (57.6)
	2	27 (32.1)	16 (31.4)	11 (33.3)
	≥3	18 (21.4)	15 (29.4)	3 (9.1)

1082 **Poster Session**

Association of 27-gene IO score with outcome in a phase Ib trial of pembrolizumab (pembro) plus chemotherapy (CT) in metastatic triple-negative breast cancer (mTNBC).

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Background: The IO score is a is a 27-gene signature developed to classify the tumor immune microenvironment derived from the 101-gene TNBCtype genomic classifications. The IO score predicts clinical outcome following immune checkpoint inhibitor therapy in NSCLC and bladder cancer, and recently was shown to predict benefit by pCR of atezolizumab plus CT over neoadjuvant CT alone in early stage TNBC (NeoTRIPaPDL1 trial). The IO score has not yet been evaluated in mTNBC or with pembro in breast cancer. **Methods:** We report preliminary associations of IO score with response from a phase Ib trial (NCT02734290). mTNBC subjects received 1st/2nd line pembro (200mg IV q3wk) plus investigator's choice paclitaxel (80mg/m2 IV q1wk, n = 15) or capecitabine (2000mg PO BID x 7d, q2wk, n = 14). Baseline (n = 23) and on-treatment (at wk 6, n = 10) biopsies were analyzed for IO score and genomic subtype by RNA exome sequencing. Objective response rate (ORR, partial or complete response, 12 weeks) and survival was determined among response-evaluable subjects (n= 21). Tumor PD-L1 was assessed by IHC (combined positive score, CPS > 10%). The IO signature was analyzed as a binary classifier (IO+/IO-) and as a continuous variable (IO score). **Results:** 39% of evaluable subjects were IO+ (n =9/23). IO+ was associated with improved clinical outcome, including ORR (IO+ 43%, IO- 29%), median progression free survival (mPFS, IO+ 138d, IO- 79d), and median overall survival (mOS, IO+ 687d, IO- 305d). IO+/IO- classification and IO scores were stable across serial biopsies (Cohen's kappa = 0.74, r = 0.84). IO score was not strongly correlated with PD-L1 CPS (r = 0.27) or sTILs (r =.09). PD-L1-/IO+ tumors constituted 31% (n = 5/16) of PD-L1- cases and exhibited favorable outcome (ORR 40%, mPFS 162d, mOS 556d). IO score and ORR varied across TNBCtype classifications (BL1 subtype: 50% ORR, 66% IO+; BL2 subtype: 0% ORR, 66% IO+; LAR subtype: 50% ORR, 0% IO+, MSL subtype: 33% ORR, 60% IO+). **Conclusions:** IO score is associated with favorable outcome following pembro + CT, and may identify PD-L1-negative cases that respond to pembro + CT. Further investigation in larger datasets is warranted to ascertain the clinical utility of IO score in this setting. Funding: Drug support and funding provided by Merck Sharpe & Dohme as part of the Merck Investigator Studies Program. Clinical trial information: NCT02734290. Research Sponsor: Merck Sharpe & Dohme as part of the Merck Investigator Studies Program.

1083 **Poster Session**

Impact of steroid premedication on atezolizumab (atezo)-induced immune cell activation: A comparative analysis of IMpassion130 and IMpassion131 peripheral blood mononuclear cells (PBMCs).

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Background: The immune checkpoint inhibitor (ICI) atezo showed disparate outcomes as first-line therapy for metastatic TNBC when combined with nab-paclitaxel (nPac) in IMpassion130 [Schmid 2018] vs solvent-based paclitaxel (Pac) in IMpassion131 [Miles 2021]. A key difference between the trials was use of steroid premedication for Pac in IMpassion131 but not for nPac in IMpassion130. In patients (pts) receiving ICIs, prior steroid exposure has been linked to worse outcome [Drakaki 2020]. Further, IMpassion130 and IMpassion131 subgroup analyses suggested reduced atezo treatment effect in taxane-pretreated pts. This post hoc biomarker study explored the impact of: 1) steroids on systemic immune cell activation with atezo+taxane; 2) prior taxane exposure on atezo-induced immune cell activation. **Methods:** PBMCs collected at baseline and at day 1, cycle 2 (wk 4) were selected from matched pts (RECIST responders, PD-L1+, no liver metastases) from IMpassion130 and IMpassion131. Single-cell RNAseq was performed and the transcriptomic profile of immune cells was analyzed using GSEA pathway analyses, cell proportion and TCR clonality. **Results:** CITEseq from 695,851 single cells was generated from 39 IMpassion130 PBMC pairs (29 atezo+nPac; 10 placebo [Pla]+nPac) and 35 IMpassion131 pairs (26 atezo+Pac; 9 Pla+Pac). At wk 4, atezo+nPac resulted in increased IFNα and IFNγ responses across multiple cell types (CD4+ and CD8+ T cells, B cells, NK cells and monocytes) and proliferation in NK cells, but reduced TNF signaling across multiple cell types. In contrast, 4 wks of Pla+nPac increased TNF signaling but decreased IFNα and IFNγ responses. In the presence of steroids, 4 wks of atezo+Pac also increased IFNα and IFNγ responses mainly in NK cells and monocytes, but not T cells, and reduced proliferative pathways across B and T cells and TNF signaling. Pla+Pac increased TNF signaling only in NK cells, but reduced proliferative signatures across cell types. The only on-treatment change differing significantly between atezo+nPac vs atezo+Pac was the increase in proliferation pathways in NK, T and B cells with atezo+nPac. There were no significant changes in proportions of cell subsets or TCR clonality. PBMCs from taxane-pretreated pts had higher RNA-based metabolic profile (OxPhos, DNA repair and IFNα). Taxane-naive but not taxane-pretreated immune cells had increased IFNγ and IFNα response after atezo+taxane. **Conclusions:** Our results suggest that atezo+taxane promotes IFNα and IFNγ responses and that steroid co-administration reduces proliferation pathways across immune cells. Prior taxane exposure was associated with an increased metabolic status, possibly rendering immune cells less sensitive to atezo-induced activation. The immune context of taxane-naive TNBC may result in more potent immune activation with atezo. Clinical trial information: NCT02425891 and NCT03125902. Research Sponsor: F. Hoffmann-La Roche Ltd.

Safety interim analysis (SIA) of atractib: A phase 2 trial of first-line (1L) atezolizumab (A) in combination with paclitaxel (P) and bevacizumab (B) in metastatic triple-negative breast cancer (mTNBC).

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Background: A substantial benefit from adding an immune checkpoint inhibitor to chemotherapy (CT) was reported in mTNBC patients (pts) with PD-L1+ tumors. However, many pts still have a poor outcome. ATRACTIB is exploring the synergism between A (anti-PD-L1 antibody) and B (a VEGF-targeted antibody) with P in mTNBC irrespective of PD-L1 status. We report results from protocol-specified SIA. **Methods:** ATRACTIB is an open-label, single-arm, phase 2 trial (NCT04408118). Pts aged ≥18 years, with unresectable locally advanced or mTNBC, ECOG performance status of 0–1, who had received no prior systemic therapy or ≥12 months since (neo)adjuvant taxane-based CT are eligible. Pts receive A (840 mg IV, days 1, 15) with P (90 mg/m^2 IV, days 1, 8, 15), and B (10 mg/kg IV, days 1, 15) on each 28-day cycle until disease progression, unacceptable toxicity, or patient withdrawal. Primary endpoint is investigator-assessed progression-free survival (PFS) as per RECIST v.1.1. Secondary endpoints include objective response and clinical benefit rates, overall survival, and safety. The trial was designed to detect a treatment effect in terms of median PFS (H_0: ≤7 months; H_1: ≥9.5 months) and 100 pts are needed to attain 80% power at a nominal one-sided α level of 5%. One SIA was planned for evaluating safety as per CTCAE v.5.0 on the first 20 pts who had completed a 3-month follow-up or reached the end of study. **Results:** From Oct 5, 2020, through Nov 21, 2021, 34 pts were enrolled at 13 sites in Spain and Germany and received at least 1 dose of study treatment. Median age was 57.5 (range 40–84) years, 23 (67.6%) pts had received prior CT for early disease, and 19 (56.0%) had visceral disease. At data cutoff (Sep 30, 2021), 25 (71.4%) pts were still receiving the drug regimen. Adverse events (AEs) led to drug discontinuation in 3 (8.8%) pts. Mean relative dose intensity was 90.2% for A, 96.5% for P, and 95.7% for B. P dose reduction was reported in 7 (20.6%) pts. Five (14.7) pts required a dose delay due to AEs (11.8% for A, 11.8% for P, and 8.8% for B). The most common AEs of any grade (G) were fatigue (47.1%; 8.8% G≥3), diarrhea (38.2%; 0% G≥3), and neurotoxicity (35.3%; 8.8% G≥3). Anemia (20.6%; 0% G≥3) and neutropenia (17.6%; 8.8% G≥3) were the most frequent hematological AEs. AEs of clinical interest (AECI) for B were hypertension (17.6%; 5.9% G≥3) and pulmonary embolism (2.9%; 0% G≥3). AECI for A were pneumonitis (2.9%; 0% G≥3), autoimmune hepatitis (2.9%; 2.9% G≥3), and alanine aminotransferase increased (2.9%; 2.9% G≥3). No treatment-related deaths were reported. **Conclusions:** The addition of A to P and B as 1L therapy for mTNBC shows a tolerable safety profile which is consistent with known safety profile of each agent without a significant synergistic toxicity. Based on the independent data monitoring committee recommendation, patient recruitment is ongoing. Clinical trial information: NCT04408118. Research Sponsor: F. Hoffmann-La Roche Ltd.

1085 **Poster Session**

Targeting kinome reprogramming in ESR1 fusion-driven metastatic breast cancer.

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Background: Genomic analysis has recently identified multiple *ESR1* gene translocations in estrogen receptor-alpha positive (ERα+) metastatic breast cancer (MBC) that encode chimeric proteins whereby the ESR1 ligand binding domain is replaced by C-terminal sequences from many different gene partners. Transcriptionally active ESR1 fusions promoted hormone-independent cell growth, motility and resistance to endocrine therapy. The diversity of partner genes creates a considerable diagnostic challenge and no targeted treatments exist for *ESR1* translocated tumors. Thus, we have established a transcriptional signature to diagnose the presence of an active ESR1 fusion (PMID: 34711608) and developed novel targeted therapies against ESR1 fusion-driven biology. **Methods:** Fifteen *ESR1* fusion cDNA constructs were expressed in ER+ breast cancer cell lines by lentiviral transduction. Cell growth was assayed by Alamar blue assay. A mass spectrometry (MS)-based Kinase Inhibitor Pulldown Assay (KIPA) and tandem mass tag-based proteomics were performed to identify ESR1 fusion-driven druggable kinases for subsequent pharmacological inhibition. **Results:** KIPA profiling demonstrated an increase of multiple receptor tyrosine kinases including RET in T47D cells expressing active ESR1 fusions. Inhibition of RET by repurposing an FDA-approved drug significantly suppressed ESR1 fusion-driven cell growth *in vitro*, suggesting that despite marked diversity in the 3' partners, common kinase activities were elevated and targetable. Proteogenomic profiling, including whole exome sequencing, RNA sequencing, and MS-based proteomics and phosphoproteomics were further performed on 22 ER+ patient-derived xenograft (PDX) tumors, which demonstrated different degrees of estradiol dependence. These integrated "omic" profiles defined targetable genes/pathways and predict tumor subsets that could be responsive to kinase inhibition therapy from this biologically heterogeneous panel of PDX tumors. WHIM18, a PDX naturally harboring the ESR1-YAP1 fusion showed elevated level of RET and CDK4/6 pathways. The tumor volumes were significantly reduced by the RET inhibitor. CDK4/6 inhibitor treatment showed similar tumor reductions to RET inhibition. Interestingly, WHIM9 PDX that expressed wild-type ESR1 conferred a comparable kinome profile to WHIM18. The tumor growth was significantly suppressed by RET or CDK4/6 inhibition. Therefore, pharmacological experiments validated proteogenomics-predicted drug response in two tested ER+ PDX models. **Conclusions:** Proteogenomics characterization of PDX tumors can drive clinical trial hypotheses. Here, we reveal therapeutic kinase vulnerabilities in ESR1 fusion-driven tumors as exemplified by RET inhibition, which will lay the framework for future clinical trials. Research Sponsor: Department of Defense, Other Foundation.

1086 **Poster Session**

Shedding of ctDNA, radiomics assessment of tumor disease volume (TDV), and concordance of mutations (mut) in synchronous liquid and tumor biopsies in metastatic breast cancer (MBC).

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Background: Genomic alterations driving MBC progression may be better captured by ctDNA reflecting clonal evolution, but it is currently unknow whether ctDNA analysis can replace tumor sequencing for clinical decision purposes. Aim: to study the concordance between mut in synchronous plasma and tumor samples prospectively collected from patients (pts) with MBC progressing on their last systemic therapy. **Methods:** MiSeq Amplicon-based NGS (custom panel of 60 cancer-related genes; *BRCA1/2* and *PALB2* not included) was performed in both tumor biopsy and plasma. The concordance of ESCAT Tier I and II mut (*PIK3CA, AKT1, ERBB2, ESR1, PTEN*) was determined and correlated with mutant allele fraction (MAF), TDV, and clinical features. Findings from liquid biopsies were classified as true positive (TP-ctDNA) if a given mut was detected in both tumor and plasma and false negative (FN-ctDNA) if only in the tumor. TDV: all metastasis volume assessed by CT scan (excluding sclerotic bone metastasis), and analyzed by an experienced radiologist using the 3DSlicer semiautomatic segmentation tool (TDV = pixel size x number of pixels). Non-shedding cases were those where any mut was detected in tumor but none in plasma. **Results:** 88 cases were collected (luminal 64, HER2+ 17, triple negative 7). Median age at diagnosis 49 years (range 28-80). Radiomics assessment could be performed in 78/88 cases. The plasma/tissue concordance at case level was 74%. Discordance came from 23 cases; in 15 cases mut was only found in tissue and in 8 cases it was only detected in plasma. At gene level, *PIK3CA* had the highest concordance (79%); in *ESR1* it was 52%. Higher concordance associated with non-luminal subtype (OR 0.08, 95%CI 0.002 – 0.59) and shorter interval between primary diagnosis and metastatic relapse (20.3 vs 51 months; p =.02), but not with MAF. FN-ctDNA occurred in 15/49 cases (31%) and associated with luminal subtype (p =.02), but not with other clinical variables. Non-shedding cases associated with older age (p =.03), luminal subtype (p =.007), low TDV (p =.0006) and < 3 metastatic sites (p =.05). In patients with visceral metastasis (n = 45), higher TDV associated with lower probability of FN-ctDNA (p =.03). All non-luminal subtypes were shedders and all but one were TP-ctDNA. In multivariate analysis, higher probability of TP-ctDNA in luminal tumors associated with tumor sampling from a progressing lesion (OR 10.8; 95% 1.5 – 122; p =.03) and shorter interval between diagnosis of metastatic disease and biopsy (OR 0.96, 95% CI 0.92 – 0.99; p =.03). **Conclusions:** Our results suggest that ctDNA can detect a significant proportion of clinically relevant mut in MBC. Patients' characteristics, tumor subtype, type of gene, and tumor volume should be integrated with ctDNA results to better inform clinical decisions. Research Sponsor: AP is supported by an ESMO Research Fellowship and ML is supported by a PERIS Grant-PIS Program.

1087 **Poster Session**

Retrospective study to estimate the prevalence of HER2-low breast cancer (BC) and describe its clinicopathological characteristics.

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Background: Approximately 50% of BCs traditionally categorized as HER2 negative (HER2-neg) express low levels of HER2 (IHC 1+ or IHC 2+/ISH-; Miglietta, *NPJ Breast Cancer* 2021). HER2-targeted therapies for HER2-low metastatic BC (mBC) are under investigation (eg, T-DXd in the phase 3 DESTINY-Breast04 study; NCT03734029), but HER2 assays currently used to select patients (pts) for approved anti-HER2 therapies are optimized for high HER2 expression and are not validated for HER2-low detection. A recent study found relatively poor agreement (<70% interrater agreement) in evaluation of IHC scores of 0 and 1+ using current HER2 assays (Fernandez, *JAMA Oncol* 2022). Our objectives were to assess the prevalence of HER2-low among HER2-neg based on rescored HER2 IHC slides after training on low-end expression scoring and to describe pt characteristics of HER2-low vs HER2 IHC 0 mBC. Preliminary results are reported for 233 of 1000 planned pts. **Methods:** This multicenter, retrospective study (NCT04807595) included pts with confirmed HER2-neg unresectable/ mBC diagnosed between 2015 and 2017. Local laboratories, blinded to historical HER2 scores, rescored HER2 IHC-stained slides. HER2 was assessed using Ventana 4B5 and other assays. BCs were categorized as HER2-low or HER2 IHC 0. The prevalence of HER2-low BC among pts originally scored as HER2-neg was measured. Demographics (eg, age, country, race) and clinicopathological characteristics were examined via medical charts/electronic health records. Concordance between historical HER2 scores and rescores was assessed. **Results:** HER2 rescores were obtained for 233 pts (mean age, 54 y). HER2-low prevalence was 63.2% overall and numerically greater in hormone receptor (HR)–positive vs HR-negative subgroups (66.1% vs 54.8%; Table). No notable differences in prevalence were seen among different HER2 assays or in demographic/baseline disease characteristics between the HER2-low and HER2 IHC 0 groups. Concordance rate between historical and rescored slides for HER2-status classification was 82.3%. The presentation will include an expanded data set (≈400 pts) with additional results. **Conclusions:** Data on HER2-low prevalence in BC is limited. Preliminary data from this study of mBC samples suggest a somewhat higher prevalence estimate (≈63%) than a previous study of primary BC samples (≈50%). Concordance was 82%; ongoing analyses with updated data will clarify the concordance between rescored and historical HER2 slides. These data can support development of best practices for identifying pts with HER2-low expression who may benefit from HER2-targeted therapies. Clinical trial information: NCT04807595. Research Sponsor: This study is funded by AstraZeneca Pharmaceuticals and Daiichi Sankyo Inc. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

Prevalence of HER2-low in HER2-neg mBC population.

Assay, %	HR positive (n=167)	HR negative (n=62)	All pts (N=233)[a]
All (N=233)[b]	66.1	54.8	63.2
Ventana 4B5 (n=90)	67.6	50.0	64.4
Other (n=141)	64.9	56.8	62.4

[a]HR status missing, n=4. [b]HER2 score missing, n=2.

1089 **Poster Session**

Survival and prognostic factors in oligometastatic breast cancer.

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Background: Clinical guidelines for the treatment of oligometastatic breast cancer (OMBC) propagate multimodality treatment including polychemotherapy and ablative local therapy for all detected disease. The aim of this aggressive approach is prolonged disease remission, or even cure, but randomized data to support this strategy lack and long-term outcomes are not well known. We report prognostic factors, and event-free survival (EFS) and overall survival (OS) in a real world, single center cohort of patients with OMBC with long-term follow-up. **Methods:** Patients with breast cancer and 1-3 distant metastatic lesions who underwent treatment in the Netherlands Cancer Institute were identified via text mining of medical files. We collected patient, tumor and treatment characteristics as well as recurrence and survival data from the medical records. The Kaplan-Meier method was used to calculate EFS and OS estimates, and Cox regression analyses to assess potential prognostic factors. **Results:** The cohort included 239 patients (of whom two males), diagnosed between 1997 and 2020. Median follow-up was 75.0 months. Fifty-one percent had hormone receptor (HR)-positive/ human epidermal growth factor receptor 2 (HER2)-negative disease, 20.1% had HER2-positive disease, and 19.2% had triple negative (TN) disease. Median age at OMBC diagnosis was 49.0 years and 47.3% of patients had synchronous disease (metastases ≤6 months of primary diagnosis). Most patients (81.2%) received chemotherapy and local therapy (surgery, radiotherapy and/or radiofrequency ablation) of all metastatic lesions (83.7%). Of 239 patients, 134 experienced disease recurrence with a median EFS of 40.0 months (95% confidence interval (CI): 28.6-51.4); 97/239 died and median OS was 93.0 months (95% CI 74.5-111.5). The table shows factors associated with favorable OS in multivariable analysis. Cox regression analysis for EFS showed similar results. **Conclusions:** In this large real world cohort of OMBC patients, EFS and OS compare favorably to survival in the general MBC population. HR-positive and/or HER2-positive subtypes, synchronous disease or long DFI, favorable response to first-line systemic therapy and local therapy of all distant lesions are independently associated with better survival. Future studies should be directed at optimizing patient selection and therapy choices in this population with the potential for cure. Research Sponsor: None.

		HR	95% CI	p-value
Subtype (primary tumor)	Triple neg	ref	-	-
	HR-positive/HER2-neg	0.18	0.10-0.32	<0.001
	HER2-pos	0.11	0.05-0.23	<0.001
Disease-free interval (DFI)	DFI short (7-24 months)	ref	-	-
	DFI long (>24 months)	0.49	0.24-1.00	0.049
	No DFI (synchronous disease)	0.29	0.15-0.57	<0.001
Response to 1st line systemic therapy	Progressive disease	ref	-	-
	Any response, not complete	0.17	0.08-0.36	<0.001
	Complete response	0.05	0.02-0.14	<0.001
Local treatment of all metastases	(ref: no local treatment of all metastases)	0.52	0.28-0.98	0.042

1090 **Poster Session**

Quantitative proteomics landscape and association with BASP1 and breast cancer metastasis.

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Background: Tumor recurrence and metastatic progression remain the leading cause for breast cancer related mortalities. The study aimed to identify differences in proteomics landscape in serum between (i) healthy controls and breast cancer patients, (ii) baseline samples at time of diagnosis from patients that later developed metastases versus those that did not and, (iii) baseline samples presented after completed treatment versus the samples collected before patients developed metastasis. **Methods:** We performed mass spectrometery-based proteome profiling of 100 serum samples from 51 breast cancer patients and 27 healthy donors. Of the 51-breast cancer patients, 29 patients did not metastasize, and 22 patients had a metastatic recurrence. Each of the 22 breast cancer patients with metastasis had 2 samples-one collected within a year of diagnosis and second one collected within a year before the patient developed metastases. Intensity-based absolute quantification (iBAQ) method was employed to convert recovered peptide information to quantificational gene protein product and then normalized to final quantificational value using an in-housed software. Protein values were normalized using z-score before differential expression analyses. FDR < 0.1 and a p-value < 0.05 was used as the cutoff to identify differentially expressed proteins. **Results:** We identified 1177 proteins in total from 100 serum samples of healthy women and breast cancer patients. PCA analysis revealed a complete separation of the breast cancer and healthy control samples. However, we found overlapping but distinct groups of metastatic and non-metastatic samples. We found 179 proteins to be differentially expressed between normal healthy control samples and baseline breast cancer samples irrespective of their metastatic status. Upon comparing baseline breast cancer samples that metastasized with breast cancer samples that did not metastasize, we found BASP1 as the top-ranked gene that was significantly upregulated in metastatic samples. We did not find any significant differences between paired baseline samples collected at diagnosis and pre-metastatic samples collected before the patient developed metastasis. **Conclusions:** Our results show distinct proteomic profiles exist between breast cancer and normal healthy control samples. Further studies are required to confirm if serum BASP1 can be used as a putative biomarker for predicting metastatic risk in breast cancer patients. Research Sponsor: U.S. National Institutes of Health.

1091 **Poster Session**

Efficacy and impact of SARS-CoV-2 vaccination on cancer treatment for patients with breast cancer: A multicenter, prospective, observational study.

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Background: Vaccination is an essential strategy to prevent infection in the SARS-CoV-2 pandemic. However, there are concerns about vaccine efficacy and the impact of vaccination on cancer treatment. Additionally, the emergence of novel variants may affect vaccination efficacy. This multi-center, prospective, observational study investigated the efficacy and impact of vaccination against SARS-CoV-2 variants on treatment among breast cancer patients in Japan. **Methods:** Breast cancer patients scheduled to be vaccinated with the SARS-CoV-2 vaccine from May to November 2021 were included. They were stratified into five groups according to their cancer treatment: no treatment, endocrine therapy, CDK4/6 inhibitor, chemotherapy, anti-HER2 therapy. Serum samples were collected before the first vaccination and after the second vaccination. Immunoglobulin (Ig)G levels against the SARS-CoV-2 S protein and neutralizing antibody titers against wild-type (WT), alpha (α), delta (δ), kappa (κ), and omicron (o) variants were measured by ELISA assay. The effect of vaccination on cancer treatment was also investigated. **Results:** There were 85 eligible patients (no treatment, n = 5; endocrine therapy, n = 30; CDK4/6 inhibitor, n = 14; chemotherapy, n = 21; and anti-HER2 therapy, n = 15) with a median age of 65 years. The overall seroconversion rate of anti-SARS-CoV-2 IgG was 95.3%. The seroconversion rate of the chemotherapy group was 81.8%. The anti-SARS-CoV-2 IgG antibody concentration was positively correlated with the lymphocyte count before vaccination ($r = 0.232$, $p = 0.039$). Overall neutralizing antibody titers against each variant were significantly lower than for WT. Overall positive rates of neutralizing antibodies against WT, α, δ, κ, and o variants were 90.2%, 81.7%, 96.3%, 84.1%, and 8.5%, respectively. A downward trend of neutralizing antibody titers against each variant was seen in chemotherapy and CDK4/6 inhibitor groups compared with other groups. Significant decreases were detected in neutralizing antibody titers against WT, α, and κ variants in the chemotherapy group, and WT and α variants in the CDK4/6 inhibitor group compared with the no treatment group. Withdrawal or postponement of systemic therapy because of vaccination was only observed in one patient. **Conclusions:** Our data support SARS-CoV-2 vaccination for cancer patients being treated with systemic therapy. However, neutralizing antibody titers against the o variant were very low even after two vaccinations among patients with or without cancer treatment. Further, a decrease in neutralizing antibody titer was suggested during chemotherapy and CDK4/6 inhibitor, raising concerns about the impact on long-term infection prevention. For these patients, infection-preventive behaviors should be recommended even after vaccination. They will also be good candidates for booster vaccinations. Clinical trial information: UMIN000045527. Research Sponsor: None.

1092 **Poster Session**

Lurbinectedin in patients with pretreated *BRCA*1/2-associated metastatic breast cancer: Results from a phase II basket study.

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Background: Lurbinectedin (L) is a selective inhibitor of oncogenic transcription that leads to cell apoptosis and shows antitumor activity against homologous recombination repair-deficient cell lines. A previous phase II study (Cruz *et al.* JCO 2018;36:3134-3143) demonstrated antitumor activity in patients (pts) with pretreated metastatic breast cancer (median of 1 prior advanced chemotherapy line) and *BRCA*1/2-mutated tumors with L 3.5 mg/m^2 or 7.0 mg flat dose (equivalent to 4.0 mg/m^2) every three weeks [q3wk]). This report focuses on the outcomes in the *BRCA*1/2-associated breast cancer cohort of a phase II Basket multitumor trial. **Methods:** This phase II study evaluated L 3.2 mg/m^2 1-hour intravenous (i.v.) infusion q3wk in a cohort of 21 female pts with pretreated *BRCA*1/2-associated breast cancer. The primary efficacy endpoint was ORR according to RECIST v1.1. Secondary endpoints included duration of response (DoR), progression-free survival (PFS), OS and safety. **Results:** Median age was 45 years (range, 29-73 years). Hormone receptor (HR)+ disease was observed in 76.2% of pts, triple negative disease in 19.0% and HER2+ in 9.5%. *BRCA1* and *BRCA2* were reported in 47.6% and 52.4% of pts, respectively. Median number of prior lines of chemotherapy for advanced disease was 2 (range, 0-3 lines). Prior poly(ADP-ribose) polymerase inhibitors and platinum compounds had been administered to 23.8% and 47.6% of pts, respectively. Confirmed partial response (PR) was observed in six pts (ORR = 28.6%; 95% CI, 11.3-52.2%). Lurbinectedin was active in both BRCA mutations: four PRs in 11 pts (36.4%) in *BRCA2* and two PRs in 10 pts (20.0%) in *BRCA*1. Median DoR was 8.6 months, median PFS was 4.1 months and median OS was 16.1 months. Stable disease (SD) was observed in ten pts (47.6%), including three pts with unconfirmed response in a subsequent tumor assessment (ORR unconfirmed = 42.9% [95%CI, 21.8-66.0]). Clinical benefit rate (PR + SD≥4 months) was 76.2% (95% CI, 52.8-91.8%). The most common grade 3/4 toxicity was neutropenia (42.9%; grade 4, 23.8%; with no febrile neutropenia). **Conclusions:** This phase II study met its primary endpoint and confirmed the activity of L in pretreated *BRCA*1/2-associated breast cancer pts. L 3.2 mg/m^2 1-hour i.v. infusion q3wk showed an acceptable, predictable and manageable safety profile. Considering the exploratory aim of this trial as well as previous results in other phase II study, further development of L in this indication is warranted. Clinical trial information: NCT02454972. Research Sponsor: PharmaMar.

1093 **Poster Session**

CK+/CD45+ (dual-positive) circulating cells are associated with prognosis in patients with advanced breast cancer.

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Background: Circulating tumor cells (CTCs) expressing epithelial markers (EPCAM, cytokeratin (CK)) and lacking CD45 (a leukocyte marker) have been associated with poor outcome in many cancer types. Nonetheless, the presence of cells expressing both CK and CD45 (CK+/CD45+), circulating in the blood of cancer patients (pts) have also been reported, but not widely investigated. Early evidence indicates that circulating dual-positive cells (DPcells) are hybrids deriving from the fusion of tumor cells and macrophages. We previously reported that it is possible to detect DPcells in the blood of pts with metastatic breast cancer (BC) and that they are associated with shorter progression-free survival (PFS), in pts with <5 CK+/CD45- CTCs. Here, we investigated the impact of DPcells on overall survival (OS) in pts with advanced BC (aBC). **Methods:** Blood samples (7.5 ml) were collected from aBC pts before starting a new therapy and processed with the FDA-approved CellSearch platform for CTCs and DPcells enumeration. The prognostic role of CTCs and DPcells was assessed through the Kaplan-Meier method using the log-rank test. Single DPcells were isolated using the DEPArray platform and underwent whole genome amplification and lowpass whole genome sequencing (Ampli1 WGA and Ampli1 Lowpass kits). **Results:** Blood samples from 341 pts with luminal (n=168), HER2+ (n=76) and triple negative (n=88) BC were analyzed. Of these, 131 samples (38.4%) contained ≥5 CTCs (CTC^{pos}), whereas DPcell were detected in 152 samples (44.6%, range 0-53), of which 66 (43.4%) were CTC^{pos} and 86 (56.6%) CTC^{neg}. Overall, DPcells were associated with a shorter OS: median OS 24.5 vs 35.0 months, p=0.046. However, when analyzing CTC^{pos} and CTC^{neg} separately, only the latter group showed a difference in OS according to DPcells presence. In particular, among CTC^{neg} pts, those with ≥4 DPcells showed a 2.3-fold shorter OS (26.7 vs 60.6 months, p=0.025). Moreover, pts with ≥4 DPcells were less likely to experience a 6-months PFS clinical benefit (p=0.015). Interestingly, in the analysis by BC subtype, DPcells were confirmed to be associated with worse OS only in pts with triple negative BC (median OS 11.5 vs 16.9, p=0.048). To explore the exiology of DPcells, 2 out of 3 cells analyzed after single-cell isolation from 1 patient were confirmed to have copy number alterations (CNA) consistent with malignant cells. CNA and mutational profiling of additional single DPcells and CTCs are ongoing. **Conclusions:** DPcells are associated with worse OS in aBC pts, with the prognostic impact primarily in pts with <5 CTCs and triple negative BC. This suggests that DPcells might be an alternative way of tumor dissemination in specific pts, in which CK+/CD45- CTCs are less prevalent. More studies are needed to better elucidate DPcell clinical significance in BC, and to confirm their fusion-hybrid origin. Research Sponsor: Lynn Sage Breast Cancer Foundation, Other Foundation, Pharmaceutical/Biotech Company.

Eribulin mesylate versus eribulin plus anlotinib in patients with advanced or metastatic breast cancer: Results of a phase II study.

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Background: Eribulin mesylate is a structurally simplified, synthetic, macrocyclic ketone analogue of Halichondrin B. We investigated the efficacy and safety of eribulin monotherapy versus eribulin plus the oral anti-angiogenesis inhibitor anlotinib in patients with advanced or metastatic breast cancer. **Methods:** This Phase II study included adult Chinese patients with locally advanced or metastatic breast cancer previously treated with at least two chemotherapy regimens, including both anthracycline- and taxane-based therapy (NCT05206656). Patients were randomized (1:1) to receive eribulin (1.4 mg/m^2, intravenously, on days 1–8), alone or in combination with anlotinib (12 mg orally once daily), in 21-day cycles. The primary endpoint was investigator-assessed disease control rate (DCR), per RECIST version 1.1. Key secondary endpoints included objective response rate (ORR), progression-free survival (PFS) and safety. **Results:** Between February 12, 2020, and July 22, 2021, 56 patients were randomized to eribulin (n=32) or eribulin plus anlotinib (n=24) (Table). Sites of metastasis were: bone (60.7%), lung (52.7%), liver (53.6%), lymph nodes (73.2%) and soft tissue (7.1%). Among all patients, the DCR was 66.7% versus 100% (treatment difference, 33.3%; P=0.007), the ORR was 37.0% versus 38.9%, and the median PFS was 3.7 months versus 9.7 months (adjusted hazard ratio, 0.20; 95% CI, 0.04 to 0.91; P=0.04) for patients receiving eribulin versus eribulin plus anlotinib, respectively. Among 36 (64.3%) patients with triple-negative breast cancer, the DCR was 55.6% versus 72.2% (treatment difference, 16.7%; P=0.300) and the median PFS was 3.6 months versus 9.7 months (log rank P=0.030) with eribulin alone versus eribulin plus anlotinib, respectively. The most frequent grade 3-4 adverse events in the eribulin and eribulin plus anlotinib groups were decreased neutrophil count (25.0% [n=8] vs. 29.2% [n=7]) elevated transaminase (6.3% [n=2] vs. 0.0%) and decreased thrombocyte count (3.1% [n=1] vs. 0.0%), respectively. **Conclusions:** Eribulin plus anlotinib was associated with a significantly better DCR, ORR and PFS than eribulin monotherapy in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. Clinical trial information: NCT05206656. Research Sponsor: None.

Patient clinical characteristics.

Variable	All patients (N=56)	Eribulin (n=32)	Eribulin plus anlotinib (n=24)
Mean age at eribulin usage ± SD (years)	48.9 ± 8.1	49.0 ± 8.2	48.8 ± 8.0
Time from diagnosis to relapse or metastasis ± SD (months)	28.2 ± 35.3	31.8 ± 40.3	23.5 ± 27.3
Surgery, n (%)	49 (87.5)	29 (90.6)	20 (83.3)
Neoadjuvant chemotherapy, n (%)	12 (21.4)	6 (18.7)	6 (25.0)
Adjuvant chemotherapy, n (%)	47 (83.9)	28 (87.5)	19 (79.2)
ER positive, n (%)	18 (32.1)	13 (40.6)	5 (20.8)
PR positive, n (%)	10 (17.9)	7 (21.9)	3 (12.5)
HER2 positive, n (%)	2 (3.6)	2 (6.2)	0 (0.0)

1095 **Poster Session**

Historical redlining and breast cancer survival in the United States: Evidence from the 2010-2017 SEER Medicare linked dataset.

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Background: Cancer is the second leading cause of morbidity and mortality in the US. Systemic racism is a critical cause of health disparities and historically disadvantaged people experience poor outcomes including poor breast cancer (BC) survival. This study aims to investigate the impact of historical redlining on all-cause and BC-specific survival among older women in the US. **Methods:** Historic 1930's Homeowner's Loan Corporation (HOLC) boundaries and grades were linked to 2010 Census tracts and the 2010-2017 SEER Medicare BC cohort. Women were included if they were 66+ years old at diagnosis, diagnosed with invasive BC, enrolled in Medicare Part A and Part B for 12 months prior to diagnosis to calculate comorbidity, and a Census tract match for HOLC grade. The independent variable was HOLC grade in two categories: A and B(not redlined), and C and D(redlined). The outcomes were all-cause and BC-specific survival, determined by Kaplan Meier Survival curves and both unadjusted and adjusted Cox regression models. End point for censoring was 12/31/2019 (all-cause) and 12/31/2018 (BC-specific). The final models were stratified by age and tumor stage at diagnosis; and adjusted for comorbidity, race and ethnicity, hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status, and interaction term between comorbidity and race. **Results:** Among 10,113 women, 62.8% resided in historically redlined Census tracts. At a mean (+SD) follow-up time of 48.5 (+28.8) months, 28.9% were deceased; 41.6% of which died of BC. Women residing in historically redlined census tracts experienced poorer BC survival (49.8 +28.2 months) than those residing in non-redlined Census tracts (57.8 +30.7 months). After controlling for covariates, residing in a historically redlined Census tract remained an independent predictor of higher mortality: HR (95%CI) = 1.11 (1.02, 1.20) and 1.24 (1.011, 1.39) for all-cause mortality and BC-specific mortality, respectively. **Conclusions:** Residing in a formerly redlined Census tract at the time of BC diagnosis is associated with worse all-cause and BC-specific mortality, even after stratifying/adjusting for important patient and tumor characteristics. Public health and government agencies stakeholders should consider historical contexts when designing and implementing equity-focused community and clinical interventions targeted at mitigating and reducing BC disparities and improving health equity. Research Sponsor: This study is part of the National Cancer Institute (NCI)–funded R01 research project (R01CA214805) led by Dr. Beyer at the Medical College of Wisconsin.

Comprehensive whole-exome and transcriptome profiling to identify actionable alterations associated with response to PARP inhibitors in breast cancer.

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Background: The use of targeted therapies identified using genetic and genomic approaches is now routine in breast cancer (BC). In this clinical lab experience study the frequency of actionable somatic alterations in DNA repair pathway genes associated with the use of PARP inhibitors (PARPi) is described. **Methods:** BC samples were sequenced with the Oncomap ExTra assay, which uses whole-exome DNA sequencing with germline subtraction to detect somatic single base substitutions, indels, and copy number alterations, and RNA sequencing to detect gene fusions. Clinically actionable alterations were defined as associated with FDA approved drugs or clinical trial enrollment. Here, the focus is on 49 repair genes associated with PARPi response: *ARID1A, ATM, ATR, ATRX, BAP1, BARD1, BLM, BRCA1/2, BRIP1, CDK12, CHEK1/2, EPCAM, ERCC1/2/3/4/5, FANCA/C/D2/E/F/G/I/L/M, MLH1, MRE11A, MSH2/6, MUTYH, NBN, PALB2, PMS2, PPP2R2A, PTEN, RAD21/50/51/51B/51C/51D/52/54L, XRCC1/2/3.* **Results:** Of 1103 BCs, 246 (22.3%) had mutations in repair genes; 69 (6.3%) were in *BRCA1/2*. Repair gene mutations were less common in $HER2^+$ cancers (n=27, 14.3%) compared to HR^+HER2^- (n=156, 23.9%) or TN cancers (n=49, 26.1%) ($p<0.01$). Across subtypes, the top four most commonly mutated of the repair genes were *PTEN* (27.2%), *ARID1A* (22.8%), *BRCA2* (14.2%), and *BRCA1* (14.2%); 33 cancers (13.4%) had mutations in multiple (≥2) repair genes. For the 69 cancers with *BRCA1/2* mutations, 11 (15.9%) carried other repair gene mutations (9 of 35 *BRCA1*; 3 of 35 *BRCA2*). RNA sequencing found 19 fusions in repair genes in 17 patients (1.5%); *CDK12* was involved in 13 (68.4%), and *RAD51C* in 3 (15.8%). Fusion incidence was more frequent in $HER2^+$ cancers ($p<0.01$) (Table). **Conclusions:** PARPi therapy is FDA approved for $HER2^-$ germline *BRCA1/2* mutated BC patients. Recent evidence suggests somatic *BRCA1/2* mutations predict PARPi benefit (Tung, NM. J Clin Oncol 2020). In addition to BRCA1/2 alterations, our study also highlights the importance of alterations in other DNA repair genes associated with response to PARPi. Trials are ongoing to determine if these genes predict for PARPi benefit. Research Sponsor: Exact Sciences Corporation.

Alterations involving DNA repair genes.

BC subtype	Patients (% of total)	*BRCA1/2* genes (%[a])	Non-*BRCA1/2* genes (%[a])	≥2 genes (%[a])	gene fusions (%[a])
All	**Patients**	1103	69 (6.3%)	177 (16.0%)	33 (3.0%)
17 (1.5%)					
HER2-/HR+	652 (59.1%)	43 (6.6%)	113 (17.3%)	20 (3.1%)	2 (0.3%)
TNBC	188 (17.0%)	16 (8.5%)	33 (17.6%)	9 (4.8%)	2 (1.1%)
HER2+	189 (17.1%)	8 (4.2%)	19 (10.1%)*	2 (1.1%)	13 (6.9%)**
NS	74 (6.7%)	2 (2.7%)	12 (16.2%)	2 (2.7%)	0 (0.0%)

NS = Not specified. [a]% within subtype. *underrepresented / **overrepresented compared to other subtypes (Fisher's Exact test, $p<0.05$).

1097 **Poster Session**

Interplay between B cell and GABA metabolism (GABAm) and association with immune evasion in breast carcinoma (BC).

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Background: GABAergic signaling has been reported to play a pivotal role in breast cancer (BC) tumorigenesis and metastasis, however, its role in immune modulation remains unclear. Recent *in vitro* and *in vivo* studies (Zhang et al., Nature, 2021) report the role of B cell-derived GABA metabolites in promoting anti-inflammatory macrophages (MM), thus limiting anti-tumor immunity. In this study, we aim to characterize the interplay between B cells and the GABAm pathway, as well as their associated immune infiltrates and cytokines. **Methods:** BC tumors (n = 9455) were analyzed by next generation sequencing (NextSeq, 592 Genes and WES, NovaSEQ) and whole transcriptome sequencing (WTS, NovaSeq) at Caris Life Sciences. Gene set variation analysis (GSVA) scores were used for GABAm pathway activity (GMPA). IFN score to test the likelihood of a tumor's response to anti PD1 therapy and Immune cell fraction (quanTIseq) were assessed by mRNA analysis. Wilcoxon-Mann-Whitney test was applied (p without, q with multiple comparison correction). Correlation coefficients were calculated using spearman correlation. **Results:** GMPA demonstrated a statistically significant positive correlation with B cells fraction ($r = 0.24$, $p < 0.0001$). When stratified by classical molecular subtypes, the positive correlations were exclusive to HR+ and HER2+ BC, and absent in TNBC. GMPA was the most enriched in HR+ BC, followed by HER2+ and TNBC. BC tumors with high B cell infiltration were then grouped into GMPA-high (B+G+, cutoff > median for both) or GMPA-low (B+/G-), which likely represented tumors with B cell-derived high and low GMPA group, respectively. The GMPA-high group demonstrated significantly less fractions of MM1 (2.8 vs 3.7) and CD8+ T cells (0.8 vs 1.2) but greater MM2 (5.3 vs 4.9). mRNA levels of the MM2 marker IL10, a proposed marker of immune evasion, was significantly overexpressed in the B+/G+ group compared to the B+/G- group (fold change, FC = 1.39). mRNA levels of GAD1, a GABA-generating enzyme, were higher in B+/G+ than B+/G- (FC = 7.19). B+/G+ group had notably less IFN score than B+/G- group (-0.37 vs -0.27). When further stratified into molecular subtypes, concurrent more MM2 (5.4 vs 5.2) and less CD8+ T cell (0.74 vs 0.91) fractions were found in B+/G+ compared to B+/G- in HR+ tumors, but not in HER2+ or TNBC tumors. B+/G+ group also demonstrated a lower IFN score (-0.38 vs -0.32) in HR+ tumors. Additionally, IL10 and GAD1 were consistently overexpressed in B+/G+ regardless of subtype, reaching FC 7.9 in HR+ tumors. $q < 0.0001$ for all comparisons. **Conclusions:** Our study is the largest clinical dataset to demonstrate the association of interplay between B cell and GABAm with immunogenicity. Our results support the potential role of B cell-derived GABAm metabolites in immune modulation in BC in a subtype-specific manner. Targeting small metabolites to modulate immune evasion in BC warrants further investigation. Research Sponsor: None.

A phase IB/II study of nivolumab in combination with eribulin in HER2-negative metastatic breast cancer (KCSG BR18-16).

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Background: Combining immune checkpoint inhibitors with chemotherapy has become a promising therapeutic strategy in metastatic breast cancer. Eribulin is a potent microtubule inhibitor and modulates the immune microenvironment of tumor cells. Therefore, combining eribulin to nivolumab may synergize antitumor efficacy in metastatic breast cancer. **Methods:** Adult patients with histologically confirmed recurrent/metastatic HER2- breast cancer were enrolled prospectively from 10 academic hospitals in Korea (ClinicalTrials.gov Identifier: NCT04061863). Key eligibility criteria included prior treatment with taxanes and/or anthracyclines, ≥1 measurable disease, and ≤2 prior cytotoxic chemotherapies in the metastatic setting. Patients received nivolumab 200 mg intravenously (IV) on day 1 plus eribulin 1.4 mg/m^2 IV on day 1 and 8 of every 3 weeks until disease progression or intolerable toxicity. The dose level was determined from safety profile of three patients in run-in phase. The primary endpoint was investigator-assessed progression-free survival (PFS) rate at 6 months. Secondary endpoints included investigator-assessed objective response rate (ORR) per RECIST v1.1, disease control rate (DCR), overall survival (OS), and toxicity profile of the combination treatment. The association between PD-L1 expression by SP142 Ab and efficacy was analyzed. **Results:** From August 2019 to June 2021, 90 patients (HR+HER2- 45 pts/TNBC 45 pts), with a median age of 51 (range 31–71), were enrolled in the study. With a median study follow-up time of 16.3 months, 68 (75.6%) patients experienced progressive disease. PFS rate at 6-months was 49.6% and 24.1% in patients with HR+HER2- and TNBC group, respectively. Median PFS was 5.6 months (95% CI: 4.3-6.8) and 3.0 months (95% CI: 1.3-4.7) for HR+HER2- and TNBC group, respectively. ORRs were 53.3% (CR:0, PR: 24) for HR+HER2- and 21.8% (CR1, PR: 12) for TNBC. Patients with PD-L1+ tumors (PD-L1 expression ≥ 1% on TC or IC) had similar ORR compared to PD-L1- tumors (ORR 50% vs. 53.8% in HR+HER2-, 30.8% vs. 29.0% in TNBC). The most common grade 3/4 adverse event was neutropenia (15/90, 16.7%), and the most common immune-related adverse events were grade 1/2 hypothyroidism (19/90, 21.1%) and grade 1/2 pruritus (16/90, 17.8%). Five patients had discontinued study treatment due to immune-related adverse events (3 pneumonitis, 1 hepatitis, 1 skin rash). **Conclusions:** In this parallel phase II clinical trial, the addition of nivolumab to eribulin showed promising efficacy and tolerable safety profile in previously treated HER2- MBC. Further survival and exploratory analyses to find predictive markers will be followed. Clinical trial information: NCT04061863. Research Sponsor: Ono Pharma (Nivolumab), Pharmaceutical/Biotech Company.

Objective response according to RECIST v1.1.

	ER+ (n)	(%)	TNBC (n)	(%)	Total (n)	(%)
CR	0	0	1	2.2	1	1.1
PR	24	53.3	12	26.7	36	40.0
SD	13	28.9	16	35.6	29	32.2
PD	8	17.8	16	35.6	24	26.7

1099 **Poster Session**

Is cure possible for breast cancer metastatic to the liver?

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Background: Metastatic breast cancer (MBC) is a lethal disease and is generally only amenable to systemic treatment. Although increasingly recommended on selected patients, local treatments, and particularly surgery, are seldom used in the therapeutic armamentarium for MBC and their long-term survival benefit is unknown. We hypothesized that combining surgery to systemic treatment for selected patients with breast cancer liver metastases could lead to long-term survival or even an option of cure. **Methods:** A retrospective study of prospectively gathered data from a surgical series of liver resections for MBC was conducted. Patients with no or limited and stable extra-hepatic disease were offered surgery after multidisciplinary discussion, if the liver metastases were responding to systemic treatment and were amenable to complete macroscopic resection. Five- and ten-year actual survivors were identified and their characteristics were explored. **Results:** From 1984 to 2020, 207 female patients underwent liver resections for MBC in our institution. There was no postoperative mortality. Postoperative complication rate was 23.3% and liver-specific complication rate was 19.0%. There was a total of 48 repeat hepatectomies. Median disease-free interval between initial breast cancer and liver metastasis was 36 ± 90.1 months. There was a median of 2 ± 1.8 liver metastases at diagnosis with a median size of 33.0 ± 18.3 mm and 73.1% of patients had radiological response before resection. Five- and ten-year overall survivals (OS) as well as 5- and 10-year disease-free survivals (DFS) were 39.6% and 12.7% as well as 14.2% and 6.4%, respectively. Median OS was 44.0 ± 47.2 months in the whole series. Focusing on the 5- and 10-year survivors, median OS were 89.5 ± 44.7 months and 144.0 ±42.6 months, respectively. In the 10-year survivors' group, median DFS was 98 ±62.3 months. Observed survivals in this study underestimate true actual survivals owing to censoring of patients lost to follow-up. **Conclusions:** Long-term survival (≥ 5 years) as well as a curative perspective (≥ 10 years survival) are achievable for selected patients with breast cancer liver metastases by combining surgery to systemic treatment. Considering the recent improvements in the results of systemic treatments, introducing surgical resection in the treatment sequences of MBC could play an even more beneficial role. Research Sponsor: None.

1100 **Poster Session**

Subgroup analysis of patients with no prior chemotherapy in EMERALD: A phase 3 trial evaluating elacestrant, an oral selective estrogen receptor degrader (SERD), versus investigator's choice of endocrine monotherapy for ER+/HER2-advanced/ metastatic breast cancer (mBC).

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Background: EMERALD demonstrated significantly prolonged progression-free survival (PFS) and a manageable toxicity profile for elacestrant vs standard of care endocrine therapy (SOC) in patients with ER+/HER2- mBC following progression on prior endocrine and CDK4/6 inhibitor therapy. Benefit was observed in the overall study population and in patients with *ESR1* mutations *(mESR1)*. Here, we report a subgroup analysis from EMERALD in patients with no prior chemotherapy. **Methods:** EMERALD (NCT03778931) is a randomized, open-label, phase 3 trial that enrolled patients with ER+/HER2– mBC who had 1–2 lines of endocrine therapy, mandatory pretreatment with a CDK4/6 inhibitor, and ≤1 chemotherapy. Patients were randomized 1:1 to elacestrant (400 mg orally daily) or SOC (investigator's choice of fulvestrant or aromatase inhibitor). Primary endpoints were PFS in all patients and patients with *mESR1*. In this analysis, we compared PFS between elacestrant and SOC in patients without prior chemotherapy. **Results:** Among the 477 patients enrolled in the trial, 77.8% (n = 371) had not received prior chemotherapy for mBC (median age = 64). Among patients without prior chemotherapy, treatment with elacestrant was associated with significantly prolonged PFS compared to SOC in both the overall population (hazard ratio [HR] = 0.68 [95% CI, 0.52-0.89] P = 0.004; median PFS 3.7 vs 2.0; 6-mo PFS 38% vs 23%; 12-mo PFS 27% vs 12%), and patients with *mESR1* (HR = 0.54 [95% CI, 0.36-0.80] P = 0.002; median PFS 5.3 vs 1.9; 6-mo PFS 44% vs 24%; 12-mo PFS 31% vs 12%). Key treatment-related adverse events (AEs) in the no prior chemotherapy elacestrant group were nausea (25.9%), fatigue (12.7%), and hot flush (11.1%). There were no treatment-related deaths in either group. **Conclusions:** Among patients with ER+/HER2– mBC without prior chemotherapy, elacestrant significantly prolonged PFS compared to SOC endocrine therapy and showed favorable outcomes in this subgroup. Clinical trial information: NCT03778931. Research Sponsor: Radius Health, Inc and the Menarini Group.

1101 **Poster Session**

Clinical and radiographic characteristics of patients with metastatic breast cancer and pseudocirrhosis: A single-center retrospective cohort study.

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Background: Pseudocirrhosis is a term used to describe changes in hepatic contour that mimic cirrhosis radiographically, but lack the classic pathologic features of cirrhosis. This radiographic finding is frequently found in patients with metastatic breast cancer (MBC); the pathophysiology and clinical consequences are poorly understood. The objective of this study is to describe the patient, tumor, and treatment characteristics associated with pseudocirrhosis, and to assess associated clinical outcomes. **Methods:** In this retrospective study, we identified patients with MBC and imaging findings consistent with pseudocirrhosis (diffuse liver contour abnormalities) who were treated at the University of California San Francisco from 2002-2021. We used chart extraction and radiology review to determine demographic characteristics, treatment history, response to treatment, imaging features, and complications of pseudocirrhosis. Comparisons between groups were made using the unpaired t-test or two-sided Fisher's exact test. **Results:** 120 patients with MBC and radiographic evidence of pseudocirrhosis were identified with the following BC subtypes: Hormone receptor (HR) positive, HER2 negative (n = 99, 82.5%), HR+/HER2+ (n = 14, 11.7%), HR-/HER2+ (n = 3, 2.5%), and triple negative (TNBC; n = 4, 3.3%). All patients with pseudocirrhosis had liver metastases (n = 120, 100.0%) and 82.5% (n = 99) had > 15 lesions. Median time from diagnosis of MBC to radiographic evidence of pseudocirrhosis was 29.2 months. Most patients received chemotherapy for MBC prior to the finding of pseudocirrhosis (n = 111, 92.5%) with median 2.0 lines. Pseudocirrhosis was observed in the setting of stable or responding disease in 50% of patients (n = 60). Patients received a median of 1.0 line of additional therapy after pseudocirrhosis diagnosis, with a median overall survival of 7.9 months from pseudocirrhosis to death. Sequelae of pseudocirrhosis included the radiographic finding of ascites (n = 97, 80.8%), gastric/esophageal varices (n = 68, 56.7%), splenomegaly (n = 26, 21.7%), GI bleeding (n = 12, 10.0%), or hepatic encephalopathy (n = 11, 9.2%). Radiographic evidence of ascites was associated with a shorter survival from MBC diagnosis compared to no ascites (42.8 vs. 76.2 months, p = < 0.001). GI/Hepatology consultation was uncommon (n = 9, 7.5%). **Conclusions:** To our knowledge, this is the largest reported case series of patients with MBC and pseudocirrhosis. Nearly all patients had HR+ disease and extensive liver metastases. Pseudocirrhosis was frequently observed in the setting of responding or stable disease, creating complexity in management. Survival was short in all patients, particularly patients with radiographic evidence of ascites. Further understanding of the pathogenesis of and risk factors for pseudocirrhosis could help improve outcomes for this condition. Research Sponsor: None.

1102 **Poster Session**

A multiple center, open-label, single-arm, phase II clinical trial of MRG002, an HER2-targeted antibody-drug conjugate, in patients with HER2-low expressing advanced or metastatic breast cancer.

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Background: MRG002 is a novel HER2-targeted ADC, composed of a sugar-modified trastuzumab, MMAE payload and a cleavable vc-linker. MRG002 was effective in HER2-low expressing breast cancer in preclinical studies. Hence, we conducted the phase II study to evaluate the safety and anti-tumor efficacy of MRG002 in HER-low breast cancer. **Methods:** HER2 low tumor expression was determined by a central lab and had to be immunohistochemistry (IHC)1+ or 2+/ISH-. Eligible patients had advanced/metastatic HER2-low expressing breast cancer that failed standard therapies. MRG002 was administered intravenously once every 3 weeks at the dose of 2.6 mg/kg, until disease progression or unacceptable toxicity which ever occurred first. The primary endpoint was objective response rate (ORR) assessed by independent review committee (IRC). The secondary endpoints were progression-free survival (PFS), disease control rate (DCR), and safety. **Results:** A total of 56 female patients with HER2-low advanced or metastatic breast cancer were enrolled at the time of data cut-off (Dec 31, 2021) and had received at least one cycle of MRG002. The median age was 55 (30-72) years. Most patients were HER2 IHC1+ (83.9%), hormone receptor positive (HR+) (85.7%), and with a ECOG PS of 1 (57.1%). Twenty-eight patients (50.0%) had received at least 2 lines of chemotherapy and the median treatment was 3. Forty-one patients (73.2%) had visceral metastasis and 31 patients (55.4%) had bone metastasis. The ORR and DCR in 49 evaluable patients were 34.7% and 75.5%, with 17 PR, 20 SD and 12 PD. Subgroup analysis indicated that the ORR was 39.5% (15/38) and DCR was 76.3% (29/38) among the evaluable patients with visceral metastasis. The tumor responses were similar in both the HER2 IHC 1+ and IHC 2+ subgroups, as is 34.1% and 37.5% respectively, which might be attributed to fewer IHC 2+ enrollment in this trial. Although only 8 HR- subjects enrolled in our study, the ORR (37.5%) and DCR (62.5%) is promising in these triple negative BC patients post to ≥2 line therapies. Most common treatment related adverse events (TRAEs) were grade 1 or 2. The most common TRAEs (≥20%) were neutrophil count decreased (53.6%), white blood cell count decreased (48.2%), AST increased (46.4%), alopecia and ALT increased (39.3%), blood lactate dehydrogenase increased(33.9%), GGT increased (32.1%), nausea (32.1%), vomiting (23.2%), constipation (23.2%), diarrhea(23.2%) and hyperglycemia (21.4%). Most common grade ≥3 TRAE(≥10%) was neutrophil count decreased(14.3%). No patients died due to MRG002. **Conclusions:** MRG002 shows promising efficacyand well tolerated in patients with HER2-low breast cancer. Further evaluation is underway. Clinical trial information: NCT04742153. Research Sponsor: Shanghai Miracogen Inc.

Patient-reported outcomes for measuring the quality of life in advanced breast cancer treated with third-line and beyond chemotherapy-based regimens: A national cross-sectional study.

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Background: Prolongation of survival and maintenance of quality of life (QoL) are the primary therapeutic goals in advanced breast cancer. Around 10% of adverse events (AEs) in the CTCAE are symptomatic AEs (e.g., nausea, sensory neuropathy), which can severely and directly affect the QoL of patients. However, seldom evidence mapped the QoL and symptomatic AEs utilizing patient-reported outcomes (PROs) in heavily pretreated breast cancer patients. This study aimed to investigate the PROs for measuring the QoL and symptomatic AEs of advanced breast cancer treated with third-line and beyond chemotherapy-based regimens in China. **Methods:** This national survey enrolled patients with advanced breast cancer receiving third-line and beyond chemotherapy-based regimens in 59 centers all over China from March to April in 2021. Each patient filled out a questionnaire containing demographic information, medical history, EORTC-QLQ-C30, and symptomatic AEs. The symptomatic AEs included fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, alopecia, fever, and limb numbness. The range method was used for the linear conversion of the PRO scores, which were converted into standardized scores of 0 to 100. **Results:** This study enrolled 1015 patients with the median age of 52 years. The QoL of all patients were poor, with the global health status score of 52.4±17.7 (Table). All the symptomatic AE scores were low among the patients. However, no significant differences were observed in global health status and symptomatic AEs between mono-chemotherapy and multi-agent chemotherapy (All $P>0.05$). **Conclusions:** The QoL of advanced breast cancer patients treated with third-line and beyond chemotherapy were poor, especially in symptomatic AEs. In addition, the EOTRC-QLQ-C30 scale appears to underestimate the differences in symptomatic AEs between mono-chemotherapy and multi-agent chemotherapy, probably due to a lack of sensitivity of the scale, which fails to match the actual clinical observations of the PROs and QoL. Therefore, new scales need to be developed for the evaluation of symptomatic AEs and QoL in advanced breast cancer.
Research Sponsor: Nature Science Foundation of China (82103634).

The comparation of the scores of QoL and symptomatic AEs between mono-chemotherapy and multi-agent chemotherapy.

Symptomatic AEs	All (n=1015)	Mono-chemotherapy (n=784)	Multi-agent chemotherapy (n=231)	*P* value
Global Health Status	52.4±17.7	52.0±17.8	53.8±17.4	0.319
Fatigue	43.0±25.8	42.8±26.3	43.8±24.2	0.622
Nausea and vomiting	47.7±28.7	48.4±28.9	45.4±27.9	0.155
Pain	48.2±27.8	47.9±28.2	49.5±26.3	0.503
Insomnia	42.8±30.7	43.1±30.4	42.0±31.6	0.518
Appetite loss	45.4±29.4	45.9±29.5	43.7±29.1	0.330
Diarrhea	55.9±32.6	55.6±32.4	57.0±33.6	0.567
Alopecia	37.0±31.6	36.5±31.1	38.4±33.3	0.534
Limb numbness	47.5±30.8	47.3±30.9	48.3±30.7	0.654

1104 **Poster Session**

A novel oral paclitaxel and HM10381 (oraxel)-treated metastatic breast cancer: A phase I study (KX-ORAX-CN-007).

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Background: This phase I study assessed the pharmacokinetics, safety, antitumor activity of oral paclitaxel and HM10381 (Oraxel) in patients with metastatic breast cancer. **Methods:** Oraxol (oral paclitaxel 205 mg/m^2 plus HM30181A 15 mg) daily for 3 consecutive days weekly for up to 16 weeks was administered to patients. The primary objective endpoint was pharmacokinetic analysis. The secondary endpoint were objective response rate (ORR) and safety. For pharmacokinetic analysis, timed blood samples were collected. **Results:** Twenty-four female patients were enrolled from Apr 2019 to Aug 2019. The median age was 53 years (range: 35 to 70 years). The mean lines and median line of treatment were 2.5 and 2, respectively. Previous breast cancer treatments included chemotherapy in 23 (96%) patients, hormonal therapy in 20 (83%) patients. Prior taxanes therapy was reported in 20 (83%) patients. There were 15 patients in efficacy dataset. The best ORR (Investigator) was PR in 40%, SD in 53%, and PD in 7%. The best overall response rate (ICRRC) was PR in 36%, SD in 57%, and PD in 7% of patients. There were no hypersensitivity-type reactions. Adverse events of interest neutropenia, neurotoxicity, and diarrhea were reported as 20 (83%), 7 (29%) and 11 (46%), retrospectively. A total of 15 (63%) patients experienced Grade ≥3 TEAEs, including neutrophil count decreased in 11 (46%) patients, WBC count decreased in 8 (33%) patients. Treatment related SAE was reported in 1 (4.17%) patient experienced febrile neutropenia, pneumonia, and septic shock. The PK data indicated that the efficacy response is not associated with oral paclitaxel exposure parameters AUC or Cmax. **Conclusions:** The study showed that Oraxol as novel oral chemotherapy agent shows promising antitumor activity in patients with metastatic breast cancer, manageable toxicity, and no hypersensitivity-type reactions. Clinical trial information: NCT04993040. Research Sponsor: Athenex Pharmaceuticals (Chong Qing) Limited.

1105 **Poster Session**

Impact of an individualized counseling program on weight loss and quality of life in breast cancer survivors.

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Background: Survivors of breast cancer who are obese have a greater than two-fold increase in mortality compared to their counterparts. We assessed the feasibility of an individualized nutrition counseling and exercise program with the goal of helping participants achieve a loss of 10% body weight. Secondary endpoints included impact on multiple metabolic parameters, cardiovascular health, and quality of life. **Methods:** We present preliminary data from a single-arm pilot trial (NCT04365569) whereby survivors of breast cancer with BMI $\geq$ 25 kg/m^2 participated in a 6-month, individualized counseling program. A registered dietitian (RD) counseled patients based upon recommendations by the American Cancer Society. The intervention included in-person (baseline, months 3 and 6) and telephone visits (months 1, 2, 4, and 5). The nutrition component included weight and body composition measures and blood work, including lipid panel and hemoglobin A1c. Cardiovascular fitness and extrapolated VO2 max were measured using SHAPE study. Quality of life was evaluated using: the Functional Assessment of Cancer Therapy – Breast Cancer (FACT-B), the Brief Pain Inventory (BPI), the Generalized Anxiety Disorder-7 (GAD-7), the Patient Health Questionnaire-9 (PHQ-9), and the NCCN Distress Thermometer. Paired statistics were used to compare changes in these aforementioned outcomes pre-and post-intervention. **Results:** A total of n=55 female breast cancer survivors (mean age 58.1± 9.13) were enrolled. N=28 completed the trial to date. While 14.3% of participants lost >10% of their baseline weight, 21.4% lost 5-10 % of their weight. Patients had a mean 45.30% drop in body fat composition overall ($p<0.001$). There was no statistically significant difference in lipids and hemoglobin A1c. In terms of cardiovascular function, a decline in mean VO_2 max of -4.71 (SD 4.71, $p <0.001$) was observed, accompanied by a decline in mean METS of -1.09 (SD 0.84, $p <0.001$). Higher compliance with the intervention was associated with losing weight (p 0.001). FACT-B scoring revealed improvements in Physical (mean +1.92, SD 3.82), Emotional (mean +1.03, SD 2.71), and Functional well-being (mean +2.70, SD 4.34) ($p <0.05$). This trial was also associated with lower indicators of depression, as evaluated by PHQ-9 scoring (mean -1.32, SD 3.19, p 0.038). Even in patients with weight gain, improvements in QoL surveys were observed, although not statistically significant, likely due to the small sample size in this subpopulation (n = 7). **Conclusions:** An individualized counseling program benefits survivors of breast cancer who are overweight by helping them reduce weight and improve their overall quality of life. While no improvements in VO2 max levels were observed, this may be partially explained by a decrease in effort on the part of participants. Further investigation into the utility of extrapolated VO2 max using the SHAPE study is ongoing. Clinical trial information: NCT04365569. Research Sponsor: Weston, Florida Internal Research.

1106 **Poster Session**

Optimal timing and interval of imaging for metastatic breast cancer.

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Background: Breast cancer is a family of diseases with varying disease trajectories based on intrinsic biology of the tumor. The time of progression varies across & within subtypes, and with increasing rates of drug resistance depending on prior therapeutic exposure. There is no strong consensus about optimal surveillance and routine imaging in patients with metastatic breast cancer (mBC), but many oncologists report that monitoring strategies are based on strategies used in clinical trials. **Methods:** We reviewed 17 prior Phase III studies that led to FDA approval in mBC. We reviewed 8 studies for ER+ mBC, 5 studies for HER2+ mBC, 2 studies for triple negative (TNBC) mBC, and 2 studies for BRCA+ mBC. We calculated rates of progression or death (POD) per month for the first year on therapy using data from survival analysis tables and compared them across the different types and lines of therapy. **Results:** Risk of progression in mBC varies based on receptor status and line of therapy (Table). There was a significant difference in POD rates between ER+ therapies compared with all other disease types (HER2+, TNBC, BRCA) ($p = 0.012$). Patients with TNBC or receiving PARP inhibitors or later line HER2 therapies had higher POD rates than those with ER+ breast cancer or receiving first line HER2 therapy (6.9% vs 4.1% per month; $p = 0.0004$). No significant difference was seen in the monitoring frequency between ER+ and HER2+ disease ($p = 0.39$). **Conclusions:** These data suggest that shorter interval imaging should be performed for patients with TNBC or receiving PARP inhibitors or later line HER2 therapies. Surveillance imaging for patients with mBC should be based on disease biology, number of prior regimens, time since initiation of therapy, and regimen efficacy. Current imaging recommendations are not data-based and do not adjust for new agents that have been approved. Oncologists should integrate these into individualized estimates to determine optimum frequency of imaging in clinical practice and research. Research Sponsor: None.

Disease Type	Trial Name	Line of Therapy	Treatment	Treatment Arm: Risk of progression or death/ month	Control	Control Arm: Risk of progression or death/ month	Monitoring frequency (Every X Weeks)	Median PFS (months)
ER+	PALOMA2	First	Palbociclib + AI	3.10%	AI	4.20%	12	24.8
ER+	MONARCH3	First	Abemaciclib + AI	3.13%	AI	4.19%	8	28.2
ER+	MONARCH2	Subsequent	Abemaciclib + Fulvestrant	4.00%	Fulvestrant	5.30%	8	16.4
ER+	BOLERO2	Subsequent	Everolimus + AI	3.51%	AI	5.06%	6	6.9
HER2+	CLEOPATRA	First	Pertuzumab + Trastuzumab + Docetaxel	3.36%	Trastuzumab + Docetaxel	5.14%	9	18.5
HER2+	HER2CLIMB	Subsequent	Tucatinib + Trastuzumab + Capecitabine	7.29%	Trastuzumab + Capecitabine	8.02%	6-9	7.8
Triple Negative	KEYNOTE 355	First	Carboplatin + Gemcitabine + Pembrolizumab	6.60%	Taxanes + Platinum	7.18%	8	9.7
Triple Negative	ASCENT	Subsequent	Sacituzumab Govitecan	7.62%	Single Agent Chemotherapy	8.27%	6	5.6
BRCA+	OLYMPIAD	Subsequent	Olaparib	6.71%	Single Agent Chemotherapy	7.65%	6	7

TPS1107 **Poster Session**

EPIK-B4: A phase 2, randomized study of metformin (MET) extended release (XR) +/- dapagliflozin (DAPA) to prevent hyperglycemia (HG) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), *PIK3CA*-mutated (mut) advanced breast cancer (ABC) treated with alpelisib (ALP) and fulvestrant (FUL).

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Background: ALP (α-selective PI3K inhibitor and degrader) is approved with FUL for pts with *PIK3CA*-mut HR+, HER2– ABC. HG is a known on-target effect of PI3K inhibition, manageable with oral anti-HG agents such as MET and dose interruptions/modifications of ALP and reversible upon discontinuation of ALP. Although HG management guidelines were refined throughout the SOLAR-1 and BYLieve studies evaluating ALP + FUL/letrozole, there remains a need for optimized strategies beyond initial MET therapy that offers earlier and more sustained improvement of HG, particularly for pts at an increased risk for severe HG. In preclinical models, the addition of a SGLT2 inhibitor to ALP (+/– MET) reduced HG while maintaining ALP efficacy. The aim of this study is to evaluate the safety and efficacy of prophylactic MET XR +/– the SGLT2 inhibitor DAPA in reducing severe HG in pts with *PIK3CA*-mut HR+, HER2– ABC on ALP + FUL with an increased risk for severe HG (grade $\geq$ 3) on ALP. **Methods:** EPIK-B4 is a Phase II, randomized (1:1), open-label, active-controlled study assessing the efficacy and safety of MET XR +/– DAPA (starting at Cycle 1 Day 1 [C1D1]) with ALP (300 mg orally [PO], once daily [QD], starting at C1D8) + FUL (500 mg intramuscularly on C1D1, C1D15, and D1 of subsequent cycles) in pts (N $\approx$ 132) with HR+, HER2–, *PIK3CA*-mut ABC after progression on/after endocrine-based treatment (Tx). MET XR is administered PO starting at 500 mg QD (titrated up to 2 g QD) and MET XR + DAPA starting at 500 mg and 5 mg QD (titrated up to 2 g and 10 mg QD), respectively. Eligible pts include adult men or postmenopausal women with confirmed HR+, HER2–, *PIK3CA*-mut ABC and $\geq$ 1 risk factor for severe HG (diabetes [fasting plasma glucose (FPG) $\geq$ 126 mg/dL and/or HbA1c $\geq$ 6.5%], prediabetes [FPG $\geq$ 100 to < 126 mg/dL and/or HbA1c 5.7% to < 6.5%], obesity [BMI $\geq$ 30], age $\geq$ 75 years); prior endocrine-based Tx (eg, FUL or oral SERD) was permitted. Randomization is stratified by baseline diabetes status. Key exclusion criteria include > 1 line of Tx in the metastatic setting; prior chemotherapy (metastatic setting) or PI3K, mTOR, or AKT inhibitor; type I or II diabetes requiring Tx; or antecedent of pancreatitis or severe cutaneous reaction. The primary endpoint is the occurrence of severe HG (grade $\geq$ 3 [glucose > 250 mg/dL] based on laboratory assessments) over the first 8 weeks of ALP + FUL. Secondary endpoints include progression-free survival, overall response and clinical benefit rates with confirmed response, safety, and tolerability. A biomarker analysis is planned as an exploratory objective. Recruitment is ongoing with enrollment planned in 56 sites across 8 countries; completion of primary data collection is anticipated in 2023. Clinical trial information: NCT04899349; EUDRACT#2021-001908-15. Research Sponsor: Novartis Pharmaceuticals Corporation.

TPS1108 **Poster Session**

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

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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 (pts) 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 pts with HER2+ MBC and was well tolerated. Adding tucatinib also reduced the risk of disease progression or death in pts 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 pts will be enrolled. Eligible pts will have advanced HER2+ disease, no progression on 4–8 cycles of prior 1L SOC, ECOG 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. Pts will be randomized 1:1 to receive either tucatinib or placebo twice daily, with T+P once every 21 days. Pts with HR+ disease may receive endocrine therapy. The primary endpoint is investigator-assessed PFS. Secondary endpoints include OS (key endpoint), 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, with additional sites planned. Clinical trial information: NCT05132582. Research Sponsor: Seagen.

TPS1109 **Poster Session**

EPIK-B5: A phase III, randomized study of alpelisib (ALP) plus fulvestrant (FUL) in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), *PIK3CA*-mutated advanced breast cancer (ABC) progressing on/after an aromatase inhibitor (AI) with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i).

Michelino De Laurentiis, Luis Costa, Joseph Gligorov, Ann Knop, Elzbieta Senkus-Konefka, José A. García-Sáenz, Peter Schmid, Aurelia Heniquez, Paolo Serra, Albert Reising, Sherko Kuemmel; Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale"-Breast Oncology Unit, Naples, Italy; Hospital Santa Maria, Lisbon, Portugal; Institut Universitaire de Cancérologie AP-HP, Sorbonne Université, Paris, France; Copenhagen University Hospital, Copenhagen, Denmark; Medical University of Gdańsk, Gdańsk, Poland; Instituto de Investigación Sanitaria Hospital Clinico San Carlos (IdISSC), Madrid, Spain; Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Novartis Pharma AG, Basel, Switzerland; Kliniken Essen-Mitte, Essen, Germany

Background: Endocrine therapy (ET) + CDK4/6i is standard of care for HR+, HER2– ABC; however, CDK4/6i resistance, in which the phosphatidylinositol-3-kinase (PI3K) pathway has a key role, remains challenging. Progression-free survival (PFS) for ≥ 2nd-line ET monotherapy post CDK4/6i is poor; prognosis may be worse in patients with a *PI3KCA* mutation. ALP (PI3K-α selective inhibitor and degrader) + FUL is approved by the European Medicines Agency (EMA) for HR+, HER2–, *PIK3CA*-mutated ABC after ET monotherapy. Outside the EMA, ALP + FUL approval includes post-CDK4/6i use. ALP + FUL has shown clinical activity and consistent safety in a small subpopulation in SOLAR-1 with prior CDK4/6i treatment (n = 9) and in BYLieve Cohort A (CDK4/6i + AI as immediate prior treatment; n = 121). The EPIK-B5 study aims to confirm the efficacy and safety of ALP + FUL in a larger population with HR+, HER2–, *PIK3CA*-mutated ABC with prior CDK4/6i + AI treatment. **Methods:** EPIK-B5 is a Phase III, randomized (1:1), double-blind, placebo-controlled study assessing the efficacy and safety of ALP (300 mg/d orally starting Cycle 1 Day 1 [C1D1]) + FUL (500 mg intramuscularly on C1D1 and C1D15, and D1 of subsequent cycles) in patients (N ≈ 234) with HR+, HER2–, *PIK3CA*-mutated ABC progressing on/after CDK4/6i + AI. Patients randomized to placebo + FUL can cross over to ALP + FUL after progression. Randomization is stratified by presence of lung and/or liver metastasis and prior CDK4/6i setting. Adult men or postmenopausal women with confirmed HR+, HER2–, *PIK3CA*-mutated ABC and ≥ 1 measurable lesion are eligible. The primary endpoint is PFS per blinded independent review committee assessment. Secondary endpoints include overall survival, overall response and clinical benefit rates, duration of and time to response, PFS by *PIK3CA*-mutation status in circulating tumor DNA, PFS on next-line treatment, time to definitive deterioration of ECOG status, quality of life (QoL), and safety and tolerability. Exploratory endpoints include biomarker analyses, additional QoL endpoints, and time to subsequent chemotherapy. Recruitment is ongoing, with enrollment planned over 2 years in 18 countries; completion of primary data collection is anticipated in 2026. Clinical trial information: NCT05038735; EUDRACT2021-001966-39. Research Sponsor: Novartis Pharmaceuticals Corporation.

TPS1110 **Poster Session**

A randomized, multicenter, placebo-controlled, phase III study to evaluate the efficacy and safety of HER2/neu peptide GLSI-100 (GP2 + GM-CSF) in patients with residual disease or high-risk PCR after both neo-adjuvant and postoperative adjuvant anti-HER2 therapy, Flamingo-01.

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Background: GP2 is a biologic nine amino acid peptide of the HER2/*neu* protein delivered in combination with Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) that stimulates an immune response targeting HER2/neu expressing cancers, the combination known as GLSI-100. In a prospective, randomized, single-blinded, placebo-controlled, multicenter Phase IIb study, no recurrences were observed in the HER2+ population after 5 years of follow-up, if the patient was treated with GLSI-100, survived and was followed from more than 6 months ($p = 0.0338$). Immunotherapy elicited a potent response measured by skin tests and immunological assays. Of the 146 patients that have been treated with GLSI-100 over 4 clinical trials, GLSI-100 was well-tolerated and no serious adverse events were observed considered related to the immunotherapy. **Methods:** This Phase 3 trial is a prospective, randomized, double-blinded, multi-center study. After 1 year of trastuzumab-based therapy, 6 intradermal injections of GLSI-100 or placebo will be administered over the first 6 months and 5 subsequent boosters will be administered over the next 2.5 years for a total of 11 injections over 3 years. The participant duration of the trial will be 3 years treatment plus 1 additional year follow-up for a total of 4 years following the first year of treatment with trastuzumab-based therapy. Patients will be stratified based on residual disease status at surgery, hormone receptor status and region. Approximately 498 patients will be enrolled. To detect a hazard ratio of 0.3 in invasive breast cancer free survival (IBCFS), 28 events will be required. An interim analysis for superiority and futility will be conducted when at least 14 events have occurred. This sample size provides 80% power if the annual rate of events in placebo patients is 2.4% or greater. Up to 100 non-HLA-A*02 subjects will be enrolled in an open-label arm. Eligibility Criteria: The patient population is defined by these key eligibility criteria: HER2/neu positive and HLA-A*02; Residual disease or High risk pCR (Stage III at presentation) post neo-adjuvant therapy; Exclude Stage IV; Completed at least 90% of planned trastuzumab-based therapy. Trial Objectives: To determine if GP2 therapy increases IBCFS; To assess the safety profile of GP2; To monitor immunologic responses to treatment and assess relationship to efficacy and safety. Accrual: Site selection and study start-up is in progress at multiple sites. Target enrollment is 598 subjects. Clinical trial information: 05232916. Research Sponsor: Greenwich LifeSciences, Inc.

TPS1111 **Poster Session**

Phase 2 trial of tucatinib plus trastuzumab deruxtecan in patients with HER2+ locally advanced or metastatic breast cancer with and without brain metastases (HER2CLIMB-04, trial in progress).

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Background: Tucatinib is an oral reversible small-molecule tyrosine kinase inhibitor highly selective for human epidermal growth factor receptor 2 (HER2). Tucatinib is approved in the US for use in combination with trastuzumab and capecitabine in adult patients with HER2+ metastatic breast cancer (MBC), with and without brain metastases, who have received ≥1 prior anti–HER2-based regimens in the metastatic setting. Trastuzumab deruxtecan (T-DXd), an antibody–drug conjugate (ADC) comprising a HER2-directed monoclonal antibody conjugated to a topoisomerase I inhibitor payload, is also approved in the US for patients with HER2+ MBC. In HER2+ breast cancer (BC) xenograft models, tucatinib increased the antitumor activity of a HER2-directed ADC comprising a HER2-directed monoclonal antibody conjugated with 8 exatecan moieties (T-Ex) when compared to T-Ex alone (Kulukian et al 2019). While significant advances have been made in the treatment of patients with HER2+ BC, treatment of metastatic disease remains a clinical challenge due to limited treatment options. **Methods:** HER2CLIMB-04 (NCT04539938) is a single-arm, open-label, multicenter, phase 2 study evaluating the efficacy and safety of tucatinib plus T-DXd in previously treated patients aged ≥18 years with unresectable, locally advanced, or metastatic (LA/M) HER2+ BC. Patients must have prior treatment with a taxane and trastuzumab (with or without pertuzumab) in the LA/M setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including a taxane and trastuzumab (with or without pertuzumab). Patients with brain metastases, including active brain metastases, may be enrolled. A safety lead-in portion of the study with 10 patients who were followed for at least 1 cycle has been completed. This portion of the study demonstrated a manageable safety profile so the trial will enroll approximately 60 response-evaluable patients (including the 10 patients from the safety lead-in), evenly distributed between patients with and without brain metastases. The primary endpoint is confirmed objective response rate (cORR) by investigator assessment per RECIST 1.1. Secondary endpoints are progression-free survival (PFS), duration of response (DOR), disease control rate (DCR) by investigator assessment per RECIST 1.1, overall survival, and safety. Exploratory endpoints will include cORR, PFS, DCR, and DOR by independent central review per RECIST 1.1, pharmacokinetic analyses, biomarker analyses, and changes in patient-reported outcomes. Efficacy and safety will be summarized with descriptive statistics. Enrollment in the US began in late 2020. Clinical trial information: NCT04539938. Research Sponsor: Seagen.

TPS1112 **Poster Session**

Targeting HER2-positive metastatic breast cancer with ARX788, a novel anti-HER2 antibody-drug conjugate in patients whose disease is resistant or refractory to T-DM1, and/or T-DXd, and/or tucatinib-containing regimens.

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Background: The overexpression and/or amplification of human epidermal growth factor receptor 2 (HER2) occurs in approximately 20% of breast cancers (BC) and is a major driver of tumor development and progression. This HER2 subtype confers aggressive tumor behavior and the HER2 receptor remains a valuable target for antibodies, bi-specifics, and antibody drug conjugates (ADC). With advances in targeted therapy, patients with HER2-positive breast cancer (HER2+ BC) may experience an improved prognosis, including survival. Novel HER2-targeted therapies are being investigated to overcome drug resistance and to help mitigate adverse events (e.g., cardiotoxicity). ARX788 is a next-generation ADC using a technology platform whereby a HER2 specific monoclonal antibody is conjugated with Amberstatin269 (AS269), a potent cytotoxic tubulin inhibitor. Site-specificity, high homogeneity, and stable covalent conjugation of ARX788 leads to its slow release and prolonged peak of serum pAF-AS269, which may contribute to the lower systemic toxicity and increased targeted delivery of payload to tumor cells at a lower effective dose compared to other HER2 ADCs. Clinical activity has been seen in Phase I HER2 breast and pan-tumor studies. **Methods:** Trial Design: ACE-Breast-03 (NCT04829604) is a global, phase 2 study designed to assess anticancer activity and safety of ARX788 in patients with metastatic HER2 positive breast cancer. Patients whose disease is resistant or refractory to T-DM1, and/or T-DXd, and/or tucatinib-containing regimens are eligible. Patients must have adequate organ function. Any brain metastases must be radiographically stable without steroid dependence. Efficacy will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by imaging every 6 weeks on study. Endpoints include objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), best overall response (BOR), duration of response (DOR), and time to response (TTR). The safety and tolerability profile will be evaluated. Blood samples will be collected at specified time points to determine serum concentrations of ARX788, total antibody, and metabolite pAF-AS269. Potential predictive and/or prognostic biomarkers at baseline and on-treatment will be analyzed for exploratory purposes. Descriptive statistics will be used to evaluate anticancer activity, safety, and tolerability. The study is currently recruiting patients. Please contact breast03trialinquiry@ambrx.com for additional information. Clinical trial information: NCT04829604. Research Sponsor: Ambrx, Inc.

TPS1113 **Poster Session**

Targeting insulin feedback to enhance alpelisib (TIFA): A phase II randomized trial in metastatic, *PIK3CA*-mutant, hormone receptor–positive breast cancer.

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Background: Breast cancer is the most common malignancy among women in the U.S. and is a leading cause of cancer-related death. Among women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer, 45% harbor activating mutations in the *PIK3CA* gene, which induces hyperactivation of phosphatidylinositol 3-kinase (PI3K) and drives cell growth and survival. The SOLAR-1 trial found that the combination of alpelisib, a PI3K inhibitor, and fulvestrant, an endocrine therapy, significantly improved progression-free survival compared to fulvestrant alone, leading to Food and Drug Administration approval in *PIK3CA*-mutated metastatic breast cancer. While PI3K inhibition induces apoptosis of cancer cells, inhibition of this pathway in the liver and skeletal muscle impairs physiologic insulin signaling leading to hyperglycemia. This affects > 60% of patients, results in grade 3-4 hyperglycemia in 36% of patients, and is a major cause of interrupted/reduced dosing or discontinuation. In preclinical models, application of a very low carbohydrate (ketogenic) diet or a sodium-glucose cotransporter 2 inhibitor (SGLT2i), a commonly used diabetes medication, minimized hyperglycemia and improved the anti-tumor efficacy of PI3K inhibition. These interventions are safe and feasible in cancer patients but have not been studied for the prevention of PI3K inhibitor-associated hyperglycemia. **Methods:** We are conducting a multicenter phase II clinical trial (NCT05090358) in patients receiving standard-of-care alpelisib plus fulvestrant to test the efficacy of three interventions (n = 106): 1) ketogenic diet, 2) low-carbohydrate diet, or 3) canagliflozin (a SGLT2i) in preventing alpelisib-associated hyperglycemia. The goal of this study is to mitigate a major toxicity of PI3K inhibitors and maximize their clinical efficacy. Eligible patients must be postmenopausal and have histologically confirmed HR-positive, HER2-negative metastatic breast cancer, ≥1 activating *PIK3CA* mutations, measurable disease per RECIST v1.1 or at least one predominantly lytic bone lesion, recurrence or progression during or after endocrine-based therapy, ECOG performance status of 0-1, hemoglobin A1c < 8%, and fasting blood glucose < = 140mg/dL. Prior CDK4/6 inhibitor use is allowed. The primary endpoint is the grade 3-4 hyperglycemia-free rate at 12 weeks. Secondary endpoints include the 6- and 12-month overall response rate, 6- and 12-month progression-free survival, alpelisib adherence, changes in systemic hormones and metabolites related to glucose homeostasis, changes in body composition, and quality of life. The first patient was enrolled on October 15, 2021. Participating sites include Memorial Sloan Kettering Cancer Center, Weill Cornell Medical Center, and the Ohio State University Wexner Medical Center. Clinical trial information: NCT05090358. Research Sponsor: Novartis.

TPS1114 **Poster Session**

A phase II, single-arm, non-randomized study of alpelisib (BYL719) in combination with continued endocrine therapy following progression on endocrine therapy in hormone receptor–positive, HER2-negative, *PIK3CA*-mutant metastatic breast cancer: A Big Ten Cancer Research Consortium Study (btcrc-BRE19-409).

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Background: The PI3K pathway is frequently altered in hormone receptor positive (HR+) breast cancer (BC) and 40% of patients have *PIK3CA* mutations. The PI3Kα-specific inihibitor, Alpelisib, is FDA-approved in combination with fulvestrant for treatment of patients with HR+ HER2 negative (HER2-) *PIK3CA* mutated, advanced BC following progression on or after a non-fulvestrant endocrine therapy (ET) based regimen. We hypothesized that the benefit seen in the seminal SOLAR-1 study that compared alpelisib plus fulvestrant to placebo with fulvestrant, was due to the addition of alpelisib, rather than the change to fulvestrant, such that addition of alpelisib to ongoing ET at time of progression could lead to similar outcomes. Unlike SOLAR-1, our study continues prior ET at time of progression and requires prior CDK4/6 inhibitor therapy. **Methods:** We designed a phase II single arm study that tests the efficacy of adding alpelisib to ongoing ET at time of progression on ET. The primary objective is to estimate the progression–free survival (PFS) of alpelisib with continued ET (aromatase inhibitor or fulvestrant) following progression in patients with HR+ HER2-, *PIK3CA* mutant advanced BC. Secondary objectives are to estimate overall response rate, clinical benefit rate, duration of response, overall survival and safety/tolerability. Correlative studies include evaluation of PIK3CA activity in circulating tumor cell liquid biopsy at baseline, C1D15, C2D1, C4D1 and at progression and correlation with primary and secondary objectives. Eligibility: Men and postmenopausal female patients with histologically confirmed ER and/or PR $\geq$1%, HER2- metastatic or unresectable BC with *PIK3CA* mutation and either measurable disease or at least one predominantly lytic bone lesion. No more than two lines of ET and no chemotherapy in the metastatic setting is allowed and patients must have received treatment with a CDK4/6 inhibitor and have progressed on ET as last line of therapy. Exclusions include prior *PIK3CA*, *mTOR* or *AKT* inhibitors in the metastatic setting, symptomatic active CNS metastases or CNS metastases that require therapeutic interventions. Statistical Analysis. The sample size calculation is based on testing the null hypothesis that the median PFS is at most 5 months against the alternative that the PFS is greater than 5 months (based on data from SOLAR-1). An increase of at least 3 months in the median PFS will be considered a sufficient efficacy signal. A sample size of 44 subjects is required to detect an anticipated increase in the median PFS from 5 to 8 months at the one-sided 0.10 significance level with 90% power, assuming a uniform accrual period of 24 months. Clinical trial information: NCT04762979. Research Sponsor: NOVARTIS, The Kerry Taylor Memorial fund.

TPS1115 **Poster Session**

A multicenter, open-label, phase 2 study of odetiglucan (IMPRIME PGG) and pembrolizumab in patients with metastatic breast cancer (mBCA) who have progressed through prior hormonal therapy.

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Background: Hormone receptor (HR) positive/ human epidermal growth factor receptor 2-negative (Her2-) breast cancer is generally considered 'immunologically cold' in comparison to TNBC or Her2+ breast cancer. Keynote-028 results showed a modest ORR of 12% to anti-PD1 antibody, pembrolizumab (PEM) in previously treated HR+/ HER2-/programmed death ligand 1-positive (PD-L1-positive) advanced breast cancer patients (pts). With limited options available, there is significant unmet need to expand clinical benefit from ICI. Odetiglucan, a novel beta glucan, acts as a pathogen-associated molecular pattern (PAMP) that drives a cascade of immune activating events. It repolarizes the immunosuppressive microenvironment, activates the maturation of antigen presenting cells and significantly enhances efficacy of ICI therapy in preclinical tumor models. In a Ph2 trial (IMPRIME 1) of odetiglucan + PEM in 44 pts with heavily pretreated metastatic TNBC, an ORR=15.9%, DCR=54.5%, mDOR=12.7mo, mPFS=2.86 mo, 12 mo OS rate=57.6%, and mOS=16.4 mo were observed. Clinical benefit was particularly evident in a subset of pts, mTNBC "converters" (12/44 pts) who were originally diagnosed with ER/PR+ disease and progressed through endocrine therapies +/- CDK4/6 inhibitors. In these 12 pts, an ORR=50%, DCR=83%, mDOR=11.2, mPFS=5.6 mo, 12-mo OS rate=64.8%, and mOS=17.4 mo were observed. **Methods:** Odetiglucan + PEM is now being explored in pts with hormone-resistant metastatic breast cancer (MBC). This is a phase 2, Simon's 2-Stage study of MBC pts who have progressed through prior hormonal therapy with >1 CDK4/6 inhibitor. Pts will receive odetiglucan 4 mg/kg/wk + PEM 200 mg Q3wk. Stage 1 will enroll 23 pts. If >4 pts have an objective response after 12 wks of treatment, the study will proceed to Stage 2 enrolling an additional 24 pts (N=47). Rejection of the null hypothesis requires >10 objective responses. Main eligibility criteria include: MBC having failed prior hormonal therapy with >1 CDK4/6 inhibitor, <2 chemotherapies, serum ABA ≥20 μg/mL, and no prior ICI exposure. Primary endpoint is ORR (RECIST v1.1); secondary endpoints are PFS, OS, DCR, DoR, and safety. Exploratory objectives assess impact of the treatment combination on immune activating events in peripheral blood and tumor biopsies, and correlate tumor microenvironmental changes with clinical benefit Select subpopulations may be explored. Point estimates with 95% confidence intervals (CIs) of ORR and DCR will be computed. Medians, first, and third quartiles with 95% CI will be estimated using Kaplan-Meier method for other secondary endpoints. Safety parameters will be summarized. The trial is sponsored by HiberCell, Inc. in collaboration with Merck & Co. ~25 US sites will participate. Clinical trial information: NCT05159778. Research Sponsor: HiberCell, Inc.

TPS1116 **Poster Session**

DOLAF: An international multicenter phase II trial of durvalumab (MEDI4736) plus olaparib plus fulvestrant in patients with metastatic or locally advanced ER-positive, HER2-negative breast cancer selected using criteria that predict sensitivity to olaparib.

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Background: PARP inhibitors have documented clinical activity in patients with HER2 negative breast cancer (BC) and a germline pathogenic variant (PV) in *BRCA1* or *BRCA2*. Defects in other genes involved in homologous recombination DNA repair (HRR) or mismatch repair pathway (microsatellite instability MSI) have been associated with preclinical cellular sensitivity to PARP inhibitors. Several preclinical and clinical studies have suggested synergy between immune checkpoint blockade and PARP inhibitors. Indeed, tumors with deficiency in HRR have higher mutagenic potential and produce a larger number of neoantigens. Around 60% of BC with a germline PV in *BRCA1/2* are ER+/HER2- tumors, and the ER-pathway remains a key target of their therapy. The combination of PARP inhibitors with endocrine therapy has shown to be superior to monotherapy. **Methods:** DOLAF is an open-label, international, multicentric, phase II trial assessing the combination of olaparib, fulvestrant, and durvalumab in ER+/HER2- metastatic or locally advanced BC with somatic or germline PV in *BRCA1, BRCA2* or other genes implicated in the HRR pathway *(ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FAND2, FANCL, MRE11A, NBN, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and RAD54L)* or in MSI status or other actionable genes (*AKT1, ESR1, FGFR1, FGFR2, FGFR3, and PIK3CA)* all based on central tumor NGS. Further an amendment in May 2021, patients with only alterations in these other actionable genes can no longer be included. Patients must have received 1 prior line of endocrine therapy for their metastatic BC, including CDK4/6 inhibitor and maximum of 1 line of chemotherapy in the metastatic setting. Patients receive olaparib (twice daily at 300 mg), fulvestrant (2 intramuscular injections of 250 mg every 28 days) and durvalumab (1500 mg intravenous every 4 weeks). The primary objective is to evaluate the progression-free survival rate at 24 weeks. Secondary endpoints include safety, overall survival, objective response rate, in the overall population and in the germline *BRCA* mutated population. With an optimum two-stage Simon design, $\alpha = 2.5\%$, $\beta = 5\%$, p0 (probability of inefficiency maximum) = 50%, p1 (probability of minimum efficiency) = 65%, it is necessary to include 158 patients. The strategy could be considered sufficiently effective if there are at least 87 patients without progression at 24 weeks. Given the lack of safety data from this association, a safety run-in phase including 6 patients has been completed without DLT. As of December 31, 2021, 266 patients have been screened of whom 102 have been treated. The first interim analysis occured in November 2021 after the inclusion of 64 evaluable patients. IDMC suggested that the trial continue as planned. Clinical trial information: NCT04053322. Research Sponsor: Astrazeneca.

TPS1117 **Poster Session**

postMONARCH: A phase 3 study of abemaciclib plus fulvestrant versus placebo plus fulvestrant in patients with HR+, HER2-, metastatic breast cancer following progression on a CDK4 & 6 inhibitor and endocrine therapy.

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Background: The use of cyclin dependent kinase 4 and 6 (CDK4 & 6) inhibitors plus endocrine therapy (ET) has transformed the management of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC). However, most patients will experience disease progression. Identification of treatment options following progression is an unmet medical need. Additionally, as CDK4 & 6 inhibitors are now being deployed in the adjuvant setting, determination of optimal therapy following metastatic relapse is an important question. In patients with disease progression following a CDK4 & 6 inhibitor-based regimen, continuing CDK4 & 6 inhibition with abemaciclib while switching the ET backbone may provide benefit and delay the need for cytotoxic chemotherapy. Abemaciclib is an oral, selective, and potent CDK4 & 6 inhibitor administered continuously and approved as monotherapy or with ET for treatment of HR+, HER2- ABC. Abemaciclib has also been approved with ET for the adjuvant treatment of HR+, HER2-, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%. Fulvestrant is a selective ER degrader (SERD) approved for treatment of HR+, HER2- ABC. The postMONARCH study investigates whether abemaciclib plus fulvestrant will improve outcomes in patients with HR+, HER2- ABC after disease relapse or progression after adjuvant or first-line treatment with a CDK4 & 6 inhibitor plus ET. **Methods:** postMONARCH is a Phase 3, global, multicenter, randomized, double-blind, placebo-controlled study in patients with HR+, HER2- ABC and with disease progression on treatment with a prior CDK4 & 6 inhibitor plus an aromatase inhibitor as initial therapy for ABC or recurrence on/after treatment with a CDK4 & 6 inhibitor plus ET in the adjuvant setting. Eligible patients are randomized 1:1 to receive abemaciclib 150 mg twice daily or placebo, plus fulvestrant. Stratification factors include geography, presence of visceral metastasis, and duration of prior CDK4 & 6 inhibitor-based regimen. The study is powered at 80% with a cumulative Type I error of 0.025 to detect the superiority of abemaciclib plus fulvestrant versus placebo plus fulvestrant in terms of investigator-assessed progression free survival. Key secondary endpoints include overall survival, PFS by blinded independent central review, objective response rate, safety, patient-reported outcomes, and pharmacokinetics. This study opened in Jan 2022, plans for approximately 122 centers in 18 countries, and anticipates enrolling ~350 patients. Clinical trial information: NCT05169567. Research Sponsor: Eli Lilly and Company.

TPS1118 **Poster Session**

KEYNOTE-B49: A phase 3, randomized, double-blind, placebo-controlled study of pembrolizumab plus chemotherapy in patients with HR+/HER2- locally recurrent inoperable or metastatic breast cancer.

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Background: HR+/HER2– advanced breast cancer that progresses on endocrine therapy is treated with chemotherapy (chemo). The phase 1b KEYNOTE-028 trial showed durable activity with pembrolizumab (pembro) monotherapy in previously treated HR+/HER2–, PD-L1–positive (combined positive score [CPS] ≥1) advanced breast cancer. KEYNOTE-B49 (NCT04895358) is a phase 3, randomized, double-blind study of pembro + chemo vs placebo (pbo) + chemo in centrally assessed PD-L1–positive, HR+/HER2– locally recurrent inoperable or metastatic breast cancer (mBC) after progression on prior endocrine therapy. **Methods:** ~800 patients (pts) with HR+/HER2– locally recurrent inoperable or mBC who are candidates for chemo (no prior chemo for metastatic disease) with PD-L1 CPS ≥1 and documented progression on prior endocrine therapy will be enrolled. Prior endocrine therapy comprises ≥2 lines (≥1 in combination with a CDK4/6 inhibitor) in the metastatic setting or 1 line with CDK4/6 inhibitor treatment for mBC in pts who had a relapse within 24 mo of primary surgery. Pts without prior CDK4/6 inhibitor treatment may enroll if they had progressed within 6 mo of starting endocrine therapy for metastatic disease and had previously relapsed within 24 mo of primary tumor surgery while on adjuvant endocrine therapy. Pts are randomized 1:1 to receive pembro 200 mg IV or pbo Q3W, each in combination with investigator's choice of chemo: paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 Q4W; nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 Q4W; liposomal doxorubicin 50 mg/m^2 IV on day 1 Q4W; or capecitabine 1000 mg/m^2 PO BID on days 1–14 Q3W. Randomization is stratified by tumor PD-L1 (CPS 1–9 vs ≥10), presence of visceral metastases (yes vs no), and chemo on-study (taxanes vs liposomal doxorubicin vs capecitabine). Treatment is continued until disease progression, unacceptable toxicity, withdrawal, or, for pembro/pbo, completion of 35 cycles (~2 years); chemo can be continued per investigator discretion. Tumor PD-L1 status is determined centrally using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies; Carpinteria, CA, USA). Radiologic assessments are performed Q9W for 54 wk and then Q12W thereafter. AEs occurring from randomization until 30 d after treatment discontinuation (90 d for serious AEs) are graded per NCI-CTCAE v 5.0. Primary endpoints are PFS per RECIST v1.1 by BICR and OS in pts with PD-L1 CPS ≥10 and ≥1 tumors, separately. Enrollment is ongoing at 204 international sites. Clinical trial information: NCT04895358. Research Sponsor: Merck & Co., Inc., Kenilworth, NJ, USA.

TPS1119 **Poster Session**

Neoadjuvant survivin-targeted immunotherapy maveropepimut-S (MVP-S) to increase Th1 immune response in Ki67-high hormone receptor-positive (HR+) early-stage breast cancer (ESBC).

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Background: HR+ ESBC is associated with suboptimal pathologic complete response rate (pCR, ~10%) following neoadjuvant cytotoxic chemotherapy. Neoadjuvant anti-endocrine therapy with aromatase inhibitors (AI) may serve as an effective alternative. Efficacy can be gauged using the surrogate Ki67 cell proliferation histologic marker. Patients with poor Ki67 response (defined as Ki67 > 10%) following neoadjuvant AI exhibit poor prognosis and therapeutic resistance to both anti-endocrine therapy and chemotherapy. In a genomic analysis among Ki67-high HR+ tumors, we identified 8-fold upregulation of BIRC5 (survivin), a gene that regulates apoptosis and the cell cycle and that is associated with poor clinical outcome. Maveropepimut-S (MVP-S, previously named DPX-Survivac) leverages the non-aqueous, lipid-based DPX delivery platform to educate a specific and persistent T cell-based immune response to 5 HLA-restricted peptides from Survivin, a cancer-associated protein commonly upregulated in several cancers. Treatment with MVP-S and intermittent, low-dose cyclophosphamide (CPA) has shown tumor infiltration of survivin-specific T cells. Previous clinical trials have shown that MVP-S is well-tolerated, immunogenic, and could lead to clinical response in several cancer indications. Further exploration of the regimen in breast cancer could extend the application of this immunotherapy for this unmet medical need. **Methods:** NCT04895761 is phase I trial evaluating the safety and immunologic effects of neoadjuvant MVP-S plus letrozole (arm A, n = 6), with/without tumor-directed MR-guided radiotherapy (arm B, n = 6), or intermittent low-dose cyclophosphamide or CPA (arm C, n = 6). Postmenopausal patients with T1c+ HR+HER2- breast cancer with Ki67 > 10% will receive two doses of MVP-S and 7 weeks of neoadjuvant letrozole prior to surgery (all arms), whereas arm B will be treated additionally with concurrent 10Gy x 2 tumor boost radiation to facilitate immunogenic cell death, and arm C (n = 6) will be treated additionally with intermittent low-dose CPA (50mg BID) to facilitate regulatory T cell depletion. The primary objective is safety. Biomarker objectives are to evaluate for each treatment arm: 1) systemic type I survivin-specific immune response, as measured by IFN-γ ELISPOT; 2) changes in immune environment by GeoMx digital spatial genomic profiling; 3) and changes in tumor infiltrating lymphocytes (TILs) and Ki67. These data will be used to identify the most immunogenic MVP-S combination therapy for study in phase II trial powered to assess clinical outcome (pCR). Clinical trial information: NCT04895761. Research Sponsor: IMV INC.

TPS1120 **Poster Session**

ARV-471, an estrogen receptor (ER) PROTAC degrader, combined with palbociclib in advanced ER+/human epidermal growth factor receptor 2–negative (HER2-) breast cancer: Phase 1b cohort (part C) of a phase 1/2 study.

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Background: ARV-471 is a novel, potent, orally bioavailable PROteolysis TArgeting Chimera (PROTAC) protein degrader that selectively targets the ER. In xenograft models, ARV-471 demonstrated substantially greater ER degradation and antitumor activity compared with the selective ER degrader fulvestrant. In the phase 1 dose escalation portion (Part A) of the first-in-human phase 1/2 study, ARV-471 monotherapy was well tolerated and showed antitumor activity in patients with ER+/HER2- locally advanced or metastatic breast cancer who had previously received endocrine therapy and a cyclin-dependent kinase (CDK)4/6 inhibitor; the clinical benefit rate (rate of confirmed complete or partial response or stable disease ≥24 weeks) was 40% (95% CI: 26%–56%) in 47 evaluable patients. The phase 2 VERITAC expansion cohort (Part B) is further evaluating ARV-471 monotherapy in this patient population. Palbociclib, a CDK4/6 inhibitor, plus fulvestrant is a standard treatment option for patients with ER+/HER2- breast cancer who have had disease progression on endocrine therapy. ARV-471 plus palbociclib resulted in substantially greater tumor growth inhibition in xenograft models compared with palbociclib plus fulvestrant, supporting further investigation of the ARV-471 plus palbociclib combination in patients with ER+ breast cancer. Here we describe Part C of the phase 1/2 study, which evaluates the safety and clinical activity of ARV-471 plus palbociclib in patients with breast cancer who previously received endocrine therapy. **Methods:** Eligible patients (aged ≥18 years) have histologically or cytologically confirmed ER+/HER2- advanced breast cancer and have received ≥1 prior endocrine therapy and ≤2 prior chemotherapy regimens for advanced disease; prior CDK4/6 inhibitor therapy is permitted. Patients with known symptomatic brain metastases requiring steroids are excluded. ARV-471 and palbociclib will be administered orally once daily in 28-day cycles; ARV-471 will be given continuously and palbociclib for 21 days followed by 7 days off treatment. Primary objectives are to evaluate the safety and tolerability of ARV-471 plus palbociclib and select the recommended phase 2 dose and schedule of the combination (based on the incidence of dose-limiting toxicities during the first cycle and the frequency and severity of adverse events and laboratory abnormalities). Secondary objectives are to assess preliminary antitumor activity of ARV-471 plus palbociclib (based on overall response rate per Response Evaluation Criteria in Solid Tumors v1.1, clinical benefit rate, progression-free survival, and duration of response) and pharmacokinetic parameters. Clinical trial information: NCT04072952. Research Sponsor: Arvinas, Inc.

TPS1121 **Poster Session**

Phase 3 ENABLAR-2 study to evaluate enobosarm and abemaciclib combination compared to estrogen-blocking agent for the second-line treatment of AR+, ER+, HER2- metastatic breast cancer in patients who previously received palbociclib and estrogen-blocking agent combination therapy.

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Background: Targeting the androgen receptor (AR) may be the next important endocrine therapy for advanced breast cancer. The AR has been demonstrated to be a tumor suppressor when activated. Enobosarm is an oral selective AR targeting agonist that activates the AR in breast cancer. Preclinical studies in CDK4/6 inhibitor resistant PDX models demonstrated combinatorial synergistic activity of enobosarm plus CDK 4/6 inhibitors. An open-label, Phase 2 study, was conducted in 136 women with heavily pretreated ER+ HER2- metastatic breast cancer that were randomized to oral daily enobosarm at a dose of 9 or 18 mg. The efficacy evaluable (EE) group were patients that were AR positive (> 10% AR nuclear staining). In the EE population with measurable disease at baseline, 10 patients had received prior endocrine therapy + a CDK 4/6 inhibitor. Subsequent treatment with enobosarm resulted in a clinical benefit rate of 50% and the best overall response rate (ORR) was 30% (2CRs and 1 PR). Of the 10 patients, 7 had AR nuclear staining ≥40%. None of the patients with AR nuclear staining < 40% responded to enobosarm. Although a small subset of the study, it appears that enobosarm has activity in patients who had ≥40% AR staining and who had progressed on standard endocrine therapy with a CDK 4/6 inhibitor. Overall, treatment with enobosarm was well tolerated with significant positive effects on quality-of-life measurements. **Methods:** The ENABLAR-2 trial is an ongoing Phase 3, randomized, open-label, efficacy and safety study in patients with AR+ ER+ HER2- MBC with AR nuclear staining of ≥40%, who have progressed after one line of systemic therapy comprising estrogen blocking agent and palbociclib. The planned sample size is 186 patients randomized 1:1 to enobosarm + abemaciclib OR fulvestrant if the first line of therapy for MBC was a non-steroidal AI plus palbociclib, until disease progression, toxicity, or loss of clinical benefit. If first line therapy for metastatic breast cancer was fulvestrant plus palbociclib, then the patient will be randomized 1:1 to either enobosarm + abemaciclib OR an AI. Randomization will be stratified by AR% nuclear staining, ≥60% versus < 60%, as well as by estrogen blocking agent such that each cohort will have the same number of subjects previously receiving fulvestrant + palbociclib in first line therapy. The key objectives are to determine the safety and efficacy of enobosarm and abemaciclib combination versus an alternative estrogen blocking agent with the primary endpoint of PFS. Secondary endpoints include ORR, duration of response, overall survival, change from baseline in Short Physical Performance Battery (SPPB), change in EORTC Quality of Life Questionnaire (EORTC-QLQ) and change in body composition as measured by DEXA. Clinical trial information: NCT05065411. Research Sponsor: Veru Inc.

TPS1122 **Poster Session**

Phase Ib/II study of BCL-2 inhibitor lisaftoclax (APG-2575) safety and tolerability when administered alone or combined with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor in patients with estrogen receptor-positive (ER^+) breast cancer or advanced solid tumors.

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Background: Various cancers evade apoptosis by overexpressing BCL-2 proteins. Investigational agent lisaftoclax (APG-2575) is a novel, potent, selective BCL-2 inhibitor, while palbociclib inhibits cyclin-dependent kinases (CDK) 4 and 6. In preclinical studies, palbociclib decreased proliferation of ER^+ breast cancer cell lines by arresting them in the G1 cycle phase. Preclinical data demonstrate favorable, complementary effects of palbociclib when combined with a BCL-2 inhibitor and support this combination in patients with ER^+/ human epidermal growth factor receptor 2-negative ($HER2^-$) metastatic breast cancer. **Methods:** This global multicenter open-label dose escalation and dose expansion study is assessing the safety of lisaftoclax monotherapy in patients with histologically or cytologically confirmed advanced solid tumors that have progressed on standard therapy or when combined with CDK4/6 inhibitor palbociclib in physiologically postmenopausal women with ER^+/ $HER2^-$ metastatic breast cancer that has progressed or relapsed after treatment with a CDK4/6 inhibitor. This trial consists of 2 parts: a phase Ib dose escalation phase using a standard 3+3 design to determine the maximum tolerated dose (MTD) of lisaftoclax as a single agent in patients with solid tumors, as well as both the MTD and recommended phase 2 (RP2D) dose of lisaftoclax when combined with palbociclib in women with ER^+/ $HER2^-$ metastatic breast cancer. Phase II of this study is a signal-seeking expansion of lisaftoclax at RP2D when combined with palbociclib in women with ER^+/$HER2^-$ metastatic breast cancer. This phase is being conducted using Simon's Minimax two-stage design. The primary objective for phase II is to determine clinical benefit response, and secondary efficacy endpoints include overall response rate, duration of response, time to response, and progression-free survival. Lisaftoclax is being administered orally once daily in a 28-day cycle at the assigned dose. Clinical trial information: NCT04946864. Research Sponsor: Ascentage Pharma Group Corp. Ltd (Hong Kong).

TPS1123 **Poster Session**

TWT-203: Phase 1b/2 dose-confirming study of CFI-402257 as a single agent in advanced solid tumors and in combination with fulvestrant in patients with ER+/HER2- advanced breast cancer after disease progression on prior CDK4/6 and endocrine therapy.

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Background: TTK (Threonine Tyrosine Kinase also known as Monopolar spindle 1 [Mps1]), is a dual-specificity serine-threonine kinase critical for anaphase promoting complex/cyclosome inhibition at the spindle assembly checkpoint, and is required for chromosome alignment and error correction. Inhibition of TTK causes cells to prematurely exit mitosis with unattached chromosomes, resulting in aneuploidy and cell death. Higher TTK tumor levels correlate with worse prognosis and may contribute to the survival and proliferation of aneuploid cells. CFI-402257, a potent and selective inhibitor of TTK inhibits the growth of a variety of human cancer-derived cell lines with IC50 of 8-40 nM. A first-in-human phase 1 study of CFI-402257 administered orally as a single agent, demonstrated a tolerable safety profile and evidence of clinical activity in patients with advanced solid tumors. The MTD was 168 mg daily, and the study expanded to 3 cohorts: solid tumors, HER2-negative breast cancer, and hormone receptor positive (HR+/HER2-) breast cancer in combination with fulvestrant. The dose limiting toxicity was manageable and reversible dose-dependent neutropenia. Investigator-confirmed partial responses (cPR) were observed in 5 patients (10.6%) with 25 (53.2%) exhibiting disease control. In the HR+/HER2- breast cancer population previously treated with cyclin dependent kinase 4/6 inhibitors (CDK4/6i) and aromatase inhibitors, there were 4 cPR's with a median duration of response of 256 days, with responses emerging after 2 cycles of therapy. Responses were observed with CFI-402257 as a single agent and in combination with fulvestrant. Based on these data, study TWT-203 will focus on advanced solid tumors and advanced HR+/HER2- breast cancers in combination with an approved endocrine therapy. **Methods**: Safety and clinical activity of CFI-402257 monotherapy will be evaluated in patients with advanced solid tumors (Part A) or in combination with fulvestrant in patients with HR+/HER2- advanced breast cancer (Part B). Part A will confirm the RP2D using a 3+3 design with a starting dose of 126 mg daily. Part B evaluates CFI-402257 in combination with fulvestrant in patients with HR+/HER2- advanced breast cancer following progression on prior CDK4/6i and endocrine therapy. Initially 6 patients will be treated with CFI-402257 and fulvestrant, and safety, tolerability, and PK evaluated, with further expansion to confirm the RP2D and characterize CFI-402257 activity. Efficacy endpoints include overall response rate and disease control rate. Safety endpoints include incidence of treatment emergent adverse events. Exploratory objectives include characterization of protein and molecular alterations relevant to the cell cycle and CFI-402257 response. Research Sponsor: Treadwell Therapeutics.

TPS1124 **Poster Session**

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

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Background: Targeting constitutively active mutant kinases with selective small molecule inhibitors is a key therapeutic pillar of precision oncology. *Phosphatidylinositol-4,5bisphosphate-3 kinase, catalytic subunit alpha* (*PIK3CA*) mutations leading to oncogenic activation of PI3Kα represent the largest opportunity for this approach in solid tumors. However, there is no selective inhibitor that targets mutant PI3Kα in the clinic. Toxicity related to non-selective inhibition of WT PI3Kα (hyperglycemia) and other PI3K isoforms limits the tolerability, dosing and efficacy of the orthosteric inhibitor, alpelisib, the only approved solid tumor PI3K inhibitor. RLY-2608, a novel oral allosteric PI3Kα inhibitor, is uniquely designed to overcome these limitations via mutant- and isoform-selective PI3Kα inhibition for greater target coverage, improved tolerability and antitumor activity. We initiated a first-in-human (FIH), study to evaluate the clinical activity of RLY-2608 as a single agent in advanced solid tumor patients (pts) with *PI3KCA* mutations and in combination with fulvestrant in pts with *PIK3CA*mutant, HR+, HER2- metastatic breast cancer (MBC). **Methods:** This is a global, multi-center, dose escalation/expansion study (NCT05216432) of RLY2608 as a single agent in adults who have advanced solid tumors and are refractory, intolerant, or declined standard therapy and RLY-2608 in combination with fulvestrant in previously treated pts with HR+/HER2- MBC. Eligibility criteria include presence of *PI3KCA* mutation (blood or tumor) per local assessment, ECOG performance status 0-1, measurable or evaluable disease per RECIST 1.1 and no prior PI3K inhibitor (except combination group 2). RLY-2608 is administered on a continuous schedule with 4-week cycles. Adverse events (AEs) per CTCAE v5, PK, biomarkers (mutant ctDNAs and insulin pathway markers) and anti-tumor activity are assessed serially. Dose escalation employs a Bayesian Optimal Interval design to identify MTD and RP2D. Following dose escalation, pts will be treated with RLY-2608 at the MTD/RP2D in a monotherapy dose expansion with 5 groups (N = 75, 15 each): 1. Clear cell ovarian carcinoma 2. Head and neck squamous cell carcinoma 3. Cervical cancer 4. Other solid tumors 5. *PI3KCA* double mutations. In addition, two expansion cohorts will enroll patients with HR+/HER2- MBC treated with RLY-2608 and fulvestrant combination (N = 30, 15 each): 1. No prior PI3K therapy 2. Intolerant to PI3K inhibitors. The primary endpoints are MTD/RP2D and AE profile for single agent and combination; key secondary endpoints are *PI3KCA* genotype in blood and tumor, PK, biomarkers, and overall response rate. US enrollment began December 2021 and ex-USA startup is underway. Clinical trial information: NCT05216432. Research Sponsor: Relay Therapeutics.

TPS1125 **Poster Session**

Phase I trial of an alpha-lactalbumin vaccine in patients with moderate- to high-risk operable triple-negative breast cancer (TNBC).

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Background: Triple-negative breast cancer (TNBC) is the subtype of breast cancer with the worst prognosis and is the subtype most often associated with germline mutations of BRCA1 and certain other genes. Alpha-lactalbumin (aLA) is a milk protein that is expressed in lactating breasts but not at other times or in other normal tissues. Expression of aLA is found in approximately 70% of TNBC (Cancers PMID: 27322324) so is an attractive immunologic target for TNBC based on the "retired protein hypothesis" (Semin Immunol PMID: 31926646). Pre-clinical studies have shown that vaccination with aLA provides treatment of established and, more potently, protection from development of autochthonous tumors in transgenic murine models of breast cancer and against 4T1 transplantable breast cancer in BALB/c mice (Nat Med PMID: 20512124). We are conducting a Phase I trial in patients with early stage TNBC to demonstrate the safety of this approach and to document the ability to produce a meaningful immunologic response to aLA. **Methods:** Patients with ER-negative, PR-negative, HER2-negative breast cancer of pathologic stage I-III or who had residual disease after standard pre-operative systemic therapy are being entered into a Phase I trial of alpha-lactalbumin with a GMP-grade zymosan adjuvant in Montanide ISA 51 VG vehicle. Participants must be within 3 years of initiation of treatment and have no evidence of recurrence. Patients receive a total of 3 vaccinations administered once every 2 weeks with doses escalated using a 3+3 trial design. Toxic events of Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or greater are considered dose-limiting. Dose levels being tested are alpha-lactalbumin/zymosan 0.01 mg/0.01 mg, 0.1 mg/0.1 mg, and 1 mg/1 mg. Patients are being monitored for toxicity until 84 days after the first vaccination or resolution of toxicity, whichever is later. Blood is being drawn prior to therapy and 14, 28, and 56 days after the first vaccination to assess cellular response using enzyme-linked immunosorbent spot (ELISpot) assays of interferon-gamma and interleukin-17 production in response to aLA. Humoral response to aLA vaccination is being assessed by enzyme-linked immunosorbent assay (ELISA). After identification of the Maximum Tolerated Dose we will expand the dose levels associated with effective tumor immunity and enroll a cohort of patients without cancer planning to undergo prophylactic bilateral mastectomy. Funding Source: Department of Defense (W81XWH-17-1-0592 and W81XWH-17-1-0593). Clinical trial information: NCT04674306. Research Sponsor: Department of Defense.

TPS1126 **Poster Session**

Phase 1 pilot study with dose expansion of chemotherapy in combination with CD40 agonist and Flt3 ligand in metastatic triple-negative breast cancer.

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Background: Only a subset of patients with metastatic triple-negative breast cancer demonstrate response to currently approved PD-1 immune checkpoint blockade, and few have durable responses. Antigen presentation defects may be a reason for this low response because deficiency of antigen-presenting DC1 dendritic cells is associated with poor anti-tumor immunity. CD40 agonists are a class of agents that activate antigen presenting cells including dendritic cells and B cells and also repolarize macrophages. Flt3 ligand is a growth factor that increases dendritic cells. In line with this, we recently demonstrated in pre-clinical models that the combination of liposomal-doxorubicin chemotherapy, a CD40 agonist, and a Flt3 ligand improves outcomes of breast cancer compared to alternate combinations. **Methods:** This is a single arm phase I pilot study of liposomal-doxorubicin, CDX-1140 (CD40 agonist), and CDX-301 (Flt3 ligand) combination therapy in patients with metastatic or unresectable locally advanced metastatic triple-negative breast cancer. Patients will be randomized to 3 lead-in arms (triplet therapy, doublet immunotherapy only, liposomal-doxorubicin only) prior to receiving full triplet therapy with fresh tissue biopsies before and after the lead-in treatment. CDX-301 will be discontinued after 2 cycles; liposomal-doxorubicin and CDX-1140 will be continued until disease progression or clinically limiting toxicities. Primary endpoint is determination of a recommended phase 2 dose based on treatment-related adverse events including dose-limiting toxicities. Secondary endpoints include anti-tumor immune response after triplet therapy, after immunotherapy alone, and after liposomal-doxorubicin alone; median progression-free survival, overall response rate, duration of response, and clinical benefit rate. Key eligibility criteria are unresectable stage III or stage IV triple-negative breast cancer (ER $\leq$10%, PR $\leq$10%, HER2/neu negative), 1st to 3rd line metastatic treatment setting (1st line patients need to be PD-L1 negative by 22C3 assay), measurable disease by RECIST 1.1 criteria, consent for pre-treatment and on-treatment biopsies of amenable soft tissue tumor lesions, no prior treatment with an anti-CD40 antibody or a Flt3 ligand, no anthracycline treatment in the metastatic setting, no prior progression while on anthracycline-based therapy or within 6 months of completing neoadjuvant chemotherapy, and no history of non-infectious pneumonitis or current pneumonitis. This trial will enroll up to 45 patients across multiple sites. Clinical trial information: NCT05029999. Research Sponsor: Celldex Therapeutics, Other Foundation.

TPS1127 **Poster Session**

Phase 1b/2 study of ladiratuzumab vedotin (LV) in combination with pembrolizumab for first-line treatment of triple-negative breast cancer (SGNLVA-002, trial in progress).

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Background: Patients with metastatic triple-negative breast cancer (mTNBC) have a poor prognosis. Treatment combinations of anti-programmed death ligand 1 (anti–PD-L1) agents with chemotherapy have shown promise in mTNBC. LV is an investigational antibody–drug conjugate directed to LIV-1, a protein highly expressed on breast cancer cells, via a humanized IgG1 monoclonal antibody conjugated to monomethyl auristatin E (MMAE) by a protease-cleavable linker. LIV-1–mediated delivery of MMAE disrupts microtubules and induces cell cycle arrest and apoptosis. LV has also been shown to drive immunogenic cell death (ICD) to elicit an immune response. LV + pembrolizumab may result in synergistic activity through LV-induced ICD, creating a microenvironment favorable for enhanced anti–PD-L1 activity. Preliminary results show LV delivered once every 3 weeks (Q3W) + pembrolizumab was tolerable with encouraging antitumor activity in patients with mTNBC (Han 2019). Additionally, interim results of weekly LV monotherapy at doses up to 1.5 mg/kg were clinically active and generally well tolerated (Tsai 2021). Based on pharmacokinetic and pharmacodynamic modeling and simulation analysis, an intermittent LV + pembrolizumab dosing regimen is being evaluated to further enhance efficacy and improve the tolerability profile. Due to an unmet medical need for patients with mTNBC who are PD-L1 low or negative, Part D will focus on this patient population. **Methods:** SGNLVA-002 (NCT03310957) is an ongoing global single-arm, open-label phase 1b/2 study of LV + pembrolizumab as 1L therapy for patients with unresectable locally advanced/mTNBC. Part D is currently enrolling ~40 patients. Eligible patients must have advanced disease with no prior cytotoxic/anti–PD-L1 treatment, PD-L1 combined positive score < 10, measurable disease per RECIST v1.1 and an ECOG score ≤1. Patients with Grade ≥2 pre-existing neuropathy or active central nervous system metastases are not permitted. Patients will receive LV at 1.5 mg/kg on Days 1 and 8 plus pembrolizumab 200 mg on Day 1 Q3W. The primary objectives are to evaluate the safety/tolerability and objective response rate of LV + pembrolizumab. Secondary objectives include duration of response, disease control rate, progression-free survival, and overall survival. Safety and efficacy endpoints will be summarized with descriptive statistics. Global enrollment is ongoing in the US, EU, and Asia. Clinical trial information: NCT03310957. Research Sponsor: Seagen Inc.

TPS1128 **Poster Session**

A phase I/II trial evaluating the safety and efficacy of eribulin in combination with copanlisib in patients with metastatic triple-negative breast cancer (TNBC).

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Background: Metastatic (met) TNBC remains a clinical challenge with limited treatment options and inevitable chemoresistance. Aberrant PI3K pathway signaling is frequently observed in TNBC. Increasing evidence shows PI3K pathway activation maintains the stemness and chemoresistance of BC stem cells (CSCs), and PI3K inhibition sensitizes CSCs to chemotherapy (chemo). Eribulin (E), a non-taxane microtubule dynamics inhibitor, showed survival benefit in met HER2 negative BC. Preclinically, E impacts tumor vascular remodeling, inhibits epithelial-to-mesenchymal transition and metastasis – key mechanisms implicated in PI3K inhibition resistance. Copanlisib (C), a potent pan-class I PI3K inhibitor (*i*), improved anti-tumor effect in E-sensitive and resistant TNBC patient-derived xenograft models, irrespective of PIK3CA/PTEN mutation (mut) status, when combined with E. This phase I/II study is aimed to determine the safety and efficacy of E+C in pts with met TNBC. **Methods:** This trial includes a phase I portion with the primary objective to determine the dose limiting toxicity (DLT) and recommended phase 2 dose (RP2D) of E+C, followed by a phase II randomized portion of E+C (at RP2D) versus (*vs*) E with the primary objective of progression-free survival (PFS). Key secondary objectives include objective response rate (ORR) and clinical benefit rate (CBR) [phase I]; and ORR and CBR, by arm and by PIK3CA/PTEN mut status and assessment of treatment induced target engagement [phase II]. Key exploratory objectives include analysis of genomic, proteomic and metabolomic changes as potential response biomarkers in tumor tissue and blood. Key eligibility criteria include pts with: met TNBC who progressed on $\leq$5 chemo lines, including anthracycline/taxane (unless contraindicated), ECOG 0-1, adequate organ function and known archival tumor PIK3CA/PTEN mut status. Key exclusions: prior E or PI3K/mTOR/AKT*i*, grade $\geq$2 neuropathy, tumor AKT mut, congenital QT prolongation, and uncontrolled diabetes or hypertension. Phase I portion will follow a 3+3 design for E+C dose escalation to enroll 18 max pts, starting at E 1.1 mg/m^2 IV and C 45 mg IV on days (D) 1/8 of 21-D cycle (C) (to E 1.4 mg/m^2 and C 60 mg max). RP2D will be defined as the highest dose level at which at most 1 of 6 pts experience DLT during C1. 88 pts will be randomized (1:1) in the phase II portion to E+C *vs* E (1.4 mg/m^2 D 1/8), stratified by PTEN/PIK3CA mut status. Response assessment by Response Evaluation Criteria in solid tumors (RECIST) v1.1 will occur every 9 weeks (+/-7 D). Tumor biopsy is required at baseline and C2D1-2, and optional at progression. A sample size of 88 achieves 80% power to detect PFS difference of median PFS 6.95 *vs* 4 months (corresponding to a hazard ratio of 0.5755) between the 2 arms, based on 1-sided two-sample log rank test at 0.1 α level. The phase I study is actively enrolling pts. Clinical trial information: NCT04345913. Research Sponsor: U.S. National Institutes of Health.

TPS1129 **Poster Session**

Evaluation of a three-part equity intervention for women of color with breast cancer.

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Background: Women of color (WOC) with breast cancer miss and fail key points in care due to racial disparities in cancer services. Conscious and unconscious bias means that these women are not treated in a timely way or as rigorously. They are offered fewer options, and the patient navigation and education needed for them to self-advocate is ignored. Black women in particular have the highest breast cancer death rates. Care delivery differs even independent of such variables as literacy, income, and education. Separately and incrementally, findings to date have shown the potential oof patient navigation, equity assessment, and mobile support to reverse these disparities. In pilot investigations — partnering with academic cancer centers — The Chrysalis Initiative (a nonprofit patient advocacy and research organization) has validated the potential of combining these approaches in a three-part intervention. Based on preliminary work, it is hypothesized patients will: experience significantly greater adherence to the recommended continuum of care, without disruption or barriers; more often seek second opinions and additional supportive resources, and engage in clinical trials; demonstrate less co-morbidities, through more preventive measures and healthful lifestyle; suffer fewer interactions perceived to be influenced by racism; undergo less financial distress, with guidance on managing and planning costs; feel more confident and more optimistic in their outlook; and achieve better clinical results and lower costs. **Methods:** To determine and document the full impact, both quantitatively and qualitatively, of the experimental three-part intervention, the trial is: delivering navigation/coaching services to the study population, using counselors who are predominantly WOC who have experienced the challenges of breast cancer care. Surveys and interviews pre- and post-intervention will add to impact measures; providing the experimental group with the BC Navi App on both iOS and Android devices. Developed in partnership with InTouch, the app supports engagement and tracking. It provides a dashboard for care evaluation to supplement EMR data; conducting an equity assessment of breast cancer services of partnering clinical programs through use of focus groups with staff, patients, and community; procedural checks; and data collection from center EHR systems. The review audits 40 domains of care based on NCCI, NCI, ASCO, ACR, and other standards. The assessment team works closely and collaboratively with each cancer center's clinical and administrative staff to reveal disparities and find consensus on ways to close gaps. This trial in progress is randomizing 200 subjects to the coaching/mobile app intervention arm and 100 to benefits of the equity assessment only, with comparison to nonWOC with breast cancer. The trial aims to disseminate the three-part intervention in easily reproducible form. Research Sponsor: Pfizer (in partnership with MD Anderson - Cooper), Conquer Cancer Foundation of the American Society of Clinical Oncology.

TPS1130 **Poster Session**

Phase I/II first-in-human CAR T–targeting MUC1 transmembrane cleavage product (MUC1*) in patients with metastatic breast cancer.

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Background: Metastatic breast cancer (MBC) remains incurable and novel immunotherapy for durable response remains an unmet need. Chimeric antigen receptor (CAR) T-cell therapy, an innovative form of immunotherapy wherein autologous T-cells are genetically modified to target tumor specific cell-surface markers, has been developed for treatment of solid tumors. huMNC2-CAR44 recognizes the growth factor receptor form of MUC1, which is the transmembrane cleavage product called MUC1*. MUC1* is a Class I growth factor receptor that is activated by ligand-induced dimerization of its truncated extra cellular domain, which activates the MAP kinase signaling pathway as well as survival pathways. Onco-embryonic growth factor $NME7_{AB}$ binds to an ectopic site on MUC1* that is only unmasked after MUC1 is cleaved and the tandem repeat domain is shed from the cell surface. The targeting head of the CAR, huMNC2, competes with $NME7_{AB}$ for binding to this ectopic site. huMNC2 does not bind to full-length MUC1, hence highly tumor-selective. 70% of solid tumor cancers express a huMNC2 reactive MUC1* and huMNC2-scFv bound robustly to 93% of the breast cancers with minimal staining of normal tissues. huMNC2-CAR44 T cells completely obliterated a variety of MUC1* positive solid tumors in NSG mice in vivo. IND enabling animal studies demonstrated that huMNC2-CAR44 T potently inhibited MUC1* positive tumors xenografted into female NSG mice, whether the tumor cells were MUC1 negative cells stably transduced with MUC1* or breast cancer cells such as T47D that naturally express MUC1*. In one study, huMNC2-CAR44 T treated mice survived tumor-free for over 12 weeks, whereas control group had to be sacrificed at 3 weeks due to disease progression. **Methods:** This is a first-in human, phase I/II trial evaluating the safety and efficacy of huMNC2-CAR44 T in patients with MBC. Key inclusion criteria include age ≥18 years, ECOGPS 0-1, available FFPE tumor sample, tumor IHC ≥30% MUC1* and preserved organ function. Dose escalation is standard 3+3 design with dosing levels ranging from 3.3x10^5 to 1.0x10^7 CAR+ cells/kg, and fludarabine/cyclophosphamide lymphodepletion pre-treatment. Phase I accepts patients with MBC that has progressed through at least 3 previous lines of therapy. The primary objective of Phase I is to determine safety and determine a recommended Phase II dose (RPIID), with the exploratory objectives of assessing CAR T cell expansion, persistence, tumor penetration and potential tumor escape. Six (6) patients have been enrolled and five (5) patients have been treated to date. Phase II will be comprised of 3 cohorts of 15 patients in each arm of luminal, HER2+ and triple negative breast cancers for a total of 45 patients in Phase II. Clinical trial information: NCT04020575. Research Sponsor: Minerva Biotechnologies.