

## 7 Metaplastic Breast Cancer: A Retrospective Chart Review of Clinical Features

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### Background

Metaplastic breast cancer (MpBC) is a rare and aggressive malignancy characterized by the differentiation of the neoplastic epithelium into epithelial and mesenchymal elements. MpBC carries a poorer prognosis compared with invasive ductal carcinoma, likely due to its histopathological and molecular heterogeneity and lack of specific treatment protocols. The rarity and complexity of MpBC calls for further inquiry into its clinical characteristics.

### Materials and Methods

An institutional review board-approved retrospective chart review was conducted on patients diagnosed with metaplastic breast cancer and non-metaplastic, triple-negative breast cancer (TNBC) from January 2000 to August 2023 at our institution. Pathology reports of breast tissue were reviewed to characterize MpBC tumors into distinct histopathological groups. The study included 186 patients with metaplastic breast cancer (MpBC) and 76 patients with non-metaplastic TNBC.

### Results

The median age of metaplastic breast cancer diagnosis was 62 years,

with stage distribution as follows: stage I (34%, n = 13), stage II (18%, n = 7), stage III (13%, n = 5), and stage IV (26%, n = 10). The racial distribution among patients with MpBC was predominantly White (126 patients, 70.0%), followed by Black (47 patients, 26.1%).

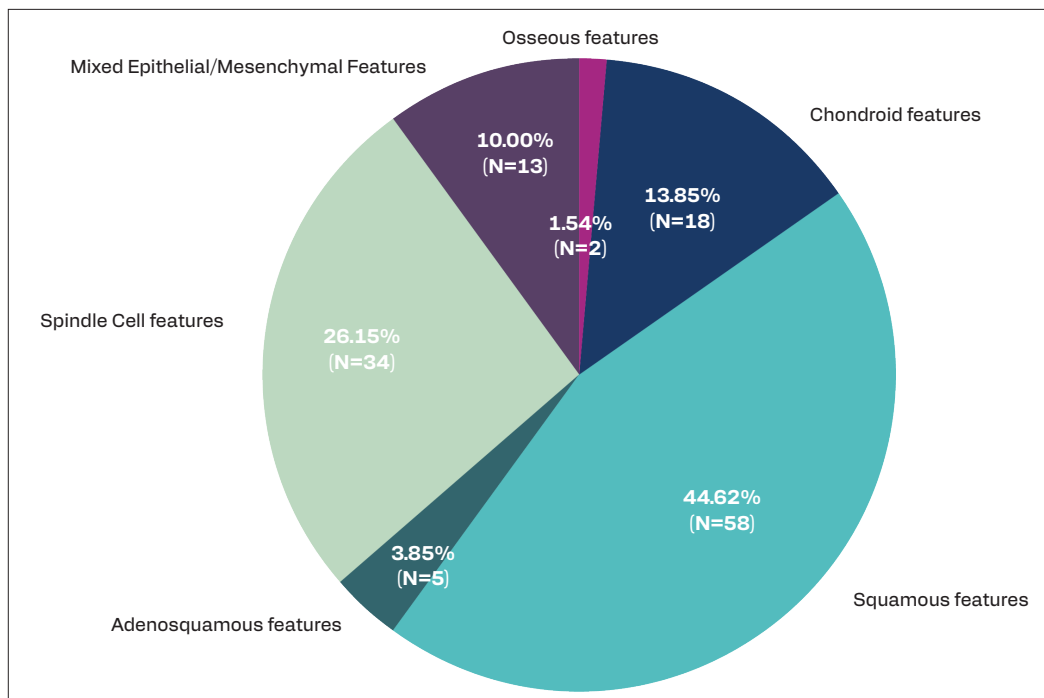
Histopathological analysis of metaplastic breast cancer tumors showed tumor differentiation into the following histological subtypes: 44.62% (n = 58) with squamous features, 26.15% (n = 34) with spindle cell features, 3.85% (n = 5) with adenosquamous features, 13.85% (n = 18) with chondroid features, 1.54% (n = 2) with osseous features, and 10.00% (n = 13) with mixed epithelial/mesenchymal features (**Figure**). No significant differences in overall survival were noted between histological subtypes.

Mutations were found in *BRCA* (9%, n = 17), *KIT* (2.7%, n = 5), *c-MYC* (2.2%, n = 4), and *p53* (1.6%, n = 3), with PD-L1 expression detected in 8.1% (n = 15), and triple-negative status identified in 24% (n = 45) of patients with MpBC. Metastases were noted in 83.9% of MpBC cases (n = 156), compared with 61.8% of TNBC cases (n = 47), most commonly affecting the lungs, bones, liver, and brain. Treatment strategies included anthracycline-based chemotherapy and combination therapy with anthracycline-based regimens and immunotherapy.

### Conclusion

This study summarizes the clinical characteristics of MpBC, highlighting its histological heterogeneity and the potential role of pathological and molecular profiling in guiding research. Further studies are required to build upon these results, with the goal of improving patient outcomes for this rare malignancy.

**Figure.**  
**Histological Features of Metaplastic Breast Cancer Tumors (N=130)**



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## 8 A Case Series Exploring Characteristics and Outcomes of Metachronous Primary Breast and Lung Cancer in a Diverse Cohort

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### Background

Despite breast and lung cancer being the most common malignancies in women, the occurrence of double primary cancers has been rarely reported in the literature. It is well established that an earlier age of diagnosis in patients with breast cancer is linked to more aggressive phenotypes, highlighting the importance of early screening in this demographic group. There is a deficiency in the literature related to secondary thoracic malignancies among this high-risk group.

### Materials and Methods

This retrospective case series reviewed a cohort of 8 patients with double metachronous, primary breast, and lung cancers at the Sylvester Cancer Center. Data on patient demographics, diagnoses, treatment modalities, and outcomes were obtained from electronic health records.

### Results

All 8 patients were biologically female with a median age of 58.5 years. Racial distribution was Asian (25%), Black (12.5%),

and White (62.5%). Of these, 80% of patients who were White identified as the Hispanic/Latinx ethnicity. Additionally, 62.5% of patients were never smokers, and 12.5% were light, former smokers. The median age of diagnosis of breast and lung cancer was 60 years and 62.5 years, respectively. The average time between both diagnoses was 1.9 years (range, 0.33-4 years). The majority (87.5%) of genetic profiles indicated a hormone receptor–positive mutation, with 33% of this genetic subset also showing an *EGFR* mutation. Overall, 75% of lung tumors were PDL-1 negative. Our review also indicates a decrease in concern for smoking. Despite no statistical significance between ethnicity and age of diagnosis of breast or lung cancer ( $P = .157$ ), there was a trend demonstrating patients who were Hispanic/Latinx as being diagnosed at an earlier age for both. There was no statistical significance between ethnicity and smoking status ( $P = .465$ ) or ethnicity and time between diagnoses ( $P = 1$ ).

### Conclusion

In this diverse, real-world cohort of patients with metachronous and synchronous lung and breast cancers, we noted interesting, hypothesis-generating observations. Trends indicated an earlier diagnosis of both breast and lung cancer in patients who are Hispanic/Latinx. Of the cohort, 75% had a dual diagnosis of breast ductal carcinoma and lung adenocarcinoma, 87.5% of individuals in our cohort displayed a hormone receptor–positive profile, and 75% had a PDL-1 negative prevalence. This case series confirms the importance of screening patients with breast cancer with low-dose CT for early detection of lung cancer. Since double primary breast and lung cancer is rare, molecular profiling with next-generation sequencing could also provide insightful information.

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## 15 Utilizing Circulating Tumor Cells to Guide HER2-Directed Therapy in IHC/FISH-Negative HER2+ Metastatic Breast Cancer

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### Background

The diagnosis of HER2-positive metastatic breast cancer (MBC) is complicated by tumor heterogeneity and temporal changes in HER2 expression. Circulating tumor cells (CTCs) serve as valuable noninvasive markers for HER2 expression when pathologic confirmation is infeasible, offering a potential therapeutic target in an otherwise high-risk population. We present a series of patients with HER2-negative MBC by immunohistochemistry (IHC)/ fluorescence in situ hybridization (FISH) who received adjunctive HER2-directed therapy

following the detection of HER2-positive CTCs.

### Materials and Methods

116 patients with HER2-positive MBC by IHC/FISH and/or HER2-positive CTCs, enrolled between 2016 and 2024 under Institutional Review Board-approved trial NU16B06 at Northwestern Medicine, were retrospectively analyzed. CTC enumerations were performed via CELLTRACKS (Menarini).

### Results

Seven patients with prior HER2-negative MBC by IHC/FISH initiated HER2-directed therapy at metastatic diagnosis based on HER2-positive CTCs. Median age at metastatic diagnosis was 63 years (range, 38-68). In addition to chemotherapy, all patients received initial HER2-directed therapy with trastuzumab, which was well tolerated. The median primary CTC count was 34 (5-1143), with a median of 17 HER2-positive CTCs (5-376). Median progression-free survival was 5.2 months (0.67-13.3), and the

median overall survival was 38.9 months (9.5-61.7). Among 5 patients with reported secondary CTC counts, 2 cleared HER2-positive CTCs, 1 demonstrated a decrease, and 2 exhibited an increase in HER2+ CTCs. All patients experienced progressive metastatic disease. Four patients underwent subsequent biopsies during their disease course: 2 were HER2-negative by IHC/FISH, and 2 were found to have HER2-low disease. Five patients received further HER2-directed therapy, including tucatinib, trastuzumab emtansine, and trastuzumab deruxtecan.

## Conclusion

While IHC/FISH remains the standard for HER2 detection, CTCs provide a complementary metric to guide HER2-directed therapy in HER2-negative MBC by IHC/FISH. Dynamic changes in HER2+ CTCs highlight their utility as predictive biomarkers for therapeutic response and indicators of disease progression. Evidence of subsequent HER2-low disease in some patients underscores the evolving nature of HER2 expression. This limited series demonstrates that noninvasive CTC monitoring may offer a potential approach to address tumor heterogeneity and guide real-time therapeutic adjustments. Prospective studies are needed to optimize patient selection for CTC-guided HER2 therapies and validate their role in improving outcomes in MBC.

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## 17 Salmonella and the Breast: A Literature Review of Salmonella-Induced Breast Abscesses

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### Background

Breast abscesses caused by salmonella are especially rare, accounting for less than 1% of cases. This study was prompted by the challenging management of a nonpregnant, nonlactating 22-year-old immunocompromised woman with multiple bilateral breast abscesses following a unique prodrome of diarrheal illness. The goal was to identify patterns, risk factors, and effective management strategies through a systematic review of the literature.

### Materials and Methods

A literature review of all the documented cases (1907-2024) of salmonella breast abscesses was conducted using PubMed to analyze demographics, clinical presentation, pathogen subtypes, geographic distribution, and treatment outcomes. Statistical analysis was performed using  $\chi^2$  tests to identify significant associations.

### Results

Demographic analysis of 41 cases revealed that women accounted for most cases (90%), with the median patient age being 32 years. The geographic distribution revealed that most cases were reported in India (37%). Statistical analysis showed a

significant association between country of origin and salmonella subtype, with more typhoidal species presenting in developing countries ( $P = .00005$ ). Travel history was documented in 15% of cases, with 83% of patients who traveled to high-risk countries presenting with a prodrome of diarrhea, highlighting exposure as a potential risk factor. Most abscesses were unilateral (90%). Immunocompromised patients were more likely to develop bilateral abscesses ( $P = .03$ ). Most patients presented with single abscesses (85%). Most patients (61%) presented with prodromal symptoms of diarrhea and fever. Successful treatment universally involved surgical drainage combined with targeted antibiotics.

### Conclusion

This literature review emphasizes the rarity of salmonella breast abscesses. The unique prodrome of diarrheal illness and fever in 61% of cases supports the suspected pathophysiology of hematogenous seeding from a systemic infection or lymphatic spread following gastrointestinal colonization. Considering factors such as country of origin, recent travel, gastrointestinal symptoms, lactation status, and immunosuppression is crucial when developing a differential diagnosis and initiating antibiotics. Awareness of rare pathogens not only highlights the importance of obtaining cultures to ensure accurate and effective treatment but also helps to prevent recurrence, mitigate unnecessary antibiotic use, and combat the growing threat of antimicrobial resistance. Ultimately, the findings of this review serve as a call to action for interdisciplinary collaboration across infectious disease, radiology, surgery, oncology, and pathology. By fostering earlier recognition and evidence-based interventions, we can achieve improved outcomes for patients facing this rare condition.

## 18 Tolerability of First-Line Treatment With Ribociclib for Metastatic Breast Cancer Using 2 Large US Data Sources

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### Background

In addition to progression-free survival (PFS) and overall survival (OS) benefits, first-line (1L) ribociclib plus endocrine therapy (ET) showed tolerable and manageable safety across the MONALEESA (ML) trials. Ribociclib plus ET is recommended by the NCCN as a category 1 preferred CDK4/6 inhibitor as a 1L treatment option for hormone receptor–positive/HER2–negative (HR+/HER2–) metastatic breast cancer with no visceral crisis in patients who are postmenopausal patients or premenopausal with ovarian ablation/suppression. We describe real-world adverse effects (AEs) of

interest with ribociclib in 2 large US datasets.

### Materials and Methods

Two cohort analyses were conducted in the Flatiron Health electronic health record (HER)-derived deidentified database and the deidentified Komodo Research Database (KRD; commercially insured, managed-Medicare [excluding fee for service] and Medicaid-insured administrative claims). Adult patients with HR+/HER2– MBC who initiated 1L RIB + ET were included. New onset of medical conditions of interest are presented.

### Results

Overall, 373 (EHR) and 350 (KRD) patients who received 1L ribociclib plus ET were included. In EHR, the mean age was 62.6 years, 49.1% were aged 65 years or older, and 17.4% were 75 years or older. In KRD, the mean age was 56.5 years, 16.3% were aged 65 years or older, and 4.6% were 75 years or older. The majority of patients received an aromatase inhibitor. The data suggest an increase in 1L use of ribociclib in 2022, as observed in KRD.

New onset any-grade AEs were: neutropenia (53.4%, EHR; 21.3%, KRD), elevated liver enzymes (9.0%, EHR; 4.6%, KRD), and QTc prolongation (4.0%, EHR; 2.0%, KRD). Evidence of newly diagnosed or suspected CV medical conditions, available only in KRD, was relatively low. The incidence of AEs for patients 65 years or older was consistent with the overall cohort.

### Conclusion

Data from 2 US databases reaffirm the safety of 1L ribociclib seen across the ML trials, with no new real-world safety signals among medical conditions of interest. In the real world, 1L ribociclib plus ET is well tolerated for patients with HR+/HER2– MBC, including patients who are older.

## 20 Impact of Ribociclib Dose Reduction on Efficacy in Patients With Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Early Breast Cancer in NATALEE

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## Background

The NATALEE trial showed statistically significant and clinically meaningful invasive disease-free survival (iDFS) with ribociclib plus a nonsteroidal aromatase inhibitor (NSAI) vs NSAI in patients with stage II/III hormone receptor–positive (HR+)/HER2–negative (HER2–) early breast cancer (EBC; HR, 0.715; 95% CI, 0.609–0.840; 4-year absolute benefit, 4.9%; median follow-up, 44.2 months). We present an exploratory analysis of efficacy in patients with and without dose reduction.

## Materials and Methods

Men and pre- and postmenopausal women with HR+/HER2– EBC were randomized 1:1 to receive ribociclib (400 mg/day; 3 wks on/1 week off for 36 months) plus NSAI or NSAI alone. Key inclusion criteria were stage II/III disease (AJCC 8th edition); patients with node-negative stage IIA disease (T2N0) were required to have additional high-risk criteria (grade 2 with Ki-67  $\geq$  20% or high genomic risk; or grade 3). Only 1 ribociclib dose reduction (400 mg/day to 200 mg/day) was allowed for the management of adverse effects (AEs). Relative dose intensity (RDI; actual cumulative dose per duration of exposure [adjusted for 3-weeks-on/1-week-off schedule] divided by planned dose intensity of 400 mg/day) was analyzed by grouping patients into low, medium, or

high RDI tertiles and summarized using Kaplan Meier methods. A stratified Cox proportional hazards model was used to compare iDFS rates with ribociclib across tertiles. The data cutoff date was Apr 29, 2024 (median follow-up, 44.2 mo).

## Results

Among 2526 patients who received treatment in the ribociclib plus NSAI arm, 27.2% had a ribociclib dose reduction, and 72.8% did not. The median time for the dose reduction was 3.3 months. The most common reason for dose reduction was an AE (23.0%); the most common AEs leading to dose reduction included neutropenia (14.0%), alanine aminotransferase increased (1.9%), and fatigue (1.0%). Baseline characteristics were balanced. Duration of ribociclib exposure was similar among patients with and without a dose reduction (median, 35.7 months in both groups). RDI did not impact iDFS rates. Patients with low, medium, and high RDI had similar iDFS rates.

## Conclusion

This post hoc exploratory analysis of NATALEE demonstrated that iDFS benefit was maintained among patients who had a dose reduction of RIB and were not impacted by ribociclib RDI. These data suggest it may be possible to implement a dose reduction of ribociclib to 200 mg/day when needed to manage AEs without compromising efficacy for patients with HR+/HER2– EBC.

## 21 Distant Disease-Free Survival Across Key Subgroups From the Phase 3 NATALEE Trial of Ribociclib Plus a Nonsteroidal Aromatase Inhibitor in Patients With HR+/HER2– Early Breast Cancer

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## Background

In NATALEE, ribociclib plus a nonsteroidal aromatase inhibitor (NSAI) demonstrated invasive disease-free survival (iDFS) and distant disease-free survival (DDFS) benefits in patients with stage II/III hormone receptor–positive (HR+)/HER2–negative (HER2–) early breast cancer (EBC). In an analysis with all patients off ribociclib, ribociclib plus an NSAI reduced the risk of distant disease recurrence vs NSAI. We present DDFS data from the 4-year landmark analysis of NATALEE across clinically relevant subgroups.

## Materials and Methods

In NATALEE, patients were randomized 1:1 to receive ribociclib (400 mg/day, 3 weeks on/1 week off for 3 years) plus an NSAI (anastrozole 1 mg/day or letrozole 2.5 mg/day for 5 years) or NSAI, with men and premenopausal women receiving goserelin.

NATALEE included patients with anatomic stage IIA (node-negative [N0] with additional risk factors or N1 [1-3 axillary lymph nodes]), IIB, or III disease per AJCC (8th edition). DDFS was a secondary end point, defined as the time from randomization to the first event of distant recurrence, second primary nonbreast invasive cancer (except for basal/squamous cell skin carcinomas), or death from any cause. DDFS was assessed across pt subgroups, including anatomic stage and nodal status, using Kaplan–Meier analysis and Cox proportional hazards model.

## Results

At the data cutoff of April 29, 2024 (median duration of follow-up for DDFS, 44.2 months, all patients off ribociclib), ribociclib plus NSAI demonstrated a DDFS benefit (HR, 0.715; 95% CI, 0.604-0.847; nominal *P* value <.0001) and a distant recurrence-free survival benefit (HR, 0.705; 95% CI, 0.589-0.844; nominal *P* value <.0001) in the intent-to-treat population. The DDFS benefit was consistent regardless of the anatomic stage. The absolute DDFS

benefit with ribociclib plus NSAI vs NSAI alone increased from 3 years to 4 years for all stage subgroups. Similarly, a consistent improvement in DDFS was observed regardless of nodal status, and the absolute DDFS benefit increased from 3 years to 4 years across nodal subgroups. The DDFS benefit with ribociclib plus NSAI vs NSAI, with an increasing benefit up to 4 years, was consistent across other clinically relevant subgroups, including menopausal and Ki-67 status.

## Conclusion

With all patients off ribociclib, ribociclib plus NSAI consistently reduced the risk of distant recurrence across clinically relevant subgroups, including N0 disease. The DDFS benefit was sustained after the 3-year ribociclib treatment duration, with increasing absolute benefit up to 4 years. These findings further support adding ribociclib to adjuvant NSAI in a broad population of patients with HR+/HER2– EBC.

## 22 Efficacy and Safety of Ribociclib + Nonsteroidal Aromatase Inhibitor in Younger Patients With HR+/HER2– Early Breast Cancer in NATALEE

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## Background

NATALEE showed a statistically significant invasive disease-free survival (iDFS) benefit of ribociclib plus nonsteroidal aromatase inhibitor (NSAI) vs NSAI (HR, 0.749; 95% CI, 0.628-0.892; *P* = .0006) in patients with hormone receptor–positive (HR+)/HER2–negative (HER2–) early breast cancer (EBC). We report ribociclib efficacy/safety in patients < 40 vs ≥ 40 years in NATALEE.

## Materials and Methods

Patients were treated with ribociclib plus NSAI or NSAI alone. Premenopausal patients received goserelin. Efficacy/safety/patient-reported outcomes were assessed (data cutoff: July 21, 2023; median follow-up, 36.7 months).

## Results

Of 5101 patients, 543 (10.6% ribociclib plus NSAI) were < 40 years (93.9% premenopausal), with 4558 (89.4% ribociclib plus NSAI) ≥ 40 years (38.2% premenopausal). Patients < 40 years were generally at higher risk prior to surgery vs patients ≥ 40 years (neoadjuvant chemotherapy, 61.1% vs 40.5%; G3, 26.5% vs 20.3%; N1-3, 70.0% vs 58.5%). Ribociclib plus NSAI showed iDFS benefit (< 40 years, HR 0.546; 95% CI, 0.321-0.929; ≥ 40 years, HR 0.780; 95% CI, 0.648-0.939), with similar trends for distant recurrence-free, recurrence-free, and distant disease-free survival. 3-year iDFS rates were higher in patients on ribociclib plus NSAI vs NSAI alone among patients < 40 years (90.1% vs 85.0%) and ≥ 40 years (90.7% vs 87.9%).

Adverse effect (AE) rates and ribociclib dose reductions/discontinuations are presented in the **Table**. Global health status and physical functioning scores showed no evidence of difference between arms in patients aged < 40 or ≥ 40 years.

## Conclusion

Adjuvant ribociclib plus NSAI showed treatment benefit in patients with HR+/HER2- EBC, including in patients < 40 years, who had more aggressive disease than patients ≥ 40 years. Safety profiles were consistent between age groups, but patients < 40 years were less likely to discontinue ribociclib due to AEs with or without prior dose reduction.

**Table.** Safety Assessed in the NATALEE Trial

Safety set, %	Age < 40 y		Age ≥ 40 y	
	RIB + NSAI n = 249	NSAI n = 267	RIB + NSAI n = 2276	NSAI n = 2175
AEs <sup>a</sup> in > 20% in RIB + NSAI arm (< 40 y)	98	84	98	88
Neutropenia <sup>b</sup>	71	8	62	4
Arthralgia	39	42	37	43
Headache	30	19	22	17
COVID-19	29	15	20	14
SARS-CoV-2 test positive	29	15	20	13
Nausea	25	9	23	8
Fatigue	24	12	22	13
Hot flush	24	25	19	19
Serious AEs <sup>a,c</sup>	8	9	15	11
AEs <sup>a</sup> leading to discontinuation <sup>d</sup> in > 1% in RIB + NSAI arm (< 40 y)	11	4	22	6
ALT increased	3	0	8	< 1
AST increased	1	0	3	0
RIB dose reduction due to AEs	27 <sup>f</sup>	–	22	–
RIB discontinuation due to AEs <sup>e</sup>	10 <sup>g</sup>	–	21 <sup>g</sup>	–
Without prior dose reduction	4	–	15	–

AEs, adverse effects; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

<sup>a</sup>All grades.

<sup>b</sup>Includes neutropenia, febrile neutropenia, and neutrophil count decreased.

<sup>c</sup>All were < 1% in any arm.

<sup>d</sup>Any component.

<sup>e</sup>Primary reason.

<sup>f</sup>Rounded from 26.5.

<sup>g</sup>Intent-to-treat population.

## 23 Clinical Outcomes in Patients With HR+/HER2- Early Breast Cancer By Prior Systemic Treatment: A Subgroup Analysis of the NATALEE Trial

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## Background

NATALEE met its primary end point with a significant invasive disease-free survival (iDFS) benefit with ribociclib plus nonsteroidal aromatase inhibitor (NSAI) vs NSAI in patients with hormone receptor–positive (HR+)/HER2–negative (HER2–) early breast cancer (EBC) that was sustained with additional follow-up (median follow-up, 33.3 months; HR, 0.749). We analyzed iDFS by prior systemic treatment (chemotherapy [CT], endocrine therapy [ET]) in NATALEE using data from the final prespecified iDFS analysis (data cutoff: July 21, 2023).

## Materials and Methods

Patients were randomized 1:1 to ribociclib 400 mg/d (3 weeks on/1 week off for 36 months) plus NSAI (≥ 60 months) or NSAI. Men

and premenopausal women received goserelin. Eligible patients had anatomic stage IIA (high-risk N0 or N1), IIB, or III EBC, regardless of prior (neo)adjuvant CT. Patients starting ET ≤12 months before randomization were included.

## Results

Of 5101 patients, 88% received prior CT, 43% had prior neoadjuvant CT, and 48% had prior adjuvant CT. Of 1432 patients with N0 disease at diagnosis, most had prior CT (78%). Most patients (73%) with prior neoadjuvant CT had stage III disease, while 19% with no prior CT had stage III disease. Overall, 69% of patients received prior ET (median duration of last prior ET was 3.2 months). An iDFS benefit with ribociclib plus NSAI was observed regardless of prior CT or duration of ET (**Table**).

## Conclusion

This subgroup analysis demonstrated an iDFS benefit with ribociclib plus NSAI vs NSAI alone in patients with HR+/HER2–EBC, regardless of duration of prior ET as well as prior (neo)adjuvant CT vs no CT, underlying the potential role of CDK4/6 inhibitors in therapeutic de-escalation of CT in EBC. A majority of patients with N0 disease at diagnosis had received prior (neo)adjuvant CT, highlighting that these patients had a risk of recurrence that was considered high enough to warrant CT.

**Table.** iDFS Benefit Observed With Ribociclib Plus NSAI vs NSAI Alone

Prior treatment, n (%)	RIB + NSAI n = 2549	NSAI Alone n = 2552	HR (95% CI)
<b>No prior CT</b>	300 (12)	307 (12)	0.82 (0.47-1.44)
<b>Prior CT</b>	2249 (88)	2245 (88)	0.74 (0.62-0.89)
<b>Prior neoadjuvant CT<sup>a</sup></b>	1085 (43)	1095 (43)	0.82 (0.64-1.03)
<b>Prior adjuvant CT<sup>a</sup></b>	1223 (48)	1220 (48)	0.69 (0.52-0.92)
<b>No prior ET</b>	793 (31)	812 (32)	0.77 (0.57-1.03)
<b>Prior ET<sup>b</sup></b>	1756 (69)	1740 (68)	0.74 (0.60-0.92)
<b>ET &lt; 12 wks<sup>b</sup></b>	744 (29)	717 (28)	0.75 (0.54-1.06)
<b>ET ≥ 12 to &lt; 26 wks<sup>b</sup></b>	650 (26)	663 (26)	0.73 (0.51-1.04)
<b>ET ≥ 26 wks<sup>b</sup></b>	358 (14)	353 (14)	0.74 (0.45-1.22)

CT, chemotherapy; ET, endocrine therapy; NSAI, nonsteroidal aromatase inhibitor, NSAI; RIB, ribociclib; wks, weeks.

<sup>a</sup> Includes 129 patients who received both neoadjuvant and adjuvant CT.

<sup>b</sup> Last ET prior to randomization.



## TPS 24 Phase Ib Dose-Finding Study of [177Lu]Lu-NeoB + Ribociclib + Fulvestrant in Patients With ER+/HER2- Advanced Breast Cancer With GRPR Expression With Early Relapse From Adjuvant Endocrine Therapy or Progression on ET + CDK4/6i for ABC

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### Background

Ribociclib (RIB) + endocrine therapy (ET) has shown significant progression-free survival and overall survival benefit in patients with hormone receptor-positive (HR+)/HER2-negative (HER2-) advanced breast cancer (ABC). However, there is an unmet need for novel therapies for patients with disease progression on or after ET with or without a CDK4/6 inhibitor (CDK4/6i). Radioligand therapies (RLTs) have shown improvements in survival vs standard of care in other disease settings. We describe the CAAA603B12101 study, evaluating the addition of [177Lu-NeoB](177Lu-NeoB), a first-in-class RLT that selectively binds GRPR, to ET plus CDK4/6i for patients with estrogen receptor-positive (ER+)/HER2- ABC plus GRPR expression with early recurrence from (neo)adjuvant ET with or without CDK4/6i or progression on ET plus CDK4/6i for ABC.

### Materials and Methods

This phase Ib, single-arm, multicenter, open-label, dose-finding study estimates the recommended dose (RD) of 177Lu-NeoB in combination with ribociclib plus fulvestrant. Eligible patients with ER+/HER2- ABC + GRPR expression: (1) experienced recurrence ≤ 12 months from completion of (neo)adjuvant ET (with or without CDK4/6i) with no treatment for ABC, (2) experienced recurrence >12 months from completion of (neo)adjuvant ET and then subsequent progression after 1 line of ET (except fulvestrant) plus a CDK4/6i for ABC, or (3) had ABC at diagnosis that progressed after 1 line of ET (except fulvestrant) plus a CDK4/6i.

In dose escalation, 4 provisional dose levels are planned in cohorts of 3 to 6 patients. The initial dose will be 100 mCi in combination with ribociclib (600 mg/day) plus fulvestrant.

Incidence rate of dose-limiting toxicities (DLTs) will be compared with predefined toxicity rate boundaries to decide whether the next cohort will receive a lower, higher, or same dose or if the trial will be terminated. Backfill will allow enrollment to a previously cleared dose level to obtain additional safety, tolerability, and efficacy data. During backfill, the cumulative incidence rate of DLTs will be compared with predefined toxicity rate boundaries to determine if escalation should be restarted from a lower level.

Primary outcomes include incidence and nature of DLTs, incidence and severity of adverse events, and incidence of dose interruptions/discontinuations/reductions. Secondary outcomes include preliminary antitumor activity, pharmacokinetics, and biodistribution. RD will consider all available data. Planned enrollment is about 48 patients and is currently open. Clinical trial ID: NCT05870579.

### Status

Currently enrolling.

## TPS 25 Phase 1/2 Study of the Novel Radioligand Therapy [177Lu]Lu-NeoB Plus Capecitabine in Patients With ER+/HER2- Advanced Breast Cancer (ABC) With GRPR Expression After Progression on Prior Endocrine Therapy Plus a CDK4/6 Inhibitor for ABC

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### Background

A CDK4/6 inhibitor (CDK4/6i) plus endocrine therapy (ET) has

become standard of care in first-line estrogen receptor–positive (ER+)/HER2–negative (HER2–) advanced breast cancer (ABC). Despite significant improvements in survival, these patients will eventually experience disease progression. Optimal treatment sequence following progression on CDK4/6i plus ET has not yet been established and is dependent on various factors. Thus, new targeted treatments are needed for patients with ET-resistant ABC. [177Lu]Lu-NeoB (177Lu-NeoB) is a first-in-class radioligand therapy that binds selectively to GRPR. NeoRay is a first-in-human trial testing 177Lu-NeoB in advanced solid tumors. We describe the CAAA603D12101 study (NeoB D1), a phase 1/2, open-label, multicenter study evaluating 177Lu-NeoB plus capecitabine, a known radiosensitizer, in patients with ER+/HER2– ABC with GRPR expression after progression on prior ET plus CDK4/6i.

## Materials and Methods

NeoB D1 includes dose-escalation and dose-optimization for 177Lu-NeoB. Eligible patients include adult men and pre/perimenopausal women with ER+/HER2– ABC. Patients can have received 1 to 3 prior lines of ET for ABC, 1 of which is required to have included a CDK4/6i. For patients with a *BRCA1/2* mutation, prior treatment with a PARP inhibitor is allowed. For patients with HER2-low disease, prior treatment

with trastuzumab deruxtecan is allowed.

In phase 1, patients will receive 177Lu-NeoB at 150 millicurie (mCi) every 6 weeks (Q6W) plus capecitabine (1000 mg/m<sup>2</sup> by mouth for 14 days, followed by 7 days off). If dose escalation is supported, then patients will be randomized to the 2 higher dose levels (200 mCi Q6W or 100 mCi Q3W); if dose escalation is not supported, then lower levels will be explored. Phase 2 will randomize patients to 2 dose levels of 177Lu-NeoB plus capecitabine based on multiple different scenarios. Treatment duration of 177Lu-NeoB is planned to be 6 administrations for the Q6W regimen and 12 administrations for the Q3W regimen.

The primary objectives of the dose-escalation are incidence and severity of dose-limiting toxicities and adverse effects and dose modifications of 177Lu-NeoB plus capecitabine. The primary objectives of the dose-optimization are objective response rate, clinical benefit rate, time to response, duration of response, progression-free survival, and overall survival. Secondary objectives include PK and biodistribution. Planned enrollment is about 58 patients. Enrollment is currently open. ClinicalTrials.gov ID: NCT06247995.

## Status

Currently enrolling.

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## 26 Risk of Recurrence in Real-World NATALEE- and monarchE-Eligible Populations of Patients With HR+/HER2- Early Breast Cancer in an Electronic Health Record-Derived Database

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### Background

NATALEE and monarchE trials showed statistically significant invasive disease-free survival benefits with the addition of a CDK4/6 inhibitor to endocrine therapy (ET) in patients with hormone receptor-positive (HR+)/HER2-negative (HER2-) early breast cancer (EBC). This analysis reports patient characteristics and efficacy in the NATALEE- and monarch-eligible populations in a US real-world electronic health record (EHR)-derived database.

### Materials and Methods

De-identified data from the Flatiron Health US EHR database

were analyzed. Patients with stage I to III HR+/HER2- EBC who met eligibility characteristics for NATALEE or monarchE were included. NAT eligibility was stage II/III disease (AJCC 8th edition) irrespective of nodal status, with criteria for stage IIA T2N0 disease (grade 2 with Ki-67  $\geq$  20% or high genomic risk; grade 3). monarchE eligibility was  $\geq$  4 positive lymph nodes (LNs) or 1 to 3 positive LNs and grade 3 and/or tumor size of  $\geq$  5 cm (cohort 1) and 1 to 3 positive LNs and Ki-67 of  $\geq$  20% (grade  $<$  3 and tumor size  $<$  5 cm; cohort 2). N1mi disease was allowed in monarchE. Recurrence-free survival (RFS) and distant recurrence-free survival (DRFS) were assessed.

### Results

Overall, 2534 patients were eligible for NATALEE and 1157 were for monarchE. Median age was 61 years in NATALEE and 60 years in monarchE. Around 1/2 of patients in NATALEE and about 2/3 in monarchE received prior chemotherapy (CT). Most patients in NATALEE had stage II disease, while most in monarchE had stage III. In both populations, most patients had N1 disease.

Median follow-up from initial diagnosis was 55.1 months (NATALEE) and 53.4 months (monarchE). Risk of invasive breast cancer recurrence (excluding invasive contralateral breast cancer) or death was clinically meaningful in both NATALEE (3 years, 89.2%; 5 years, 81.4%) and monarchE (3 years, 83.4%; 5 years, 72.1%). 5-year RFS rates decreased with increasing stage and nodal status. The risk of distant recurrence or death was considerable in both NATALEE (3 years, 90.4%; 5 years, 83.1%) and monarchE (3 years, 85.2%; 5 years, 74.6%). Five-year DRFS rates by stage and nodal status had trends similar to RFS rates; rates were comparable for N0 and N1 in NATALEE. Patients who did not receive CT had slightly better 5-year RFS and DRFS rates vs patients who received CT.

### Conclusion

This real-world analysis reflects current treatments and shows about 2 times as many patients with HR+/HER2- EBC met NATALEE vs monarchE eligibility criteria. The relatively high distant recurrences 5 years or more in NAT- and monarchE-eligible populations highlight the notable risk of early recurrence and need for risk reduction strategies.

## 27 Elacestrant vs Standard of Care in ER+, HER2- Advanced or Metastatic Breast Cancer With *ESR1*-Mutated Tumors: *ESR1* Allelic Frequencies and Clinical Activity From the Phase 3 EMERALD Trial

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## Background

The phase 3 EMERALD trial (NCT03778931) reported significantly prolonged progression-free survival (PFS) and manageable safety with elacestrant vs standard-of-care (SOC) endocrine therapy (ET) in patients with estrogen receptor–positive (ER+)/HER2–negative (HER2–) metastatic breast cancer (mBC) and tumors harboring *ESR1* mutation after progression on prior ET plus CDK4/6 inhibitor (CDK4/6i; median PFS 3.8 months vs 1.9 months; HR, 0.55; 95% CI 0.39–0.77;  $P = .0005$ ). In patients with prior ET plus CDK4/6i  $\geq 12$  months and *ESR1*-mutated tumors, median PFS with elacestrant was 8.6 months vs 1.9 months with SOC ET (HR, 0.41; 95% CI 0.26–0.63). The PFS benefit was maintained with elacestrant across *ESR1*-mutation variants *D538G*, *Y537S*, and *Y537N*, representing about 90% of *ESR1*-mutated tumors. Variant allele frequency (VAF) in ctDNA correlates with tumor burden and predicts outcomes in patients with mBC. This analysis evaluates the benefit of elacestrant in patients with high vs low *ESR1* VAF.

## Materials and Methods

Patients with ER+/HER2– mBC and 1 to 2 lines prior ET, mandatory CDK4/6i,  $\leq 1$  chemotherapy were randomized 1:1 to elacestrant or SOC. A post hoc subgroup analysis was performed in patients with *ESR1*-mutated endocrine-sensitive tumors (prior exposure to ET plus CDK4/6i  $\geq 12$  months) detected in plasma ctDNA using Guardant Health360 gene panel to evaluate the

benefit of elacestrant vs SOC by *ESR1* VAF. Based on median VAF, high and low VAF were defined as 1.2% or greater and less than 1.2%, respectively.

## Results

In patients who received prior ET plus CDK4/6i  $\geq 12$  months, elacestrant was associated with a clinically meaningful improvement in median PFS vs SOC in patients with high or low *ESR1* VAF: high VAF ( $n = 79$ ), median PFS with elacestrant was 9.1 months vs 1.9 months for SOC (HR, 0.36; 95% CI 0.19–0.69); low VAF ( $n = 79$ ), median PFS with elacestrant was 8.6 months vs 1.9 months SOC (HR, 0.51; 95% CI 0.26–0.99). In patients with the coexistence of *ESR1*-mutations and *PIK3CA*-mutated tumors, elacestrant was associated with longer PFS vs SOC (5.5 months vs 1.9 months; HR, 0.423; 95% CI 0.18–0.94) even though 89% of *ESR1*-mutation were characterized having lower VAF vs *PIK3CA* VAF.

## Conclusion

In patients with longer prior ET plus CDK4/6i, both *ESR1* and *PIK3CA* mutations are drivers of cancer growth, but even at a low VAF, *ESR1*-mutations become clinically significant. Elacestrant was associated with an improvement in median PFS vs SOC in ER+/HER2– mBC regardless of the type of *ESR1*-mutation variant or level of VAF (high or low). A longer PFS benefit was observed with elacestrant vs SOC in patients with tumors harboring coexisting *ESR1* and *PIK3CA* mutations despite 89% of patients having a lower *ESR1*-mutation VAF compared with *PIK3CA*-mutation VAF. In patients with ER+/HER2– mBC who received a longer duration of prior ET plus CDK4/6i and with tumors harboring coexisting *ESR1* and *PIK3CA* mutations, elacestrant can be used before PI3K/AKTi, chemotherapy, or antibody-drug conjugate-based regimens.

# TPS 28 ELEGANT: Elacestrant VS Standard Endocrine Therapy in Women and Men With Node-Positive, Estrogen Receptor-Positive, HER2-Negative, Early Breast Cancer With High Risk of Recurrence in a Global, Multicenter, Randomized, Open-Label Phase 3 Study

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## Background

Adjuvant endocrine therapy (ET) is the standard of care (SOC) for treating estrogen receptor–positive (ER+)/HER2–negative (HER2–) early breast cancer (EBC). Despite advances to optimize adj treatment in high-risk ER+/HER2– EBC, there continues to be a risk of local and metastatic (incurable) recurrence that persists, and new therapies with desirable safety profiles are warranted. Elacestrant is a next-generation oral SERD that provides a novel mechanism of action that has shown both SERD (degradative) and SERM (partial agonist) activity that differs from currently available adjuvant ET. In the EMERALD trial, elacestrant significantly prolonged progression-free survival (PFS) vs SOC ET in the overall population (HR, 0.70; 95% CI, 0.55–0.88;  $P = .0018$ ) and in patients with *ESR1*-mutated tumors (HR, 0.55; 95% CI, 0.39–0.77;  $P = .0005$ ). In patients with *ESR1*-mutated tumors who received prior ET plus CDK4/6 inhibitor (CDK4.6i) at 12 months or longer, median PFS with elacestrant was 8.6 months vs 1.9 months with SOC ET. In a preoperative, window of opportunity ER+/HER2– EBC trial (SOLTI-1905-ELIPSE), elacestrant was associated with complete cell cycle arrest (defined as Ki67 < 2.7%) rate of 27% and a statistically significant mean change from baseline, shifting tumor

biology toward a more endocrine-sensitive and less proliferative tumor phenotype. Given that elacestrant demonstrated efficacy in metastatic breast cancer regardless of *ESR1*-mutation status relative to SOC ET and has shown biologic activity in EBC, it is hypothesized that elacestrant can prolong invasive breast cancer-free survival (IBCFS) in patients with high-risk EBC who received prior adjuvant ET with or without CDK4/6i.

## Materials and Methods

ELEGANT (NCT06492616) is a global, multicenter, open-label phase 3 study designed to evaluate elacestrant vs SOC ET (aromatase inhibitor or tamoxifen) in patients with EBC and a high risk of recurrence. Patients will be randomized 1:1 to continue SOC ET or to elacestrant for a duration of 5 years. Eligible patients are women or men with ER+/HER2– node-positive EBC who have completed 24 to 60 months of adjuvant ET with or without CDK4/6i, and an ECOG performance status of  $\leq 1$ . Patients who received a prior CDK4/6i or a PARP inhibitor must have already completed or discontinued these treatments. Pre/perimenopausal women and men will be administered a LHRH agonist. Exclusion criteria include inflammatory breast cancer, history of prior invasive breast cancer, and > 6 month continuous interruption of prior SOC adjuvant ET or discontinuation of adjuvant ET > 6 months prior to randomization. The primary end point is IBCFS. Key secondary end points include distant relapse-free survival, overall survival, invasive disease-free survival, safety, patient-reported outcomes—quality of life, and pharmacokinetics.

## Status

Planned enrollment is 4220 patients; recruitment is ongoing.

## 30 Imlunestrant, an Oral Selective Estrogen Receptor Degradator, as Monotherapy and Combined With Abemaciclib, for Patients with ER+, HER2– Advanced Breast Cancer, Pretreated With Endocrine Therapy: Results of the Phase 3 EMBER-3 Trial

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## Background

Imlunestrant is a brain-penetrant oral selective estrogen receptor degrader (SERD) and pure estrogen receptor (ER) antagonist that delivers continuous ER inhibition, including in *ESR1*-mutant cancers.

## Materials and Methods

In this phase 3 open-label trial, we evaluated progression-free survival (PFS) and safety of imlunestrant monotherapy and combination with abemaciclib in patients who are pretreated with endocrine therapy (ET) and have ER-positive (ER+), HER2-negative (HER2-) advanced breast cancer (ABC) that recurred or progressed on/after an aromatase inhibitor, alone or with a CDK4/6 inhibitor (CDK4/6i). Patients were randomized 1:1:1 to imlunestrant (400mg daily), physician's choice standard-of-care (SOC; fulvestrant or exemestane) ET or imlunestrant plus abemaciclib (150mg twice daily). Primary end points were investigator-assessed PFS of imlunestrant vs SOC in patients with *ESR1* mutations and all patients, and imlunestrant plus abemaciclib vs imlunestrant in all concurrently randomized patients. Secondary end points included OS (tested if the corresponding PFS was statistically significant), PFS by BICR, overall response rate, and safety.

## Results

Of 874 randomized patients (imlunestrant, n = 331; SOC, n = 330; imlunestrant plus abemaciclib, n = 213), 256 had *ESR1* mutation (imlunestrant, n = 138; SOC, n = 118). Imlunestrant significantly improved PFS vs SOC in patients with *ESR1* mutations (HR, 0.62; 95% CI, 0.46-0.82;  $P < .001$ ; median PFS 5.5 months vs 3.8 months) but not in the overall population (n = 661; HR, 0.87; 95% CI, 0.72-1.04;  $P = .12$ ). Imlunestrant plus abemaciclib significantly improved PFS vs imlunestrant in all patients (n = 426; HR, 0.57; 95% CI, 0.44-0.73;  $P < .001$ ; median PFS 9.4 months vs 5.5 months) regardless of presence of mutations in *ESR1* or PI3K pathway and regardless of prior treatment with CDK4/6i. OS analyses were immature. Common all-grade treatment-emergent adverse effects (TEAEs) with imlunestrant vs SOC were fatigue (23% vs 13%), diarrhea (21% vs 12%), and nausea (17% vs 13%), mostly grade 1. Common grade 3 or higher TEAEs were anemia (2% vs 3%), and neutropenia (2% each). Common all-grade/grade 3 or higher TEAEs with imlunestrant plus abemaciclib were diarrhea (86%/8%), nausea (49%/2%), and neutropenia (48%/20%). Grade 3 or higher TEAEs rates for imlunestrant, SOC, and imlunestrant plus abemaciclib were 17%, 21%, and 49%, respectively. Discontinuation of imlunestrant and imlunestrant plus abemaciclib due to AEs was low (4% and 6%, respectively).

## Conclusion

Imlunestrant significantly improved PFS vs SOC in patients with *ESR1* mutations, and imlunestrant plus abemaciclib significantly improved PFS vs imlunestrant in all patients regardless of *ESR1* mutation status. Imlunestrant as monotherapy had a favorable safety profile alone and combined with abemaciclib, thus providing an all-oral targeted therapy option for ET-pretreated patients with ER+, HER2- antibody-drug conjugate.

## UPDATES TO THE MANAGEMENT OF THE AXILLA

The March issue of *ONCOLOGY* highlights axillary management strategies regarding surgery. Anita Mamtani, MD, and Andrea V. Barrio, MD. The review encompasses advances and controversies over surgical management relating to the axilla for breast cancer.



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## TPS 31 Real-World Sacituzumab Govitecan Treatment Patterns and Outcomes in Second-Line or Later Metastatic Triple-Negative Breast Cancer: Leveraging Electronic Health Records and Manual Curation of a US Database

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### Background

Triple-negative breast cancer (TNBC) is an aggressive type of breast cancer that grows and spreads quickly, has limited treatment options, and tends to have a poor prognosis. The 5-year relative survival rate for metastatic TNBC is 14.3%, consistently lower than other breast cancer subtypes. Sacituzumab govitecan-hziy is FDA approved for patients with metastatic TNBC who have received 2 or more prior therapies, with 1 or more in the metastatic setting. Here, we aim to describe real-world demographics, clinical characteristics, treatment patterns, and outcomes for patients with metastatic TNBC treated with sacituzumab govitecan in the second-line setting or later. The present study builds on findings of 2 recent observational studies in the ConcertAI Patient360 database and Flatiron Health electronic health record (EHR)-derived deidentified database and is designed to include a larger sample size and longer follow-up to further characterize early adoption and more recent real-world utilization patterns of SG for treatment of metastatic TNBC.

### Materials and Methods

The Integra Connect-PrecisionQ de-identified database harmonizes real-world EHR data of more than 3.2 million lives and more than 5000 providers across community oncology clinics in the US. The database contains structured patient-level data enhanced by manual curation, including diagnosis codes, laboratory values, comorbidities, treatments (dose, duration), unstructured fields comprising physician notes, biomarker testing details, reasons for treatment discontinuation, medical events, response, disease progression, etc. Adult patients diagnosed with metastatic TNBC treated in US community oncology practices receiving second-line sacituzumab govitecan from April 1, 2020, through December 31, 2023, will be included. Patients with any other primary cancer diagnosed or who participated in a clinical trial during the study observation period will be excluded.

### Status

Data from up to 500 patients with metastatic TNBC treated with sacituzumab govitecan will be curated, with follow-up data through October 31, 2024. The planned analyses include descriptions of baseline demographic and clinical characteristics, treatment patterns, and clinical outcomes. Key clinical end points of interest are time to treatment discontinuation or death, time to next treatment or death, overall response rate, real-world progression-free survival, and real-world overall survival.

## TPS 38 ELCIN: Elacestrant in Women and Men With CDK4/6 Inhibitor-Naive Estrogen Receptor-Positive, HER2-Negative Metastatic Breast Cancer: An Open-Label, Multicenter, Phase 2 Study

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### Background

Endocrine therapy (ET) plus a CDK4/6 inhibitor (CDK4/6i) is the mainstay treatment in first-line estrogen receptor-positive/HER2-negative (ER+/HER2-) metastatic breast cancer; however, a subset of patients is unable to tolerate CDK4/6i, and resistance to ET emerges. Intrinsic resistance mechanisms include alterations in the PI3K/AKT/mTOR or cell cycle pathways; acquired



resistance mechanisms include *ESR1* mutations, which emerge in up to 50% of patients during prolonged aromatase inhibitor therapy in metastatic breast cancer. In the phase 3 EMERALD trial (NCT03778931), elacestrant significantly prolonged progression-free survival (PFS) vs standard-of-care (SOC) ET and was associated with a manageable safety profile in patients with ER+/HER2– metastatic breast cancer previously treated with ET plus CDK4/6i, leading to its approval as the first clinically available oral SERD. Elacestrant significantly reduced the risk of progression or death vs SOC ET by 30% in the overall population (HR, 0.70; 95% CI, 0.55-0.88;  $P = .002$ ) and by 45% in patients with *ESR1* mutated tumors (HR, 0.55; 95% CI, 0.39-0.77;  $P = .0005$ ). Preclinical studies demonstrated that elacestrant is equally active in both in vitro and in vivo models of ER+/HER2– breast cancer, regardless of prior exposure to CDK4/6i. Based on preclinical models and clinical efficacy data, elacestrant may improve clinical outcomes in patients who are CDK4/6i-naïve and provide a convenient all-oral treatment option if combined with CDK4/6i. The phase 2 ELCIN trial (NCT05596409) will evaluate efficacy and safety of elacestrant in patients with ER+/HER2– metastatic breast cancer who received prior ET and no prior CDK4/6i in the metastatic setting.

## Materials and Methods

ELCIN is an open-label, multicenter, single-arm phase 2 trial. Eligible patients are women or men with ER+/HER2– metastatic breast cancer who received 1 to 2 lines of prior ET and no prior CDK4/6i or chemotherapy in the metastatic setting. Patients must have measurable disease per RECIST v1.1 or a mainly lytic bone lesion (for bone disease only), ECOG performance status of 0 to 1, adequate bone marrow and organ function, and no active or newly diagnosed central nervous system metastases or visceral crisis. Patients will receive elacestrant at 345 mg once daily. The primary objective is investigator-assessed PFS. Secondary objectives are overall response rate, duration of response, clinical benefit rate, overall survival, patient-reported outcomes, quality of life, and safety. Exploratory objectives include elacestrant efficacy according to *ESR1* mutation status, changes in biomarkers, including allele mutation frequencies (cfNAs), and the relationship between efficacy end points.

## Status

ELCIN has a planned sample size of 60 patients; recruitment is ongoing worldwide.

## 42 Exploring the Treatment Gap in High-Risk HR+, HER2– Early Breast Cancer: Eligible Patients Not Receiving Abemaciclib in the US

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### Background

Real-world risk of recurrence in patients with node-positive, hormone receptor–positive (HR+), HER2-negative (HER2–) early breast cancer who have N1 disease with additional high-risk features or N2/N3 disease is 29% at 5 years when treated with standard adjuvant endocrine therapy (ET). Adjuvant abemaciclib plus ET is approved and recommended for these patients to reduce the risk of recurrence, with about 8% lower rate of recurrence at 5 years vs ET alone. Retrospective, single-institution studies have reported adjuvant abemaciclib utilization rates of about 50% in eligible patients. This real-world study describes characteristics of eligible patients not

receiving adjuvant abemaciclib across more than 250 US cancer clinics.

## Materials and Methods

This retrospective study used the US nationwide Flatiron Health electronic health record-derived de-identified database. Adult patients with HR+, HER2–, node-positive, early breast cancer (stage IA-IIIc) who underwent breast cancer surgery and then initiated adjuvant ET-based therapy from January 2023 to March 2024 were selected. N1/N1mi disease was Grade 3 or 5 cm or more. Adjuvant abemaciclib use was assessed through June 2024. The database does not capture comorbidities, financial considerations, or patient/physician discussion. Baseline characteristics were summarized descriptively.

## Results

Overall, 3170 patients met eligibility criteria. Median age was 62 years (IQR, 51-71). Patients were mostly female (98%), White (62%) and treated in a community setting (83%). Median follow-up was 9 months (IQR, 6-12). Of eligible patients, 1902 (60%) did not receive abemaciclib; characteristics are summarized (Table). Older age and N1 disease were associated with highest percentage of not receiving abemaciclib.

## Conclusion

In this real-world study, 60% of patients with node-positive, high-risk HR+, HER2– early breast cancer meeting eligibility



criteria for adjuvant abemaciclib did not receive this recommended therapy. The most affected subgroups were older patients (who had similar efficacy and adverse effect rates as younger patients in the phase 3 monarchE trial [NCT03155997]) and patients with N1 plus high-risk features (who have a 2-fold or more recurrence

risk vs patients with N1 disease without these high-risk features). Education on recurrence risk and consistent benefit of adjuvant abemaciclib in the approved node-positive, high-risk early breast cancer population, may increase abemaciclib utilization to optimize treatment and prevent incurable metastatic disease.

**Table.** Characteristics and Percentage of Eligible Patients Who Did Not Receive Abemaciclib

Characteristic	Eligible patients in overall cohort	Patients not receiving abemaciclib	
	n	n	%
<b>Age</b>			
<sup>3</sup> 65 years	1330	932	70
< 65 years	1840	970	53
<b>Race</b>			
White	1952	1152	59
Black	327	177	54
<b>Ethnicity</b>			
Hispanic or Latino	242	164	68
Not Hispanic or Latino	2130	1229	58
<b>Practice setting</b>			
Community	2618	1587	61
Academic	438	243	55
<b>Socioeconomic status</b>			
Lowest of 5 levels	498	305	61
Highest of 5 levels	549	313	57
<b>Pathological nodal status</b>			
N1/N1mi*	1738	1200	69
N2	1041	517	50
N3	349	155	44

\* Both N1 and N1mi (micro-metastases) must be grade 3 or tumor size <sup>3</sup> 5 cm.

## TPS 43 ADELA: A Double-Blind, Placebo-Controlled, Randomized Phase 3 Trial of Elacestrant + Everolimus vs Elacestrant + Placebo in ER+/HER2- Advanced Breast Cancer Patients With *ESR1*-Mutated Tumors Progressing on Endocrine Therapy

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### Background

ET plus CDK4/6 inhibitor (CDK4/6i) is the standard of care (SOC)

in first-line estrogen receptor–positive/HER2-negative (ER+/HER2–) advanced breast cancer; however, tumors eventually develop resistance. Constitutive activation in PI3K/AKT/mTOR pathway can contribute to endocrine resistance in breast cancer. The *ESR1* mutation is a common type of acquired resistance that emerges in 40% to 50% of patients in the metastatic setting after prolonged aromatase inhibitor exposure. There is an unmet need for novel therapeutic approaches to overcome resistance mechanisms and improve outcomes in patients with ER+/HER2– advanced breast cancer with *ESR1*-mutated tumors progressing after ET plus CDK4/6i. Elacestrant is a next-generation oral SERD that binds to ER-alpha, inducing its degradation. In the phase 3 EMERALD study (NCT03778931), elacestrant improved progression-free survival (PFS) vs SOC ET in patients with *ESR1*-mutated tumors (HR, 0.55; 95% CI, 0.39-0.77;  $P = .0005$ ). Differences were notable among patients who received prior ET plus CDK4/6i 12 months or more; median PFS with elacestrant was 8.6 months vs 1.9 months with SOC ET (HR, 0.41; 95% CI, 0.26-0.63). Crosstalk between ER and PI3K/AKT/mTOR pathways provides a rationale for evaluating elacestrant with everolimus (an mTORC1 inhibitor). The phase 3 ADELA study (NCT06382948) compares elacestrant plus everolimus vs. elacestrant plus placebo in patients with ER+/HER2– advanced breast cancer with *ESR1*-mutated tumors progressing on ET plus CDK4/6i.

## Materials and Methods

ADELA is an international, multicenter, double-blind, placebo-

controlled phase 3 trial. Eligible patients are adults (>18 years) with ER+/HER2– advanced breast cancer with *ESR1*-mutated tumors, previously treated with 1 to 2 lines of ET for advanced breast cancer, and evidence of disease progression on prior ET plus CDK4/6i for advanced after 6 months or more. Patients receiving CDK4/6i-based adjuvant therapy are eligible (disease progression must be confirmed after 12 months or more of treatment but less than 12 months following CDK4/6i completion). Other criteria include adequate organ function and ECOG performance status of 0 to 1. Exclusion criteria include prior chemotherapy for advanced breast cancer and active uncontrolled/symptomatic brain metastasis. Patients will be randomized 1:1 to 28-day cycles of elacestrant at 345 mg plus everolimus at 7.5 mg by mouth or elacestrant at 345 mg plus placebo by mouth until disease progression or unacceptable toxicity, based on dose determined in phase 1/2 ELEVATE trial (NCT05563220). Patients will receive dexamethasone mouthwash during the first 8 weeks. Stratification factors are the presence of visceral metastases (yes vs no) and duration of prior CDK4/6i ( $\geq 12$  months vs  $< 12$  months). The primary objective will evaluate BIRC-based PFS. Secondary end points included investigator-assessed PFS, overall survival, overall response rate, clinical benefit rate, duration of response, time to response, the best percentage change in tumor burden, safety, and health-related quality of life.

## Status

Planned enrollment is 240 patients; recruitment is ongoing.

## 45 A Phase 3 Randomized Study of Adjuvant Sacituzumab Tirumotecan Plus Pembrolizumab vs Treatment of Physician's Choice in Patients With Triple-Negative Breast Cancer Who Received Neoadjuvant Therapy and Did Not Achieve a Pathological Complete Response at Surgery

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## Background

TROP2 expression is higher in triple-negative breast cancer (TNBC) vs other breast cancer subtypes, and high expression is associated with poor prognosis. Sacituzumab tirumotecan (also known as MK-2870/SKB264) is a novel antibody-drug conjugate composed of anti-TROP2 antibody coupled to a cytotoxic belotecan derivative via a novel linker (average drug/antibody ratio, 7.4). In a prior phase 3 study OptiTROP-Breast01 (NCT05347134), sacituzumab tirumotecan alone improved progression-free survival (HR, 0.31; 95% CI, 0.22-0.45;  $P < .00001$ ) and overall survival (OS; HR, 0.53; 95% CI, 0.36-0.78;  $P = .0005$ ) vs chemotherapy in patients with heavily pretreated advanced TNBC. The current standard of care (SOC) for patients with newly diagnosed, high-risk, early-stage TNBC is neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab after surgery. Patients who do not achieve pathological complete response (pCR) with the current SOC have higher rates of recurrence and

mortality vs patients who achieve pCR. This study (NCT06393374) evaluates adjuvant sacituzumab tirumotecan plus pembrolizumab vs treatment of physician's choice (pembrolizumab ± capecitabine) in patients with TNBC who received neoadjuvant therapy and did not achieve pCR at surgery.

## Materials and Methods

This phase 3, multicenter, open-label study is enrolling patients 18 years and older with centrally confirmed TNBC per the most recent American Society of Clinical Oncology/College of American Pathologists guidelines. Patients have non-pCR after 5 or more cycles of neoadjuvant pembrolizumab plus chemotherapy, including 1 or more cycles of anthracycline-based neoadjuvant therapy. Patients must provide tissue from the surgical specimen for central TROP2 assessment and be able to continue on adjuvant pembrolizumab. Randomization must be conducted 12 weeks or

less from surgical resection (window may be extended in consult with the sponsor). Patients are randomized 1:1 to pembrolizumab 400 mg every 6 weeks for 5 doses plus sacituzumab tirumotecan 4 mg/kg every 2 weeks for 12 doses or physician's choice chemotherapy with pembrolizumab at 400 mg every 6 weeks for 5 doses with or without capecitabine at 1000 to 1250 mg/m<sup>2</sup> twice daily on days 1 to 14 and days 22 to 35 every 42 days for 4 cycles until completion of therapy or disease recurrence, unacceptable toxicity, or withdrawal. Randomization is stratified by residual tumor and lymph node status, TROP2 expression, and intention to use capecitabine. Primary end point is invasive disease-free survival. Secondary end points are OS, distant recurrence-free survival, patient-reported outcomes, and safety.

## Status

Enrollment began in Q2 2024.

## 46 Neoadjuvant Pembrolizumab or Placebo Plus Chemotherapy Followed by Adjuvant Pembrolizumab or Placebo for High-Risk, Early-Stage Triple-Negative Breast Cancer: Overall Survival and Subgroup Results From the Phase 3 KEYNOTE-522 Study

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## Background

In the phase 3 KEYNOTE-522 (NCT03036488), neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab significantly improved pathological complete response and event-free survival (primary end points) vs neoadjuvant placebo plus chemotherapy followed by adjuvant

placebo in patients with high-risk, early-stage triple-negative breast cancer (TNBC). At the prespecified analysis of overall survival (OS; secondary end point; data cutoff, March 22, 2024), the HR favored pembrolizumab (0.66; 95% CI, 0.50-0.87;  $P = .0015$ , crossing the prespecified significance boundary of 0.00503). We present OS results in prespecified subgroups based on residual cancer burden (RCB) and post hoc OS analyses in patients with baseline T2N0 disease.

## Materials and Methods

Eligible patients with previously untreated, nonmetastatic, centrally confirmed TNBC (stage T1c N1-2 or T2-4 N0-2 per AJCC) were randomized 2:1 to neoadjuvant pembrolizumab at 200 mg every 3 weeks or placebo plus 4 cycles of paclitaxel plus carboplatin, followed by 4 cycles of doxorubicin or epirubicin plus cyclophosphamide. After definitive surgery, patients received adjuvant pembrolizumab or placebo for 9 cycles or until recurrence or unacceptable toxicity. The Kaplan-Meier method was used to estimate the subgroups for OS. HRs (95% CIs) for OS subgroups were based on the Cox regression model with the Efron method of

tie handling with treatment as a covariate. RCB was assessed by the local pathologist at the time of definitive surgery.

## Results

1174 patients were randomized to pembro ( $n = 784$ ) or placebo ( $n = 390$ ). At the data cutoff for OS (March 22, 2024), median follow-up was 75.1 months (range, 65.9-84.0). Data are shown in the **Table**. RCB rates were 63.5% with pembrolizumab vs 56.2% with placebo for RCB-0, 8.8% vs 11.5% for RCB-1, 18.4% vs 20.3% for RCB-2, and 5.1% vs 6.7% for RCB-3. At 5 years, OS rates (95% CIs) in patients with baseline T2N0 disease were 93.3% (89.9%-95.6%) with pembrolizumab vs 89.2% (83.2%-93.1%) with placebo. OS in subgroups based on PD-L1 expression will also be presented.

## Conclusion

In patients with high-risk, early-stage TNBC, neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab showed clinically meaningful improvements in OS vs neoadjuvant chemotherapy alone, with the highest OS benefit observed in patients with the least RCB.

## 48 Prevalence of “HER2 Ultra-Low” Among Advanced Breast Cancer Patients With Historical IHC0 Status

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## Background

This study aimed to assess the prevalence of “HER2 Ultra-Low” (faint membrane staining in  $>0$  but  $\leq 10\%$  of tumor cells) expression based on re-scored HER2 IHC0 biopsy slides.

## Materials and Methods

From all 3 US Mayo Clinic campuses, a total of 300 patients with advanced breast cancer (stages III-IV), and clinically documented HER2 IHC0 status between January 2017 and January 2023, were identified. One biopsy slide per patient (IHC assay: VENTANA Pathway anti-HER2/neu (4B5) rabbit monoclonal primary antibody) was digitized and scanned at 40x magnification. Two Mayo Clinic pathologists independently reported HER2 status and

tumor stain percentage for each slide based on 2023 ASCO-CAP guidelines. Patients were considered “HER2 Ultra-Low” if their slide was scored as IHC0 with  $>0\%$  but  $\leq 10\%$  staining. Cohen’s  $\kappa$  was used to quantify the agreement between pathologists.

## Results

Among 300 re-scored patients (mean age of 57.8 years (SD = 13.5)), 285 patients (95%) remained classified as IHC0 by at least 1 pathologist. Of these ( $n = 285$ ), 60% ( $n = 171$ ) were determined as “HER2 Ultra-low” by at least 1 pathologist. The rate of “HER2 Ultra-Low” per pathologist ranged from 43% ( $n = 121$ ) to 45% ( $n = 104$ ). The overall inter-pathologist concordance was 57%; patients with no observable HER2 IHC staining accounted for the majority of the concordant patients (**Table**).

## Conclusion

About 3 in 5 patients with advanced breast cancer originally classified as HER2 IHC0 met the “HER2 Ultra-Low” criteria by at least 1 pathologist, implying that a significant number of additional patients may benefit from HER2 targeted therapy. The relatively low concordance between HER2 expert pathologists in identifying lower levels of HER2 expression suggests the need for increased precision enabled by digital tools, leveraging artificial intelligence, training for community practice pathologists, and continuing to follow best practice recommendations in determining HER2 IHC status.

**Table on next page (p. 28)**



**Table.** Concordance Among 2 Pathologists' (P1/P2) Review of IHC Biopsy Slides

	P2 no observable IHC staining	P2 "HER2 ultra-low"	P2 IHC 1+	P2 IHC2+/indeterminate	P1 total, n (%)
<b>P1 — No observable IHC staining</b>	104 $\kappa = 0.47$	23	2	0	129 (43)
<b>P1 — "HER2 ultra-low"</b>	48	54 $\kappa = 0.17$	2	0	104 (35)
<b>P1 — IHC 1+</b>	7	44	11 $\kappa = 0.21$	0	62 (21)
<b>P1 — IHC 2+/ indeterminate</b>	1	0	2	2 $\kappa = 0.57$	5 (2)
<b>P2 — total</b>	160 (53%)	121 (40%)	17 (6%)	2 (1%)	300
				Concordance	171 (57)
				Discordance	129 (43)
<b><math>\kappa</math>: <math>\leq 0.2</math> poor, 0.21-0.4 fair, 0.41-0.6 good, 0.81-1 very good.</b>					

## 49 Clinical Characteristics and Treatment Persistence in US Patients With HR+/HER2-, Node-Positive Early Breast Cancer Treated With Abemaciclib: Real-World Study From First Year After Approval

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### Background

Abemaciclib in combination with endocrine therapy (ET) is approved for adjuvant treatment of adult patients with hormone receptor–positive/HER2-negative (HR+/HER2–), node-positive, early breast cancer at high risk of recurrence. This retrospective study describes clinical characteristics and treatment persistence in patients with HR+/HER2–, node positive early breast cancer initiating abemaciclib.

### Materials and Methods

Data were accessed from the Flatiron Health electronic database. Adult patients with node-positive, stage I to III early breast cancer-initiating abemaciclib from October 2021 (FDA approval) to November 2022 at 150 mg twice daily (BID) were analyzed. The persistence rate was defined as the percentage of patients remaining on abemaciclib at 3 months, allowing for a 60-day or less medication gap.

### Results

A cohort of 354 patients with a median follow-up time from abemaciclib initiation of 8.8 months were selected. The median age was 56 years, 25.4% were  $\geq 65$  years old, 12.7% were Black, 4.0% were Asian, and most patients (80.8%) received care in a community setting. Over half (55.4%) of patients were postmenopausal; 57.9% had an ECOG performance status (PS) 0, while 25.1% had ECOG PS 1. Approximately 33.9% had 1 or more comorbidity and 12.1% had 2 or more comorbidities with diabetes (14.1%) being the most frequent. Most patients had stage II (41.8%) or III (38.4%) disease, nodal status N1 (45.2%) or N2 (35.3%), and tumor grade 2 (52.3%). Abemaciclib was initiated at a median of 11.1 months after early breast cancer diagnosis. Prior to abemaciclib initiation, most patients received radiotherapy (96.3%) and chemotherapy (83.1%), with 46.3% receiving neoadjuvant chemotherapy. Most patients (74.0%) initiated ET 1.6 months prior to abemaciclib initiation. The median time to abemaciclib initiation

from breast surgery was 6.7 months. The most frequent regimen was abemaciclib plus aromatase inhibitors (91.0%). At 3 months, 81.6% of patients were persistent; 5.6% resumed abemaciclib after more than 60-day interruption, and 11.3% discontinued due to adverse effects. Additional information on dose modifications will be presented.

## Conclusion

In this real-world study of utilization of abemaciclib in the first year after approval for early breast cancer, an older, less fit, and more racially diverse population than participated in the monarchE trial, as well as a higher proportion of patients with lower nodal status was observed. The high 3-month persistence rate suggests abemaciclib for early breast cancer is well tolerated in routine clinical practice.

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## 52 Correlation and Prediction of Complete Pathologic Response Rates and Ki-67 in Patients Receiving Neoadjuvant Immunotherapy for Triple-Negative Breast Cancer

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### Background

Clinical and pathological response to neoadjuvant chemotherapy for breast cancer varies significantly. A complete pathologic response (CPR) is found to be more common in cases of triple-negative breast cancer (TNBC) receiving neoadjuvant therapy. However, even within these groups, response to chemotherapy can still vary, giving credence that there may be other markers that have an influence or can help better predict the likelihood of CPR rate. Ki-67 is a histologic proliferation marker, which has been confirmed to be an independent predictive and prognostic factor in early breast cancer. Many studies have previously investigated Ki-67 as a prediction tool using older chemotherapy regimens; however, with the advent of new immunotherapy-based neoadjuvant treatment regimens, little data on Ki-67 has been elucidated.

### Materials and Methods

Between 2017 and 2022, 65 patients with TNBC were identified from our Tumor Registry. Ki-67 was available for 37 patients, 27 of whom received neoadjuvant immunotherapy as part of their treatment. These data were used to construct univariate and multivariate models to determine the correlation between CPR and a high Ki-67 ( $\geq 20\%$ ).

### Results

Overall, no correlation was noted between patients receiving neoadjuvant immunotherapy and CPR ( $R^2$  0.003,  $P = .65$ ). The mean Ki-67 value was 65.7% in patients with CPR who received neoadjuvant immunotherapy. Patients without CPR after neoadjuvant immunotherapy had an average of 55.6% positively stained cancer cells. A moderate correlation between Ki-67 and CPR was noted between neoadjuvant immunotherapy group ( $R^2$  0.12,  $P = .07$ ) and neoadjuvant nonimmunotherapy group ( $R^2$  0.17,  $P = .23$ ) with no statistical significance.

### Conclusion

This study underscores the known positive relationship between a high Ki-67 and CPR in patients with TNBC receiving neoadjuvant chemotherapy. It further demonstrates that a high Ki-67 has the potential to accurately predict CPR in patients receiving neoadjuvant immunotherapy for their TNBC. Larger studies will be needed to investigate these findings further.

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## 56 Paternal vs Maternal Inheritance of a BRCA Mutation: Is There a Difference in Presentation and Stage of Breast Cancer at Diagnosis?

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### Background

*BRCA* mutations are often associated with a strong family history of breast and/or other cancers, leading to testing and screening before a diagnosis. Paternal family history genetic inheritance may be underrecognized, leading to *BRCA* testing done only at the time of diagnosis and hence later stage of breast cancer at diagnosis. We investigated the differences in presentation and subsequent management between patients with maternal *BRCA* (*M-BRCA*) vs paternal *BRCA* (*P-BRCA*) lineage for patients diagnosed with breast cancer. To our knowledge, there are no current studies that exist in the published literature regarding the

impact of *BRCA* lineage on breast cancer stage and presentation.

## Materials and Methods

Retrospective chart review was performed to identify patients with newly diagnosed breast cancer who were also *BRCA* positive from 2010 to 2022. Pedigree was reviewed, and the lineage of the mutation was assigned as definitively or likely paternal or maternal; we excluded patients whose lineage could not be determined. Comparisons were made between the inheritance groups using a 2-sample independent t-test and binomial regression models.

## Results

A total of 219 patients who are *BRCA*-positive with newly diagnosed breast cancer were identified, with 134 patients meeting inclusion criteria where lineage could be determined (Table); 59 (44%) having P-*BRCA* with 75 (55%) having M-*BRCA*. Overall, 111 (83%) had invasive cancer and 23 (17%) had ductal carcinoma in situ (DCIS). P-*BRCA* patients were more likely to be diagnosed with invasive cancer, compared with

M-*BRCA* (91.5% vs 76.0%;  $P = .028$ ), and more likely to be node-positive (23.7% vs 10.7%;  $P = .0498$ ). There was a trend toward larger tumor size and receipt of neoadjuvant treatment for paternally linked *BRCA* mutation, (23.6 mm vs 20.4 mm and 39.7% vs 29.3%); however, these were not significant. Patients with P-*BRCA* also tended to be diagnosed with cancer at a younger age compared with M-*BRCA*, were slightly more likely to be diagnosed with cancer before genetic testing, had fewer MRI detected cancers and more detected by physical exam, but these were also not statistically significant.

## Conclusion

Our results support the hypothesis that P-*BRCA* patients are more likely to present with later stage disease (invasive vs DCIS, node positivity) with a trend toward increased discovery of *BRCA*-positivity after diagnosis, and by physical exam in lieu of MRI. These data confirm the need for wider testing and awareness related to *BRCA* transmission through paternal lineage. A larger sample size may show statistical significance among trending variables.

**Table.** Patient Characteristics of Paternal vs Maternal Inheritance of *BRCA* Mutation

	P- <i>BRCA</i> <sup>a</sup> (n=59; 44.0%)	M- <i>BRCA</i> <sup>a</sup> (n=75; 56.0%)	Effect size (95% CI)	P value
<b>Age at diagnosis, y</b>			3.9 (-0.4, 8.2)	.0753
Mean	44.7	48.6		
Range	27.5-77.5	26.7-85.1		
<b>Age at genetic testing, y</b>			2.6 (-1.7, 7.1)	.2129
Mean	44.1	46.7		
Range	26.0-81.0	23.0-83.2		
<b>Mean tumor size, mm</b>			-3.2 (-9.6, 3.2)	.3205
Mean	23.6	20.4		
Range	1.0-86.0	2.0-60.0		
			Prevalence ratio (95% CI)	P value
<b>Stage at presentation, n (%)</b>			0.35 (0.14-0.89)	.0283
Stage 0 <sup>c</sup>	5 (8.5)	18 (24.0)		
Invasive cancer	54 (91.5)	57 (76)		
<b>Metastatic disease, n (%)</b>			—	N/A
Non-metastatic	59 (100)	72 (96.0)		
Metastatic	0 (0.0)	3 (4.0)		
<b>Node positivity, n (%)</b>			2.22 (1.00-4.94)	.0498
Negative (n=114)	45 (76.3)	67 (89.3)		
Positive (n=20)	14 (23.7)	8 (10.7)		

Table on p. 31



Table continued from p. 30

<b>Neoadjuvant treatment, n (%)</b>			1.27 (0.57-2.85)	.212
Neoadjuvant treatment	23 (39.7)	23 (39.7)		
No neoadjuvant treatment	35 (60.3)	53 (70.7)		
<b>Genetic testing, n (%)</b>			1.05 (0.77-1.40)	.7549
Prior to diagnosis	25 (43.1)	33 (45.8)		
Following diagnosis	33 (56.9)	39 (54.2)		
<b>Receptor profile, n (%)</b>				
HR+, HER2+	24 (44.4)	25 (43.9)	1.01 (0.67-1.54)	.9505
HR+, HER2-	3 (5.6)	0 (0)	—	—
HR-, HER2+	1 (1.9)	1 (1.8)	1.05 (0.07-16.4)	.9692
HR-, HER2-	20 (37.0)	28 (49.1)	0.75 (0.49-1.17)	.205
				Fisher exact P value
<b>Tumor size, n (%)</b>				.73051
≤ 20 mm	27 (50.0)	31 (57.4)		
> 20 to ≤ 50	23 (42.6)	20 (37.0)		
> 50 mm	4 (7.4)	3 (5.6)		
<b>Mode of detection, n (%)</b>				.49681
Physical exam	27 (45.8)	28 (37.3)		
Mammography	21 (35.6)	25 (33.3)		
MRI	6 (10.2)	15 (20.0)		
Ultrasound	5 (8.5)	5 (6.7)		
Incidental	0 (0.0)	1 (1.3)		
Unknown	0 (0.0)	1 (1.3)		

<sup>a</sup>P-BRCA is defined as patients with likely paternally linked BRCA mutation inheritance.  
<sup>b</sup>M-BRCA is defined as patients with likely maternally linked BRCA mutation inheritance.

<sup>c</sup>Stage 0 is defined by ductal carcinoma in situ without an invasive component.

HER-2 +/- = human epidermal growth factor receptor 2 positive/negative; HR+/- = hormone receptor positive/negative.

## 57 Tumor Morphology Concordance in Multifocal/Multicentric Triple-Negative and HER2+ Breast Cancers

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### Background

There are a number of studies examining exceptional responders to neoadjuvant chemotherapy (NAC) and the potential to eliminate breast surgery. Thus far, patients with multifocal/multicentric (MF/MC) tumors have been excluded from surgery omission studies and mastectomy is often recommended. Obligatory mastectomy may be overtreatment for patients who achieve pathological complete response (pCR) after NAC. One potential application of surgical

omission studies could be excision of the primary tumor for patients with MF/MC tumors, and avoid mastectomy. This is only possible if response rates, or the morphology of the multiple sites, are similar.

The objective of the study is to evaluate for biomarker and morphology concordance between the main tumor and satellite sites of multifocal/multicentric triple-negative breast cancer (TNBC) and HER2-positive tumors.

### Materials and Methods

We performed a retrospective chart review of MF/MC tumors within our institutional database. Of those, we selected patients with TNBC or HER2-positive tumors. The following characteristics were collected and analyzed: number of foci, size of foci, number of core biopsies performed, clinical stage, foci

concordance, systemic therapy (neoadjuvant or adjuvant), surgery type, pathologic complete response (pCR) status (ypT0/ypTis). The surgical pathology slides were re-reviewed by a single pathologist to assess for tumor morphology and biomarker concordance.

## Results

There were a total of 315 patients with MF/MC disease. We identified 45 patients with TNBC and HER2-positive tumors. There were 3 patients with clinical multifocal disease by imaging but were found to be unifocal on final pathology. The median number of foci was 2 (1-4). The median size of the largest foci was 2.5 cm (0.3 -12.5). The most common clinical stage was 2 (40%). There were 13 patients treated with neoadjuvant and 29 patients treated with upfront surgery.

Of the 13 patients treated with NAC, 1 had a pCR (TNBC)—all tumor foci responded uniformly. Of the TNBC patients who received NAC, 1 patient's surgical excision slides were not available and of the HER2-positive patients who received NAC, 1 patient's surgical excision slides were not available for re-review of concordance.

Of the 10 evaluable patients with remaining disease,

morphology was concordant among 8/10 (80%). The 2 discordant patients had incidental invasive lobular carcinoma on final pathology, and both patients had only 1 preoperative core biopsy. Nine out of 13 (69%) patients underwent mastectomy.

There were 29 patients treated with upfront surgery. Of the patients with TNBC with upfront surgery, 5 patients did not have surgical excision slides available, and of the HER2-positive patients with upfront surgery, 1 patient did not have surgical excision slides available for pathology re-review of concordance.

Of the 23 evaluable patients treated with upfront surgery, morphology was concordant among 21/23 (91%). There were 18 out of 29 (62%) upfront surgery patients who underwent mastectomy.

## Conclusion

Tumor morphology and biomarkers were similar among separate tumor foci for a majority of patients with TNBC and HER2-positive disease. Further analyses are warranted with larger sample sizes to assess the feasibility of breast conservation (lumpectomy of the main site) in patients with multifocal/multicentric tumors after NAC.

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## 59 Are Choosing Wisely Guidelines Applicable to Patients With a High Ki-67 Proliferation Index and Magee Equation Score?

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### Background

Choosing Wisely guidelines discourage routine axillary staging in older women with early-stage hormone receptor–positive/HER2-negative (HR+/HER2–), clinically node-negative (cN0) breast cancer. This study aimed to determine if sentinel lymph node biopsy (SLNB) can be safely omitted in such patients with guidance of the Ki-67 index and Magee Equation (ME) score.

### Materials and Methods

Patients diagnosed with early-stage (tumor <5 cm), HR+/HER2–, and cN0 breast cancer from January 2010 to December 2012 were retrospectively identified from a prospectively maintained single-institution registry. Patients with bilateral breast cancer, distant metastases, clinically suspicious lymph nodes, and receipt of axillary lymph node dissection were excluded. Variables included age, race, tumor size, Nottingham score, nuclear grade, HR H-scores, Ki-67 percentage, clinical T stage, type of surgery, number and pathologic status of nodes retrieved, ME result, recurrence, and follow-up time.

Low, intermediate, and high Ki-67 indices were defined as 0% to 15%, 16% to 30%, and 31% to 100%, respectively. ME

utilizes the Nottingham score, HR H-scores, tumor size, and Ki-67 percentage to estimate the Oncotype DX Recurrence Score. ME result was defined as either low ( $\leq 25$ ) or high ( $> 25$ ). Primary end point was recurrence-free survival (RFS) at 5 years. Secondary end points were locoregional recurrence-free survival (LRFS) and overall survival (OS).

### Results

Of 538 patients who met inclusion criteria, 435 (79%) underwent sentinel lymph node biopsy (SLNB). Median follow-up time was 6.1 years. Ki-67 index was low, intermediate, high, and unknown in 312 (58%), 138 (26%), 76 (14%), and 12 (2%) patients, respectively. ME was low, high, and unknown in 415 (77%), 42 (8%), and 81 (15%) patients, respectively. In multivariable analysis adjusting for clinical T stage, nuclear grade, and HR H-scores, neither the Ki-67 index ( $P = .65$ ) or ME score ( $P = .45$ ) were associated with a difference in relapse-free survival (RFS), local recurrence-free survival (LRFS), or overall survival (OS). In patients who had both an elevated Ki-67 index or ME, no patient had a nodal burden greater than 2 positive nodes. In patients who did not undergo SLNB, Ki-67 index and ME score were not associated with differences in outcomes.

### Conclusion

In this study, patients with early-stage HR+, cN0 breast cancer with an elevated Ki-67 index and ME score, a surrogate marker of increased genomic risk, were not at risk for worse outcomes, including RFS, LRFS, or OS. These results suggest that SLNB can be safely omitted in this population even when a patient has high Ki-67 indices or ME, as the lack of this pathological nodal information does not affect the postoperative treatment plan.

## 78 Comparison of Positive Margin Rate of Breast Cancer in Higher BMI Patients

Caroline Lippe,<sup>1</sup> Harper Niver,<sup>1</sup> W. Bradford Carter<sup>1</sup>

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### Background

There is about a 20% risk of positive margins in lumpectomy cases for breast cancer. For success to clear the cancer in question, a clear surgical margin must be taken. We hypothesized that those patients with higher BMIs may have more breast tissue, therefore allowing a larger specimen to be removed at the time of surgery, leading to a lower positive margin rate. We will also determine if those with a greater BMI will have more tissue removed from the specimen during their operation.

### Materials and Methods

This was a retrospective chart review analysis of patients who underwent lumpectomy and re-excision of margins over 5 years. Patients who were included in our study were female, with estrogen receptor–positive/HER2-negative (ER+/HER2–) breast cancer. Patients were then divided based on body mass index (BMI) and characteristics of their tumor specimen investigated.

### Results

A total of 1461 patients underwent lumpectomy between 2017 and 2022. Out of those patients, 81 met our criteria and underwent re-excision of margins. Additionally, 24 patients were found to have a BMI greater than 30. The average specimen diameter with those patients with a BMI greater than 30 was 6.54 cm compared with 4.95 cm in those with lower BMIs. In those patients where specimens were weighed, those patients with BMIs greater than 30,



the average specimen was 48.17 g vs 16.95 g in patients with lower BMIs. Of note, 78 patients had re-excision of margins due to ductal carcinoma in situ, while 2 patients had re-excision for invasive ductal carcinoma and one patient for lobular carcinoma in situ.

## 82 Efficacy, Safety, and Biomarker Analysis of ICARUS-BREAST01: A Phase 2 Study of Patritumab Deruxtecan (HER3-DXd) in Patients With HR+/HER2- Advanced Breast Cancer

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### Background

Despite the improved clinical outcomes achieved with endocrine therapy (ET) plus CDK4/6 inhibitors (CDK4/6i) in hormone receptor-positive/HER2-negative (HR+/HER2-) advanced breast cancer, few effective therapeutic agents are available beyond progression. HER3 expression is associated with poor prognosis and resistance to PI3K/AKT/mTOR inhibitors and ET. Patritumab deruxtecan (HER3-DXd) is an antibody drug conjugate composed of an anti-HER3 monoclonal antibody conjugated to a

### Conclusion

Positive margins are a possible complication of lumpectomy, about a 20% risk, that can be mitigated by a larger amount of tissue. We show that patients who have a higher BMI allow more tissue to be taken and therefore lower risk of positive margin.

topoisomerase I inhibitor by a cleavable peptide linker. The phase 2 ICARUS-BREAST01 (NCT04965766) trial is an academic, multicenter, single-arm, phase 2 study evaluating activity, safety, and biomarkers of response/resistance to HER3-DXd in patients with HR+/HER2- advanced breast cancer who progressed on CDK4/6i and 1 line of chemotherapy.

### Materials and Methods

Adult patients were enrolled to receive HER3-DXd at 5.6 mg/kg intravenously every 3 weeks until progression or unacceptable toxicity. The primary end point was confirmed objective response rate (cORR) by local investigator assessment. Secondary end points were clinical benefit rate (CBR), progression-free survival (PFS), duration of response (DOR), and safety. Exploratory translational analyses were conducted on blood and tumor samples.

### Results

At the April 16, 2024, data cutoff, 99 patients were included and 19 were still on treatment. Median age was 57.0 years (IQR, 48.0-66.0 years), median duration of prior CDK4/6i was 13.7 months (IQR, 2.9-42.0 months). At a median follow-up of 15.3 months (95% CI, 13.0-17.2) cORR was 53.5% (95% CI, 43.2%-63.6%), CBR was 62.6% (95% CI, 52.3%-72.1%), median PFS was 9.2 months (95% CI, 8.0-12.8), and median DOR was 9.3 months (95% CI, 8.2-not evaluable). Treatment-emergent adverse effects (TEAEs; any grade  $\geq 3$ ) occurred in 98.0%/50.1% of patients. TEAEs led to dose reduction/discontinuation in 20.2%/11.1%. The most frequent treatment-related TEAEs were fatigue (82.8%/10.1%), nausea (74.7%/14.1%), and diarrhea (52.5%/10.1%); 8 patients (8.1%) had centrally adjudicated interstitial lung disease (6 grade 1, 2 grade 2). Data on HER3 expression and translational analyses on tumor and blood samples will be presented.

### Conclusion

HER3-DXd showed clinically meaningful activity and a manageable safety profile in patients with HR+/HER2- advanced breast cancer that progressed after  $\geq 2$  lines of therapy. Further studies are warranted to confirm the role of HER3-DXd in this setting.

## TPS 83 ELAINE 3: Open-Label, Randomized, Multicenter, Phase 3 Study of the Efficacy and Safety of Lasofoxifene Plus Abemaciclib for Treating Locally Advanced or Metastatic, ER+/HER2-, Breast Cancer With an *ESR1* Mutation

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### Background

Mutations of the *ESR1* gene are thought to drive resistance to endocrine therapy (ET) in patients with estrogen receptor–positive/HER2-negative (ER+/HER2-) metastatic breast cancer, especially after a CDK4/6i inhibitor (CDK4/6i). Lasofoxifene is an oral, next-generation ET and ER antagonist at the breast. Two phase 2 studies examined the effects of lasofoxifene in women with ER+/HER2-, *ESR1*-mutated metastatic breast cancer that progressed on previous ET and CDK4/6i. The phase 2 ELAINE 1 trial (NCT03781063) showed numerically greater progression-free survival (PFS; median, 5.6 months vs 3.7 months; HR, 0.669; 95% CI, 0.445-1.125;  $P = .138$ ), objective response rate (ORR, 13% vs 3%;  $P = .124$ ), and clinical benefit rate (CBR, 37% vs 22%;  $P = .117$ ) vs the ER degrader fulvestrant, with a favorable safety profile.

In the phase 2 ELAINE 2 trial (NCT04432454), lasofoxifene

plus abemaciclib was well tolerated with a median PFS of about 13 months, ORR of 56%, and CBR of 66%. The efficacy of abemaciclib/fulvestrant in postMONARCH was also shown to be superior vs fulvestrant/placebo (median PFS, 6.0 months vs 5.3 months; HR, 0.73; 95% CI, 0.57-0.95; nominal  $P = .02$ ) in non-biomarker–selected patients with metastatic breast cancer who progressed on CDK4/6 inhibitors and aromatase inhibitors (AIs) with a similar HR in patients with *ESR1* mutations. The promising results of the ELAINE 1 and 2 trials supported initiation of the registrational phase 3 ELAINE 3 trial (NCT05696626).

### Materials and Methods

ELAINE 3 is an open-label, phase 3, multicenter study that evaluated the efficacy, safety, and tolerability of lasofoxifene plus abemaciclib vs fulvestrant plus abemaciclib. Women (pre- and postmenopausal) and men were aged 18 years or older; and had ER+/HER2-, locally advanced breast cancer and/or metastatic breast cancer; 1 or more acquired *ESR1* mutation; progression on an aromatase inhibitor plus palbociclib or ribociclib as their first hormonal therapy for advanced breast cancer/metastatic breast cancer; and 1 or fewer chemotherapy line in the advanced/metastatic setting. Patients will be randomized 1:1 to lasofoxifene at 5 mg/day plus abemaciclib at 150 mg BID, or fulvestrant 500 mg IM (on days 1, 15, and 29, then monthly), plus abemaciclib 150 mg twice daily, until progression, death, unacceptable toxicity, or study withdrawal. End points include PFS (primary), ORR, overall survival, CBR, duration of response, time to response, time to cytotoxic chemotherapy, quality of life (including FACT B-ES sexual and vaginal health domain), and safety. Blood samples for circulating tumor DNA (ctDNA) will be collected for genomic analyses at screening; at weeks 4 and 8, and every 8 weeks thereafter; and at the final visit. Outcomes with lasofoxifene / abemaciclib vs fulvestrant/abemaciclib will be compared using a stratified Cox proportional hazards model and stratified log rank test. Target sample size is up to 500 to provide 90% power with a 1-sided type I error rate of 0.025 after 285 PFS events.

### Status

Recruitment has been initiated and is expected to occur over 18 months.

## 86 Elacestrant Combinations in Patients With Estrogen Receptor-Positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer: Update From ELEVATE, a Phase Ib/2, Open-Label, Umbrella Study

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## Background

After first-line endocrine therapy (ET) plus CDK4/6 inhibitor (CDK4/6i) in estrogen receptor–positive/HER2-negative (ER+/HER2–) metastatic breast cancer, tumors eventually develop resistance. In the phase 3 EMERALD trial (NCT03778931), elacestrant significantly improved progression-free survival (PFS) vs standard-of-care (SOC) ET (*ESR1*-mutated tumors HR, 0.55; 95% CI, 0.39-0.77; *P* = .0005; all patients HR, 0.70; 95% CI, 0.55-0.88; *P* = .0018) with a manageable safety profile in patients with ER+/HER2– metastatic breast cancer previously treated with ET plus CDK4/6i. To address various resistance mechanisms, the phase 1/2 ELEVATE trial (NCT05563220) evaluates elacestrant with everolimus, alpelisib, capivasertib, ribociclib, palbociclib, or abemaciclib.

## Materials and Methods

Eligible patients have ER+/HER2– metastatic breast cancer, 1 to 2 lines of prior ET. The phase 1b objective is to identify the recommended phase 2 dose (RP2D) of each combination. The phase 1/2 ELECTRA (NCT05386108) evaluated the RP2D of elacestrant plus abemaciclib. The phase 2 objective is to evaluate PFS with each combination at the RP2D.

This analysis reports updated RP2D safety for abemaciclib, everolimus, and palbociclib combinations and phase 1b safety for the other combinations.

## Results

As of October 15, 2024, most common treatment-emergent adverse events (TEAEs) 15% or more for the following RP2D combinations are reported: elacestrant at 345 mg plus abemaciclib at 150 mg twice daily (*n* = 30): diarrhea (80%; 7% grade 3/4), nausea (63%; 7% grade 3/4), fatigue (43%, 7% grade 3/4), vomiting (43%; 0 grade 3/4), constipation (30%; 0 grade 3/4), median PFS was not reached, median observation time was 4.6 months at data cut-off; elacestrant at 345 mg plus everolimus at 7.5 mg (*n* = 57): nausea (51%; 2% grade 3/4), diarrhea (40%; 5% grade 3/4), stomatitis (33%; 4% grade 3/4), median PFS was not reached, median observation time was 2.8 months at data cut-off; elacestrant at 345 mg plus palbociclib plus 125 mg (*n* = 7): neutropenia (57%; 43% grade 3/4, mostly related to palbociclib). Most common TEAEs (≥35%) in the ongoing phase 1b combinations at the current test doses are reported: elacestrant at 172 mg plus ribociclib at 600 mg (*n* = 6): neutropenia (50%; 33% grade 3/4, mostly related to ribociclib), nausea, vomiting, fatigue (each 50%, 0 grade 3/4); elacestrant at 258 mg plus capivasertib at 320 mg (*n* = 7): fatigue, nausea (57% each, 0 grade 3/4), vomiting, diarrhea (43% each, 0 grade 3/4); elacestrant at 258 mg plus alpelisib at 200 mg (*n* = 6): nausea (83%; 0 grade 3/4), rash, hyperglycemia (50% each; 17% grade 3/4), stomatitis, blurred vision, dizziness (each 50%; 0 grade 3/4).

## Conclusion

The evaluated combinations continue to demonstrate a known safety profile consistent with each drug plus SOC ET and no increased risk of associated AEs. Elacestrant has the potential to become the ET partner for multiple targeted agents, providing an all-oral treatment option in patients with ER+/HER2– metastatic breast cancer, delaying chemotherapy or antibody-drug conjugate–based regimens.

## 87 Elacestrant Plus Abemaciclib Combination in Patients With Estrogen Receptor-positive, HER2-Negative Advanced or Metastatic Breast Cancer

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## Background

After first-line endocrine therapy (ET) plus CDK4/6 inhibitor (CDK4/6i) in estrogen receptor–positive/HER2-negative (ER+/HER2–) metastatic breast cancer, tumors develop resistance to intrinsic alterations in the cell cycle or PI3K/AKT/mTOR pathways or to acquired *ESR1* mutation that emerges in up to 50% of patients. In the phase 3 EMERALD trial (NCT03778931), elacestrant significantly prolonged progression-free survival (PFS) vs standard-of-care (SOC) ET with manageable safety in patients with ER+/HER2– metastatic breast cancer previously treated with ET plus CDK4/6i (*ESR1*-mutated tumors: HR, 0.55; 95% CI, 0.39–0.77;  $P = .0005$ ; all patients: HR, 0.70; 95% CI, 0.55–0.88;  $P = .0018$ ). In patients with *ESR1*-mutated tumors that received prior ET plus CDK4/6i at 12 months or more, the median PFS with elacestrant was 8.6 months vs 1.9 months with SOC ET. The rationale for combining elacestrant plus abemaciclib is to overcome different resistance mechanisms and enable an all-oral treatment option. Elacestrant plus abemaciclib is being evaluated in the phase 1b/2 ELECTRA (NCT05386108) and ELEVATE (NCT05563220) trials. This pooled analysis reports updated safety and preliminary efficacy in patients with prior ET+CDK4/6i exposure (excluding abemaciclib).

## Materials and Methods

Eligible patients must have received prior ET for metastatic breast cancer, including 1 or more lines of ET, with or without CDK4/6i (excluding abemaciclib), or chemotherapy (ELECTRA only). Safety was evaluated in all patients who received elacestrant plus abemaciclib. The efficacy evaluable population includes patients from ELECTRA phase 1b.

## Results

As of October 15, 2024, 57 patients received elacestrant plus abemaciclib. In 42 patients who received the recommended phase 2 dose (RP2D; elacestrant at 345 mg once daily plus abemaciclib at 150 mg twice daily), the majority had 1 to 2 lines of prior ET (97%), prior CDK4/6i (100%), prior chemotherapy (16%) and visceral metastases (71%). At the RP2D, the most common all-grade adverse effects (AEs;  $\geq 20\%$ ) were diarrhea ( $n = 35$ , 83%; 5% grade 3), nausea ( $n = 27$ , 64%; 5% grade 3), vomiting ( $n = 17$ , 41%; 2% grade 3), fatigue ( $n = 15$ , 36%; 5% grade 3), neutropenia ( $n = 14$ , 33%; 26% grade 3), anemia ( $n = 10$ , 24%; 7% grade 3), constipation ( $n = 9$ , 21%; 0% grade 3) and decreased appetite ( $n = 9$ , 21%; 0% grade 3). No grade 4 AEs were observed. In efficacy-evaluable patients from ELECTRA phase 1b, median PFS was 8.7 months in all patients ( $n = 27$ ), 8.7 months in patients with prior ET in metastatic breast cancer ( $n = 24$ ), 8.7 months in *ESR1*-mutated tumors ( $n = 11$ ), 7.2 months in *ESR1* mutation not detected ( $n = 12$ ). Median PFS by dose level was 8.7 months (elacestrant 345 mg daily + abemaciclib 150 mg twice daily,  $n = 12$ ), 7.5 months (elacestrant at 345 mg daily plus abemaciclib 100 mg twice daily,  $n = 7$ ), and 8.4 months (elacestrant 258 mg daily plus abemaciclib 100 mg twice daily,  $n = 8$ ).

## Conclusion

The safety of elacestrant plus abemaciclib was consistent with the known profile of abemaciclib plus standard ET. Elacestrant plus abemaciclib showed clinically important efficacy regardless of *ESR1*-mutation status. Elacestrant has the potential to become the ET backbone to enable an all-oral treatment option, delay chemotherapy or antibody-drug conjugate–based regimens. Phase 2 is ongoing.

## 88 Eflapegrastim, a Long-Acting Granulocyte Colony–Stimulating Factor, Administered the Same Day as Chemotherapy in Patients With Early-Stage Breast Cancer: Results From a Multicenter, Open-Label Study

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## Background

Patients with early-stage breast cancer receiving docetaxel and cyclophosphamide chemotherapy have a risk of severe neutropenia and febrile neutropenia. The National Comprehensive Cancer Network recommends GCSF to reduce the risk of febrile neutropenia. Eflapegrastim—a novel, long-acting, recombinant human GCSF linked to human IgG4 Fc fragment—showed improved bone marrow residence vs pegfilgrastim that may allow for same-day dosing. In the phase 3 trials ADVANCE (NCT02643420) and RECOVER (NCT02953340), eflapegrastim administered about 24 hours post docetaxel and cyclophosphamide was noninferior to pegfilgrastim in reducing the duration and incidence of severe neutropenia. This study evaluated the safety of a same-day dose of eflapegrastim.

## Materials and Methods

This multicenter, open-label phase 1 study (NCT04187898) enrolled patients with confirmed early-stage breast cancer (stage I-IIIa), aged 18 years or older who were candidates for docetaxel and cyclophosphamide. Patients received subcutaneous eflapegrastim (single, fixed dose of 13.2 mg [3.6 mg GCSF]) 0.5 hours ± 5 minutes post docetaxel and cyclophosphamide (docetaxel 75 mg/m<sup>2</sup> plus cyclophosphamide 600 mg/m<sup>2</sup>). Primary end point: time to recovery of absolute neutrophil counts (ANC) from nadir to ≥1.5×10<sup>9</sup>/L in cycle 1. Secondary end points: incidence of severe neutropenia (ANC <0.5×10<sup>9</sup>/L) and febrile neutropenia (ANC <0.5×10<sup>9</sup>/L and temperature >38.3°C or 2 consecutive readings ≥38.0°C over 2 hours), duration of severe neutropenia,

and incidence of neutropenic complications (anti-infective use/hospitalization). Treatment-emergent adverse effects (TEAEs) of interest are reported here.

## Results

Fifty-three patients (mean [SD] age: 62.7 [11.9] years; female: 100%) from 13 US sites, were enrolled (White: 62.3%; Black: 9.4%; others: 28.3%). Patients were relatively healthy (ECOG 0, 52.8% [n = 28]; ECOG 1, 47.2% [n = 25]). Efficacy in cycle 1 was evaluable in 49 patients, with mean (SD) time to ANC recovery: 1.8 (1.1) days; incidence of severe neutropenia: 42.9% (n = 21); mean (SD) duration of severe neutropenia; 0.7 (0.9) days; and incidence of febrile neutropenia: 2% (n = 1). No neutropenic complications occurred during the study. Safety was assessed in all 53 patients who received 1 or more doses. Overall, 43 patients (81.1%) experienced any TEAEs of musculoskeletal pain. Common musculoskeletal TEAEs in 10% or more of patients: bone pain (52.8%; n = 28); back pain (26.4%; n = 14), pain in extremity (20.8%; n = 11); arthralgia (17.0%; n = 9), and myalgia (13.2%; n = 7). No deaths occurred during the study.

## Conclusion

Eflapegrastim given on the same day as docetaxel and cyclophosphamide chemotherapy may reduce the time to ANC recovery and related complications in early-stage breast cancer. The AEs observed were consistent with those observed with other GCSF products.

## TPS 89 A Randomized Phase 3 Study of First-Line Saruparib (AZD5305) Plus Camizestrant Versus CDK4/6i Plus Physician's Choice Endocrine Therapy or CDK4/6i Plus Camizestrant in Patients With HR+/HER2- Advanced Breast Cancer With BRCA1/BRCA2/PALB2 Mutations (EvoPAR-B)

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## Background

Emerging evidence indicates that homologous recombination deficiency (HRD) contributes to resistance to CDK4/6 inhibitors (CDK4/6i) plus endocrine therapy (ET). Patients with germline or somatic mutations in *BRCA1*, *BRCA2*, and/or *PALB2* genes (*BRCA1* mutation/*BRCA2* mutation/*PALB2* mutation) and hormone receptor-positive/HER2-negative (HR+/HER2-) advanced breast

cancer have poorer outcomes with first-line standard-of-care CDK4/6i plus ET than patients without these mutations. Clinical benefit with PARP inhibitors (PARPi) has been demonstrated in patients with HRD breast cancer, and PARPi are approved for the treatment of patients with germline *BRCA1/BRCA2* mutations and HR+ /HER2– early or advanced breast cancer. Clinical trials have shown that PARPi use in early lines of therapy can result in a greater magnitude of benefit. PARPi use may also induce reversion mutations that restore homologous recombination proficiency, potentially sensitizing tumors to CDK4/6i. Saruparib (AZD5305) is a first-in-class highly selective PARP1 inhibitor that has increased potency and improved pharmacokinetic and pharmacodynamic properties compared with other approved PARPi. The phase 3 EvoPAR-Breast01 study (NCT06380751) is evaluating the efficacy and safety of saruparib plus camizestrant, a next-generation oral selective estrogen receptor degrader (SERD) and pure estrogen receptor antagonist, vs physician’s choice of CDK4/6i plus ET or CDK4/6i plus camizestrant in participants with germline/somatic *BRCA1* mutation/*BRCA2* mutation/*PALB2* mutation HR+ /HER2– advanced breast cancer.

## 96 Elacestrant Real-World Progression-Free Survival of Adult Patients With ER+ /HER2–, Advanced Breast Cancer: A Retrospective Analysis Using Insurance Claims in the United States

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### Background

Endocrine therapy (ET) plus CDK4/6 inhibitor (CDK4/6i) is the standard-of-care (SOC) for first-line estrogen receptor–positive/HER2-negative (ER+ /HER2–) advanced or metastatic breast cancer. Sequential ET monotherapy or combinations are used second line post-ET plus CDK4/6i. Combination regimens in second-line or late metastatic breast cancer can be associated with significant toxicities and high discontinuation rates. *ESR1* mutations, a type of acquired resistance, eventually emerge in up to 50% of patients after first-line treatment for ER+ /HER2– metastatic breast cancer. In the phase 3 EMERALD trial (NCT03778931),

### Materials and Methods

EvoPAR-Breast01 is a randomized, open-label, 3-arm, multicenter, global study. Study design and eligibility criteria are shown in the **Figure**. Participants will be randomized 2:2:1 to receive saruparib plus camizestrant, physician’s choice CDK4/6i (abemaciclib, ribociclib, or palbociclib) plus physician’s choice ET (fulvestrant, letrozole, anastrozole, or exemestane), or physician’s choice CDK4/6i plus camizestrant, respectively. Treatment will continue until disease progression per RECIST v1.1, unacceptable toxicity, or participant-initiated withdrawal. The primary end point is progression-free survival (PFS) by blinded independent review committee in the saruparib plus camizestrant vs CDK4/6i plus ET arms. Overall survival (OS) is a secondary end point. Planned statistical analyses of PFS and OS will be conducted using a stratified log-rank test.

### Status

Participant enrollment is ongoing across 185 trial locations in 20 countries. Approximately 500 participants will be randomized across the 3 arms.

patients with *ESR1*-mutated tumors had a 45% reduction in risk of progression or death with elacestrant vs SOC ET (median progression-free survival [PFS] 3.8 months vs 1.9 months; HR, 0.55; 95% CI, 0.39-0.77;  $P = .0005$ ). In patients with 12 months or more prior ET plus CDK4/6i, the median PFS with elacestrant was 8.6 months vs 1.9 months with SOC ET (HR, 0.41; 95% CI, 0.26-0.63). Elacestrant was FDA-approved in January 2023 for the treatment of postmenopausal ER+ /HER2– *ESR1*-mutated metastatic breast cancer with progression after at least one line of ET. Sufficient time has passed since approval to characterize the real-world use of elacestrant in the current treatment landscape. This study aims to describe the real-world PFS of elacestrant overall and in patients with no prior exposure to fulvestrant, only 1 to 2 lines of ET, 3 or more lines of ET, and/or visceral metastases.

### Materials and Methods

Adults with diagnosed ER+ /HER2– metastatic breast cancer who initiated elacestrant in a real-world setting between January 2023 and May 2024 were identified in the Komodo Research Database. Demographic information described at index date (time of first administration of elacestrant) included metastatic sites identified during the 6-month baseline period prior to index date and prior metastatic breast cancer treatments. Real-world PFS was defined as time from index date until earliest outcome (start of next line of metastatic breast cancer therapy to progression or death). Patients were censored at first occurrence of end of data availability or end of health plan enrollment.



## Results

A total of 276 patients treated were evaluated (median age 63 years, 86% visceral metastases, 90% prior CDK4/6i, 61% prior fulvestrant). Real-world PFS was prolonged with elacestrant in patients with prior fulvestrant and in the overall population in all subgroups (**Table**).

## Conclusion

In a real-world setting, elacestrant showed a consistent real-world PFS benefit among all patients with ER+/HER2– metastatic breast cancer and across clinically relevant subgroups. The real-world PFS with elacestrant exceeded the overall median PFS in EMERALD and is longer when patients are treated in earlier lines.

**Table.** Real-World Median Progression-Free Survival

	mPFS, mo (95% CI)	
	Patients with no prior fulv (n = 106)	All patients (n = 276)
<b>Overall mPFS</b>	9.4 (5.4-NR)	6.8 (5.5-10.4)
<b>1-2 lines prior ET</b>	9.4 (5.4-NR)	8.0 (5.5-NR)
<b>≥ 3 prior lines ET</b>	NR (5.4-NR)	6.8 (5.3-NR)
<b>Visceral mets</b>	7.3 (5.4-NR)	6.1 (5.4-9.4)

ET, endocrine therapy; fulv, fulvestrant; mPFS, median progression-free survival; mets, metastases; NR, not reached.

## 97 Treatment Discontinuation Among Patients With Stage IV HER2– Negative Breast Cancer

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## Background

To describe treatment discontinuation among patients with stage IV HER2-negative (HER2) breast cancer from first to fourth line of treatment (LOT) based on electronic medical records across 3 academic cancer centers in the US.

## Materials and Methods

This was a retrospective cohort study of adult patients with stage IV HER2– breast cancer who started their first LOT between 2017 and 2021 at Huntsman Cancer Institute, H. Lee Moffitt Cancer Center

& Research Institute, or Winthrop P. Rockefeller Cancer Institute. Patient data were extracted via chart review. The rate of and reasons for discontinuation were analyzed descriptively. Time to next treatment (TTNT) was estimated using Kaplan-Meier methods with censoring at the date of the last follow-up or December 31, 2021, whichever earlier.

## Results

A total of 232 patients were analyzed with a median age (IQR) of 56.6 years (47.8-67.5). 85.8% had hormone receptor–positive (HR+) breast cancer. At each LOT, less than 75% of patients discontinued, of which 20-30% did not receive a subsequent LOT (1st LOT: 21%; 2nd LOT: 24%; 3L: 32%). Among patients with documented reasons for discontinuation, disease progression was most common at between 67.6% and 79.7%, followed by adverse drug events between 19.6% and 35.1% (**Table**). TTNT decreased with LOT for patients with HR+ breast cancer from 14.8 months at the first LOT to 7.0 months and 4.4 months at the second and third LOT, respectively, and ranged between 4.1 months to 5.2 months for those with HR-negative breast cancer across LOT.

## Conclusion

The attrition rate of 20% to 30% of patients who discontinued treatment after each LOT without subsequent treatment was high among patients with stage IV breast cancer. The most effective treatment options should be used in earlier LOT in this patient population since patients may not receive subsequent LOT.

**Table on p. 31**



**Table.** Reasons for Discontinuation From First to Fourth LOT

	LOT 1	LOT 2	LOT 3	LOT 4
<b>N</b>	232	144	83	50
<b>Median follow up, months</b>	27.2	13.9	8.1	5.1
<b>Remained on treatment, n (%)</b>	39 (16.8%)	26 (18.1%)	5 (6.0%)	6 (12.0%)
<b>Died while on treatment, n (%)</b>	11 (4.7%)	9 (6.3%)	4 (4.8%)	6 (12.0%)
<b>Discontinued treatment, n (%)</b>	182 (78.4%)	109 (75.7%)	74 (89.2%)	38 (76.0%)
<b>With explicit reasons for discontinuation, n (%)</b>	139 (59.9%)	92 (63.9%)	69 (83.1%)	37 (74.0%)
<b>Progression</b>	99 (71.2%)	73 (79.3%)	55 (79.7%)	25 (67.6%)
<b>Adverse drug events</b>	35 (25.2%)	18 (19.6%)	15 (21.7%)	13 (35.1%)
<b>Others</b>	17 (12.2%)	12 (13.0%)	9 (13%)	5 (13.5%)

LOT, lines of therapy.

Note: Patients may have more than 1 reason for discontinuation. Others include patient preference, transition to supportive care, loss to follow-up, lack of insurance coverage, and cessation of patient assistance program.

## TPS 99 Phase 3, Randomized, Open-Label TroFuse-010 Study of Sacituzumab Tirumotecan Alone and With Pembrolizumab Versus Treatment of Physician's Choice Chemotherapy in Patients With HR+/HER2- Unresectable Locally Advanced or Metastatic Breast Cancer

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### Background

Additional therapies are needed to improve outcomes in patients with hormone receptor-positive/HER2-negative (HR+/HER2-) breast cancer that progressed on endocrine therapy (ET) plus CDK4/6 inhibitors (CDK4/6i). TROP2 is commonly overexpressed in patients with HR+/HER2- metastatic breast cancer and is associated with poor prognosis. Sacituzumab tirumotecan (sac-TMT; MK-2870/SKB264) is a novel anti-TROP2 antibody-drug conjugate composed of an anti-TROP2 antibody coupled to a cytotoxic belotecan derivative via a novel linker (average drug/antibody ratio, 7.4). In a phase 1/2 study, intravenous sac-TMT alone had antitumor activity in patients with previously treated HR+/HER2- metastatic breast cancer (ORR, 36.8%). TroFuse-010 evaluates sac-TMT alone or with pembrolizumab vs treatment of physician's choice chemotherapy in patients with HR+/HER2- unresectable locally advanced or metastatic breast cancer who have not previously received chemotherapy.

### Materials and Methods

This phase 3, randomized, open-label study (NCT06312176) is enrolling patients 18 years and older with HR+/HER2- unresectable locally advanced or metastatic breast cancer, ECOG performance status 0 to 1, and a tumor sample for central assessment of TROP2 expression and HR, HER2, and PD-L1 status. Patients are candidates for chemotherapy and had either (a) PD after 1 line or more of ET, 1 of which was with a CDK4/6i; (b) PD 6 months or less after starting first-line ET plus CDK4/6i, where the CDK4/6i was discontinued before the PD; (c) PD less than 6 months after starting first ET plus CDK4/6i where the CDK4/6i was discontinued before the PD and PD on an additional ET, either as monotherapy or with a PI3K or mTOR inhibitor; or (d) relapse during or 12 months or less after completing CDK4/6i given as adjuvant therapy with ET. Key exclusion criteria are prior chemotherapy in the metastatic setting and, if treated with prior (neo)adjuvant chemotherapy, recurrence 6 months or less after completion of chemotherapy. Patients are randomized 3:3:2 to intravenous sac-TMT 4 mg/kg every 2 weeks, intravenous sac-TMT 4 mg/kg every 2 weeks plus pembrolizumab 400 mg every 6 weeks, or physician's choice chemotherapy (paclitaxel, nab-paclitaxel, capecitabine, or liposomal doxorubicin) until radiographic PD, unacceptable toxicity, patient withdrawal, or discontinuation criteria are met. Randomization is stratified by PD-L1 combined positive score, TROP2 expression, and region. Primary end points are PFS per RECIST v1.1 by blinded independent central review (BICR) with sac-TMT vs physician's choice chemotherapy and sac-TMT plus pembrolizumab vs physician's choice chemotherapy. Secondary endpoints include OS, PFS per RECIST v1.1 by BICR with sac-TMT plus pembrolizumab vs sac-TMT, overall response rate, duration of response, patient-reported outcomes, and safety.

### Status

Active recruitment is ongoing.

## 100 Non-Pharmacological Interventions for Managing Abemaciclib-Associated Adverse Events in Patients With Early/Advanced HR+/HER2- Breast Cancer: A US-Based Health Care Provider Survey

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### Background

Diarrhea, nausea, fatigue, and abdominal pain are the most common patient-felt abemaciclib-associated adverse effects (AEs). This study describes the use and perceived effectiveness of nonpharmacological interventions (NPI) by health care providers (HCPs) in abemaciclib-associated AEs in early or advanced hormone receptor-positive/HER2-negative (HR+/HER2-) breast cancer.

### Materials and Methods

A cross-sectional survey was conducted between July and October 2023 among US-based health care providers (HCPs; advanced practice providers [APP], oncologists, and pharmacists), with 12 months or more of experience in breast cancer care and supporting abemaciclib treatment. Eligible HCPs completed a 1-time online survey, designed based on literature and insights from exploratory qualitative work, which

included interviews of 9 HCPs (3 from each specialty of HCPs). HCPs selected and ranked (based on perceived effectiveness) recommendations for NPI. Data were collected via online structured questionnaires with closed-ended questions and analyzed descriptively.

### Results

Overall, 46% (282/608 eligible) HCPs (APP: 91, oncologists:91, pharmacists:100) completed the survey; 85% HCPs had 5 years or more of experience treating breast cancer; less than 90% recommended NPI for managing abemaciclib-associated AEs. Diarrhea: “Assessment of fluid-intake/hydration status” was the most recommended NPI (65.6% HCPs) and perceived effective (49.6% HCPs), followed by “emphasis on the importance of hydration” (63.5%; 47.9%). Nausea: “Taking medication with food” topped recommendations (63.5%) and was perceived as most effective (55.3%). Fatigue: “moderate exercise (walking/biking/swimming)” was most recommended (57.8%) and effective (51.4%); “creating rest-time in the day” (57.4%; 49.3%) closely following. Abdominal pain: “Keeping side effect (SE) diary to track SEs frequency and severity for follow-ups” (44.3%) was most recommended and effective (32.6%), alongside “taking medication with food” (40.4%; 33.3%) and “Recommend patient monitor diet to assess SE’s cause” (40.8%; 32.6%). Compared with oncologists, a greater portion of APP and pharmacists considered NPI to be effective.

### Conclusion

NPIs are commonly utilized by APP, oncologists, and pharmacists for management of abemaciclib-associated diarrhea, nausea, fatigue, and abdominal pain. HCPs recommend NPIs they perceive as effective and that are unique for each patient-felt symptom. These data describe common approaches that can be used in addition to pharmacological interventions to manage AEs effectively and to optimize therapy.

## 102 Novel Prognostic and Predictive Locoregional Biosignature for Risk Stratification of Early-Stage Hormone Receptor-Positive Breast Cancer

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### Background

The role of adjuvant therapy for patients with early-

stage, hormone receptor–positive (HR+) invasive breast cancer (IBC) following breast-conserving surgery (BCS) has been the subject of the ongoing investigation. Past studies have heavily relied on risk stratification based on clinicopathological features and have failed to identify a true low-risk population that can omit adjuvant therapy without increasing the risk of locoregional recurrence (LRR). Integration of molecular markers using a multiomic approach offers the potential to enhance risk assessment through tumor biology assessment. This study evaluates the use of multiomic biosignatures to predict LRR risk and radiation therapy (RT) and endocrine therapy (ET) benefits for early-stage HR+/HER2-negative (HER2–) IBC.

## Materials and Methods

A total of 782 patients with IBC (T1/2N0/1M0, HR+, HER2–) treated with BCS (1986-2022) were identified from a multi-institutional cohort. Two biosignatures were developed that calculate individualized results for the prognosis, decision score (DS), and prediction of RT benefit, RT score (RTS) on 10-point scales. The association between 10-year LRR risk, the biosignatures, the benefit of RT and ET, and the interaction between RTS and RT was assessed using multivariable Cox proportional hazards analysis (MVA).

## Results

The median age of the cohort was 64 years, with a median follow-up of 11 years. Overall, 78% (n = 610) of the patients received RT and 39% (n = 307) received ET with 31% (n = 242) of the total receiving both ET and RT. With the inclusion of biosignatures (DS/RTS), MVA found age older than 50 years (HR, 2.4;  $P < .001$ ) was associated with increased LRR as were increasing DS (continuous HR, 3.3;  $P < .001$ ) and RTS (interaction with RT  $P < .001$ , HR, 3.5), while receipt of RT had HR, 0.2 ( $P < .001$ ) and ET had HR, 0.7 ( $P = .17$ ). In patients 50 years or older, excluding N1 disease, (n = 630), increasing DS (continuous) was associated with increasing LRR risk HR, 4.0 per 5 units ( $P < .001$ ) and RTS and RT interaction was significant ( $P < .001$ ). For 22% of patients (n = 141) with categorical (LRS  $\leq 4$ ), average 10-year LRR risks were 5% or more for patients treated with/without ET and with/without RT, where ET ( $P = .85$ ) and RT ( $P = .97$ ) were not associated with LRR risk.

## Conclusion

The biosignatures were prognostic for LRR risk and predictive for RT benefit and identified a clinically low 10-year LRR risk group. This initial cross-validation indicates that the test may be a useful tool to aid in the assessment of the benefit of adjuvant therapy in early-stage HR+/HER2– IBC.

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## TPS 105 ALISertib in Combination With Endocrine Therapy in Patients With Hormone Receptor-Positive, HER2-Negative Recurrent or Metastatic Breast Cancer: the Phase 2 ALISCA-Breast1 Study

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## Background

Despite the wide range of available treatment options for patients with hormone receptor–positive/HER2-negative (HR+/HER2–) recurrent or metastatic breast cancer, optimal treatment after progression on CDK4/6 inhibitors (CDK4/6i) remains unclear. Several mechanisms of resistance to CDK4/6i have been postulated, including increased expression of Aurora kinase A (AURKA), a key regulator of mitosis associated with poor prognosis in multiple tumor types. Further implicated in CDK 4/6i resistance, high c-Myc or RB1 loss of function (LOF) have been associated with transcriptional co-regulation or synthetic lethality, respectively, with AURKA. Alisertib is a highly selective, reversible, ATP-competitive, orally administered, small-molecule AURKA inhibitor with antiproliferative activity in HR+ breast cancer-derived cell lines and breast cancer xenograft models. Greater alisertib sensitivity has been reported in models with elevated AURKA or c-Myc expression, or RB1 LOF. Clinically, alisertib showed efficacy in phase 1 and 2 trials, including objective response rates



(ORRs) of 19.6% to 20% and median progression-free survival (PFS) of 5.4 months to 5.6 months alone or with fulvestrant in patients with HR+/HER2-, endocrine-resistant MBC. The most common treatment-related grade  $\geq 3$  adverse events (AEs) were neutropenia, anemia, and leukopenia.

## Methods

ALISCA-Breast1 (NCT06369285) is a randomized phase 2 study. Primary objective: to determine the optimal alisertib dose level administered with selected endocrine therapy (ET) for use in future studies based on observed safety (AEs, serious AEs per CTCAE v5.0) and efficacy (ORR, duration of response, disease-control rate, PFS, overall survival). Secondary objectives: to identify biomarkers correlating with efficacy; to evaluate alisertib pharmacokinetics (PK). Key inclusion criteria: age 18 years or older; ECOG performance status 0 or 1; confirmed HR+, HER2-, recurrent or metastatic breast adenocarcinoma not amenable to curative therapy; available tumor tissue for biomarker analyses; progression on or after 2 or more prior ET lines in recurrent or metastatic setting; prior CDK4/6i with ET in recurrent or metastatic setting; 1 or more measurable target lesion per RECIST v1.1. Patients who are premenopausal are eligible if amenable to treatment with a luteinizing hormone-releasing hormone agonist. Key exclusion criteria: prior chemotherapy

in recurrent or metastatic setting; bone-only disease not meeting the measurability definition per RECIST v1.1; prior AURKA-specific or pan-Aurora-targeted agents; active infection; patients who are immunocompromised; unstable brain metastases; uncontrolled symptomatic visceral disease. Eligible patients will be randomized 1:1:1 to alisertib 30 mg, 40 mg, or 50 mg orally twice daily on days 1 to 3, 8 to 10, and 15 to 17 every 28 days and combined with physician's choice of anastrozole, letrozole, exemestane, fulvestrant, or tamoxifen not previously used in the recurrent or metastatic setting or progressed upon in the adjuvant setting. Up to 50 patients will be enrolled per arm at multiple centers in the US and Europe. Treatment will continue until disease progression, unacceptable toxicity, or consent withdrawal. Stratification factors: time to recurrence/progression after initiating CDK4/6i therapy (< 12 months or  $\geq 12$  months); presence of visceral disease (yes/no). All patients will undergo sparse PK sampling. Tumor tissue will be centrally assessed for biomarkers, including but not limited to *RB1*, *MYC*, *TP53*, *ESR1*, PI3K/AKT pathway, *HER2*, and *AURKA* genomic alterations and/or expression levels. The study is expected to determine the optimal alisertib dose to combine with ET and may identify biomarker(s) that define patients deriving the greatest benefit from alisertib-containing therapy.

## 106 Extended Adjuvant Neratinib in HER2+/HR+ Early Breast Cancer in Clinical Routine: Interim Analysis of the Multinational, Prospective, Noninterventional Study ELEANOR (N=300)

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## Background

Despite modern HER2-directed treatment options, relevant recurrence risk persists in patients with extensive local disease and/or lack of pathologic complete response (pCR) to neoadjuvant therapy. Neratinib is approved in Europe for extended adjuvant therapy in adult patients with HER2-positive (HER2+)/hormone receptor-positive (HR+) early breast cancer who completed adjuvant trastuzumab-based therapy less than 1 year ago. In this population, the phase 3 ExteNET study (NCT00878709) demonstrated an absolute 5.1% improvement in 5-year invasive disease-free survival (iDFS) with neratinib compared with placebo (90.8% vs 85.7%; HR, 0.58; 95% CI, 0.41-0.82). Exploratory post hoc analyses demonstrated a more pronounced benefit in patients who don't have a pCR and/or in those completing neratinib therapy. Diarrhea was the most common adverse effect (AE) in the neratinib arm (39% grade 3 without primary diarrhea prophylaxis). ELEANOR (NCT04388384) is the first noninterventional study of the real-world use and management of neratinib given after the current adjuvant standard of care in patients with HER2+/HR+ early breast cancer in Germany, Austria, and Switzerland.

## Materials and Methods

A total of 300 patients diagnosed with HER2+/HR+ early breast cancer were planned to be enrolled in accordance with the European Medicines Agency/Swissmedic product specifications. The primary objective is to assess patient adherence to neratinib (ie,  $\geq 75\%$  of prescribed treatment days). Secondary objectives

focus on patient and tumor characteristics, pretreatment and neratinib treatment details, effectiveness, safety, and health-related quality of life. Results of the preplanned interim analysis based on 300 enrolled patients observed for a minimum of 3 months are reported.

## Results

At the data cut-off on August 5, 2023, 286 patients qualified for the main analysis set and 288 patients for the safety analysis set, respectively. Median age at inclusion was 52.0 years, 73.4% (210/286) of patients were at increased risk of disease recurrence having AJCC stage I or higher or N+ or non-pCR after neoadjuvant treatment. Overall, 37.4% (107/286) and 31.8% (91/286) of patients received adjuvant/post-neoadjuvant trastuzumab monotherapy or trastuzumab/pertuzumab, respectively, and 22.4% (64/286) of patients received post-neoadjuvant trastuzumab-emtansine (T-DM1). In patients who had non-pCR following neoadjuvant treatment, 55.4% (62/112) received post-neoadjuvant T-DM1. Dose escalation strategy (neratinib starting dose < 240 mg) was used in 44.4% (128/288) of patients, and 86.8% (250/288) of patients received diarrhea prophylaxis. AEs were consistent with the known safety profile of neratinib with incidence of grade 3 or higher diarrhea by worst grade less common in patients starting on a lower dose of neratinib (15.6% vs 23.8%). At the time of this preplanned interim analysis with an estimated median observation time for disease-free survival of 14.0 months, 6 patients (6/286, 2.1%) had experienced a relapse and one patient died since starting neratinib treatment, resulting in a 12-month DFS rate of 97.4% (95% CI, 94.6-98.7).

## Conclusion

This preplanned interim analysis provides data on the use of neratinib in a contemporary cohort of predominantly higher-risk patients and after completion of pertuzumab- and T-DM1-containing adjuvant regimens in routine clinical practice. Preliminary effectiveness data appears to be consistent with previous data and the integration of treatment management strategies such as diarrhea prophylaxis and neratinib dose escalation were shown to enhance treatment tolerability.

## 107 Neratinib-Based Combination Treatments for Patients With HER2-Positive Breast Cancer Brain Metastases

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### Background

Breast cancer brain metastases (BCBM) contribute to substantial morbidity and mortality in patients with HER2-positive (HER2+) metastatic breast cancer. The central nervous system (CNS) is a common site of recurrence in patients with HER2+ breast cancer, and there is an ongoing need for safe and effective treatments. Neratinib, an oral, irreversible pan-HER tyrosine kinase inhibitor, is FDA-approved for the extended adjuvant treatment of early-stage HER2+ breast cancer and in combination with capecitabine for HER2+ advanced or metastatic breast cancer. We summarize prospective data of neratinib-based combinations in HER2+ BCBM.

### Materials and Methods

We conducted a literature review of neratinib combinations for HER2+ BCBM, focusing on prospective trials reporting CNS outcomes. CNS-specific data were extracted from studies restricted to patients with untreated/active brain metastases (phase 2 TBCRC 022 [NCT01494662]) or asymptomatic/stable brain metastases (phase 3 NALA [NCT01808573] and phase 2 NEfERT-T [NCT00915018]). TBCRC 022, a dedicated HER2+ BCBM trial, assessed neratinib combinations in patients with no prior lapatinib (cohort 3A; neratinib plus capecitabine) or with prior lapatinib (cohort 3B; neratinib plus capecitabine), in patients with previously untreated brain metastases (cohort 4A; neratinib plus T-DM1), and in patients progressing after CNS-directed therapies with no prior T-DM1 (cohort 4B; neratinib plus T-DM1) or in patients with prior T-DM1 (cohort 4C; neratinib plus T-DM1). Also available were descriptive CNS outcomes for (1) patients with baseline CNS metastases previously treated with HER2-directed therapy in NALA (neratinib plus capecitabine vs lapatinib plus capecitabine) and (2) patients who are metastatic treatment-naïve in NEfERT-T (neratinib plus paclitaxel vs trastuzumab plus paclitaxel). End

points included CNS objective response rate (CNS-ORR) per composite/volumetric (TBCRC 022) or RECIST (NALA and NEfERT-T) (assessed locally or centrally), or ORR per Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM; assessed centrally). Cumulative 1-year incidence of intervention for CNS disease or incidence of progressive CNS disease were reported for the NALA CNS subgroup.

### Results

The analysis includes 212 patients: 93 with untreated/active BCBM from TBCRC 022; 101 (16.3% of ITT) from NALA; and 18 (3.8% of ITT) from NEfERT-T. No patients had received prior tucatinib and only 2 patients in TBCRC 022 cohort 4 had received prior trastuzumab deruxtecan. Across all 3 studies, 131 patients had measurable/target CNS lesions at baseline and were evaluable for CNS-ORR (TBCRC 022: n = 49 in cohort 3 and n = 44 in cohort 4; NALA: n = 32; NEfERT-T: n = 6). In TBCRC 022, CNS-ORRs were 49% (18/37 in cohort 3A; neratinib plus capecitabine), 33% (4/12 in cohort 3B; neratinib plus capecitabine), 50% (3/6 in cohort 4A; neratinib plus T-DM1), 29% (5/17 in cohort 4B; neratinib plus T-DM1), and 24% (5/21 in cohort 4C; neratinib plus T-DM1). In NALA, CNS-ORRs were 26% (5/19 pts; neratinib plus capecitabine) vs 15% (2/13; lapatinib plus capecitabine). In NEfERT-T, CNS-ORRs were 100% (3/3; neratinib plus paclitaxel) vs 33% (1/3; trastuzumab plus paclitaxel). In TBCRC 022, RANO-BM ORRs were 24% (9/37; cohort 3A), 17% (2/1; cohort 3B), 33% (2/6; cohort 4A), 35% (6/17; cohort 4B), and 29% (6/21; cohort 4C). In the NALA CNS subgroup (n = 101), 1-year cumulative incidence of intervention for CNS disease was 26% for neratinib plus capecitabine vs 36% for lapatinib plus capecitabine, and 1-year cumulative incidence of progressive CNS disease was 26% (neratinib plus capecitabine) vs 42% (lapatinib plus capecitabine). Diarrhea was the most common grade 3 or higher toxicity.

### Conclusion

Data from prospective trials of neratinib-based combinations show consistent intracranial activity across various treatment settings in untreated/active and asymptomatic/stable HER2+ BCBM. Clinical guidelines and real-world analyses further support the use of neratinib combinations for HER2+ BCBM. Notably, neratinib plus T-DM1 had intracranial efficacy in patients with previously untreated brain metastases and patients who had undergone multiple local CNS-directed and/or systemic therapies, including prior T-DM1. In addition to the established CNS activity of tucatinib and trastuzumab deruxtecan, the combination of neratinib with other FDA-approved drugs represents a promising approach to the treatment of HER2+ BCBM in clinical practice, although the optimal sequence of treatments is not known.