FUTURE ONCOLOGY
2025, VOL. 21, NO. 11, 1317–1324
https://doi.org/10.1080/14796694.2025.2481825

Taylor & Francis
Taylor & Francis Group

CLINICAL TRIAL PROTOCOL

OPEN ACCESS Check for updates

ELAINE 3: phase 3 study of lasofoxifene plus abemaciclib to treat ER+/HER2-, *ESR1*-mutated, metastatic breast cancer

Matthew P. Goetz[a], Seth A. Wander[b], Thomas Bachelot[c], Alexandre de Nonneville[d], Einav Nili Gal-Yam[e], Sarah L. Sammons[f], Sherry Shen[g], Chris Twelves[h], Gina Boruta[i], David J. Portman[i] and Senthil Damodaran[j]

[a]Department of Oncology, Mayo Clinic, Rochester, MN, USA; [b]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [c]Department of Medical Oncology, Centre Leon Berard, Lyon, France; [d]Department of Medical Oncology, Institut Paoli Calmettes, Aix Marseille Université, Centre de Recherche en Cancérologie de Marseille (CRCM), Inserm U1068, CNRS U7258, Marseille, France; [e]Oncology Department, Breast Oncology Institute Sheba Medical Center, Ramat Gan, Israel; [f]Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [g]Department of Medicine, Memorial Sloan Kettering Cancer Center/Evelyn H. Lauder Breast and Imaging Center, New York, NY, USA; [h]Department of Medical Oncology, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [i]Sermonix Pharmaceuticals, Columbus, OH, USA; [j]Department of Breast Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA

ABSTRACT

Endocrine therapy (ET) is recommended for patients with estrogen receptor-positive (ER+) metastatic breast cancer (mBC), but most patients will develop treatment resistance, often due to mutations in the ER-α-coding gene, *ESR1*. Therapeutic options are limited for endocrine-resistant mBC, particularly following treatment with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). Lasofoxifene had anti-tumor activity in two separate phase 2, open-label studies (ELAINE 1 and 2) when given as monotherapy or combined with abemaciclib. The phase 3, randomized ELAINE 3 trial will evaluate the efficacy and safety of lasofoxifene/abemaciclib versus fulvestrant/abemaciclib for locally advanced or metastatic, ER+/HER2- breast cancer with an *ESR1* mutation that progressed after ET-CDK4/6i treatment. Enrollment is planned for up to 500 patients to evaluate progression-free survival as the primary endpoint.

Clinical trial registration: www.clinicaltrials.gov identifier is NCT05696626.

ARTICLE HISTORY
Received 1 November 2024
Accepted 17 March 2025

KEYWORDS
Abemaciclib; *ESR1* mutations; fulvestrant; lasofoxifene; metastatic breast cancer; progression-free survival; safety

1. Introduction

1.1. Background and rationale

Breast cancer is the leading cause of cancer deaths in women globally [1], and the second leading cause in the US [2]. Almost 170,000 US women are estimated to be living with metastatic breast cancer (mBC) by 2025 [3], with a 5-year survival rate of approximately 30% [4]. Endocrine therapy (ET) with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is recommended for patients with estrogen receptor-positive (ER+) mBC [5]. Studies have shown median overall survival in patients treated with aromatase inhibitor (AI)-CDK4/6i combinations to be approximately 5 years or more [6–8]; however, most patients will ultimately develop resistance to treatment. Mutations in the ER-α-coding gene, *ESR1*, are acquired during treatment with AIs (alone or with a CDK4/6i) and drive ET resistance, resulting in tumor progression [9–12]. These *ESR1* mutations are in the ligand-binding domain, conferring ligand-independent, constitutive ER activity, and are found in up to 40% of tumors [13–16]. Therapeutic options are limited for endocrine-resistant mBC, particularly following treatment with a CDK4/6i [17,18].

Lasofoxifene is an oral, next-generation ET that antagonizes the ER in breast cancer cells harboring *ESR1* mutations [19]. Studies of breast cancer cells that overexpress *ESR1*-mutant and wild-type (WT) ERs demonstrated that lasofoxifene had equal potency in *ESR1*-mutant and WT ERs, compared with tamoxifen, fulvestrant, raloxifene, and other ER-targeting compounds, which showed reduced potency in the mutant versus WT ER [19]. Lasofoxifene also stabilizes an antagonistic conformation of the Y537S-mutant ER, and, either alone or with palbociclib, inhibits tumor suppression and metastasis significantly more than fulvestrant [20]. Clinically, lasofoxifene is known to be tissue selective, with ER agonist effects in bone and vaginal tissues, but neutral in the uterus, without an increased risk of uterine neoplasia [21–23]. In the phase 3, PEARL trial of postmenopausal women with osteoporosis, lasofoxifene reduced the risk of invasive ER+ breast cancer by 83% [21]. Subsequently, in two phase 2 studies, ELAINE 1 [24] and ELAINE 2 [25], lasofoxifene exhibited anti-tumor activity in women with *ESR1*-mutant, ER+/HER2- mBC after progression on previous AI-CDK4/6i therapy.

ELAINE 1 (NCT03781063) was an open-label, randomized trial evaluating lasofoxifene versus fulvestrant monotherapy conducted at 47 sites in the United States, Canada, and Israel [24]. A total of 52 women with *ESR1*-mutant breast cancer who previously had AI-CDK4/6i's (92% palbociclib; 0% fulvestrant; 6% chemotherapy) were randomized to lasofoxifene and 51 to fulvestrant with progression-free survival (PFS) as the primary endpoint [24]. Patients treated with lasofoxifene monotherapy had numerically greater PFS (median 5.6 vs 3.7 months; $p = 0.138$; hazard ratio [HR] 0.669 [95% CI, 0.434–1.125]), objective response rate (ORR, 13.2% vs 2.9%; $p = 0.124$), and clinical benefit rate (CBR, 36.5% vs 21.6%; $p = 0.117$) versus fulvestrant

CONTACT Matthew P. Goetz Goetz.Matthew@mayo.edu Department of Oncology, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, USA

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14796694.2025.2481825.

Article highlights

Background and Rationale
- Endocrine therapy (ET) is recommended for patients with estrogen receptor-positive (ER+) metastatic breast cancer (mBC), but most patients will develop treatment resistance, often due to mutations in the ER-α-coding gene, *ESR1*.
- Treatment options for these patients are limited, particularly following treatment with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i).
- Lasofoxifene, an oral, next-generation ET and breast ER antagonist, has exhibited anti-tumor activity in phase 2, open-label studies (ELAINE 1 and 2) when given as monotherapy or combined with abemaciclib.

Study Design and Setting
- ELAINE 3 is a phase 3, open-label, randomized, multicenter trial evaluating the safety and efficacy of lasofoxifene/abemaciclib versus fulvestrant/abemaciclib for the treatment of locally advanced or metastatic, ER+/HER2- breast cancer with an *ESR1* mutation that progressed after AI-CDK4/6i treatment.

Eligibility Criteria
- Participants will be pre and postmenopausal women and men aged ≥18 years with measurable (RECIST 1.1) or non-measurable ER+/HER2- advanced or metastatic breast cancer.

Interventions
- Patients will receive either oral lasofoxifene 5 mg once a day plus oral abemaciclib 150 mg twice a day or fulvestrant 500 mg IM on days 1, 15, and 29 and once every 4 weeks thereafter plus oral abemaciclib 150 mg twice a day.

Efficacy and Safety
- The primary endpoint is progression-free survival (PFS) per RECIST 1.1 based on blinded independent central review. Key secondary endpoints are objective response rate, overall survival, clinical benefit rate, duration of response, and time to response.
- PFS will be reported as the median time to event using Kaplan–Meier methods. Comparisons will be made using a stratified log-rank test, and hazard ratios will be computed using a stratified Cox proportional hazards model with 95% CIs.
- AEs will be assessed for type, severity, course, duration, seriousness, and relationship to treatment.
- If data from the ELAINE 3 trial confirm the safety and efficacy of lasofoxifene/abemaciclib, this combination will become a potentially important therapeutic option for women with ER+/HER2- mBC harboring *ESR1* mutations in the difficult-to-treat, post-CDK4/6i setting.

[24]. The small sample size of this phase 2, signal-seeking study limited the statistical power and conclusions of this study [24]. A favorable safety profile was reported in both treatment groups, with the most frequently reported adverse events (AEs) being grade 1 and 2 diarrhea, nausea, fatigue, arthralgia, and hot flushes with lasofoxifene, and fatigue, arthralgia, and increased aspartate aminotransferase with fulvestrant; no unexpected AEs were observed [24].

ELAINE 2 (NCT04432454) was an open-label, multicenter, single-arm trial conducted at 16 US sites to evaluate the combination of lasofoxifene and abemaciclib in women with *ESR1*-mutant, ER+/HER2- mBC, after progression on a previous ET and CDK4/6i (90% palbociclib; 79% fulvestrant; 41% tamoxifen; 48% chemotherapy) [25]. A total of 29 women were studied for the primary endpoint of safety and tolerability as assessed by adverse events (AEs) and related mortality [25]. Lasofoxifene combined with abemaciclib was generally well tolerated, with most AEs being grade 1 to 2 in severity. The most frequently reported AEs included diarrhea, nausea, vomiting, and fatigue [25]. AEs with the treatment combination were consistent with the safety profiles of the individual agents [25]. Efficacy results showed a median PFS of 12.9 months (56 weeks) and CBR of 65.5% [25]. In 18 patients with measurable target lesions, ORR was 55.6% (95% CI 33.7% to 75.4%) with 10 patients experiencing a confirmed partial response (PR) (Figure 1) [25]. Notably, historical PFS data with various ET combinations, particularly abemaciclib-containing regimens, in the post-CDK4/6i setting ranges from 2.7 to 7.3 months in all patients studied and 3.0–5.6 months in those with *ESR1* mutations (Figure 2) [27–33]. Given the median PFS of 12.9 months in patients who received numerous prior lines of treatment in ELAINE 2 [25], the combination of lasofoxifene and abemaciclib warrants further study.

Exploratory analyses of both ELAINE trials found that the *ESR1* mutant allele fraction (MAF) decreased or became undetectable on treatment when compared with baseline, providing evidence for strong target engagement of lasofoxifene with the ER. Among 61 patients with evaluable cell-free circulating tumor DNA (ctDNA) at baseline and week 8 in ELAINE 1, a decrease in *ESR1* MAF was found in 82.9% of patients treated with lasofoxifene and 61.5% of those treated with fulvestrant (median percent change −87.1% vs −14.7%, respectively) [24]. Among 26 evaluable patients in ELAINE 2, 80.8% of patients treated with lasofoxifene/abemaciclib had *ESR1* MAF decrease from baseline to week 4 [25].

1.2. Objectives and trial design

The phase 3, registrational, ELAINE 3 trial was initiated based on the promising anti-tumor activity of lasofoxifene both as monotherapy and when combined with abemaciclib in the ELAINE 1 and ELAINE 2 trials, respectively. The objective of ELAINE 3 (NCT05696626), an open-label, randomized, international, multicenter study, is to compare the efficacy, safety, and tolerability of lasofoxifene combined with abemaciclib versus that of fulvestrant combined with abemaciclib for treating adults with locally advanced or metastatic, *ESR1*-mutated, ER+/HER2- breast cancer who have disease progression on an aromatase inhibitor (AI) combined with a CDK4/6i. The recent postMONARCH trial confirmed fulvestrant plus abemaciclib as an appropriate comparator arm for ELAINE 3, with a median PFS of 6.0 months and a 27% improvement in PFS versus fulvestrant alone, with similar efficacy between patients in the *ESR1* mutation subgroup and the overall population [29]. Study enrollment is currently underway at community clinic and academic hospital sites in North America, Europe, and Asia.

2. Methods

2.1. Participants

Participants are women (pre- or postmenopausal) or men aged ≥18 years, with ER+/HER2- non curable locally advanced breast cancer (aBC) and/or mBC, with either measurable (according to Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) or non-measurable disease; histologic or cytologic confirmation of ER+/HER2- disease based on most recent or archival biopsy; ≥1 *ESR1* point mutation in the *ESR1* ligand-binding domain as assessed in ctDNA from blood using Guardant 360 as the clinical trial assay; clinical evidence of progression on an AI in combination with palbociclib or ribociclib as their first hormonal treatment for aBC/mBC; ≤1

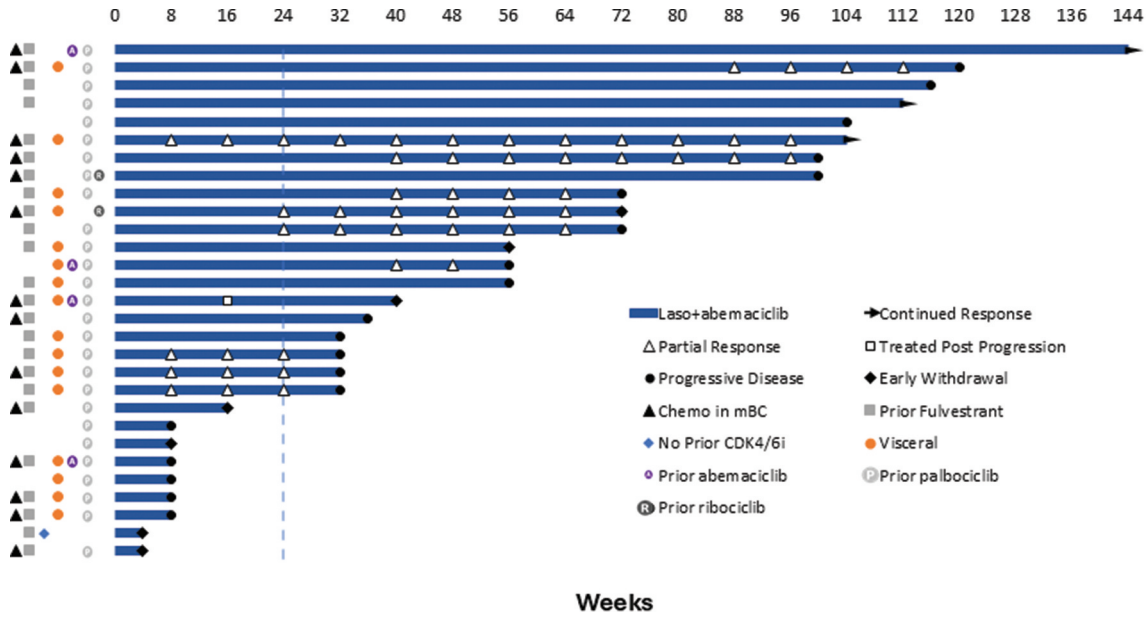

Figure 1. Patient response in the ELAINE 2 study [25,26]. CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; LAS, lasofoxifene; mBC, metastatic breast cancer.

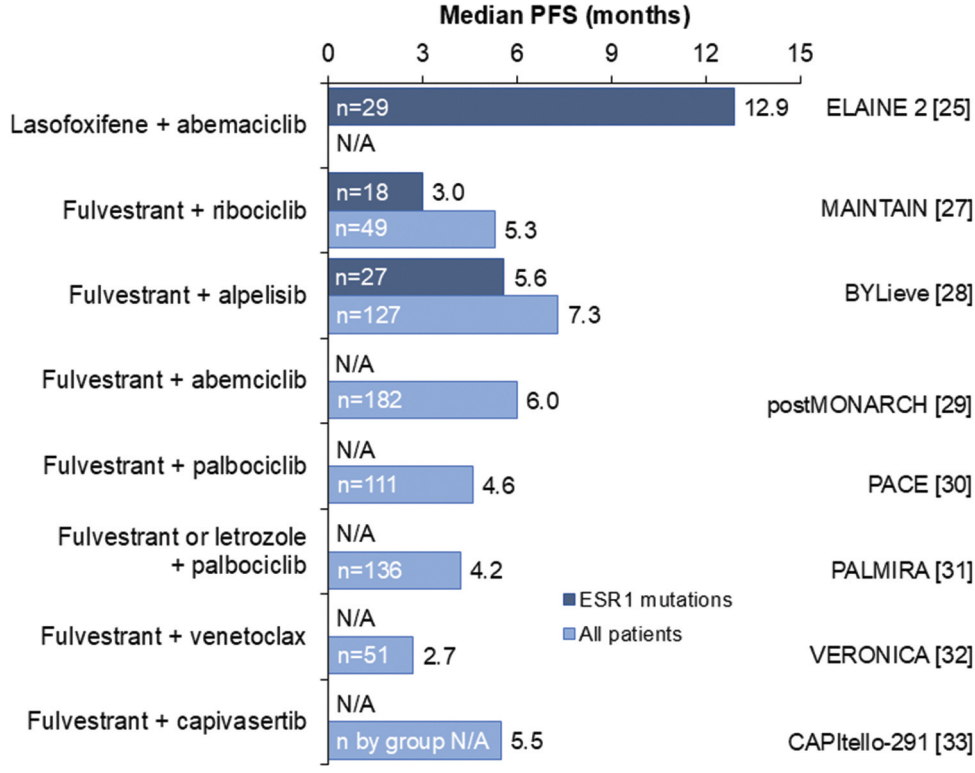

Figure 2. Median progression-free survival in ELAINE 2 and other studies with endocrine therapy combinations after progression on cyclin-dependent kinase 4/6 inhibitors in patients with *ESR1* mutations and in all patients [25,27–33]; N/A, not analyzed/studied or not reported; PFS, progression-free survival.

cytotoxic chemotherapy regimen before study entry (≥14 day washout); no evidence of progression for ≥6 months on an AI-CDKi combination; Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1; and acceptable organ function based on laboratory values (Table 1). Premenopausal women must maintain ovarian suppression during the study and use a double barrier method of contraception.

Exclusion criteria include visceral crisis requiring immediate cytotoxic chemotherapy; lymphangitic carcinomatosis of the lung or grade 3/4 interstitial lung disease; untreated and/or unstable brain metastases; history of progression on abemaciclib, fulvestrant, or other selective estrogen receptor degrader (SERD); known *RB1* mutations or deletions that confer resistance to CDK4/6i (by investigator opinion); radiotherapy within 30 days

Table 1. Participant inclusion and exclusion criteria.

Inclusion	Exclusion
Female or male	Visceral crisis needing chemotherapy
Age ≥18 years	Lymphangitic carcinomatosis of the lung
ER+/HER2-, local aBC and/or mBC	Brain metastasis
≥1 acquired *ESR1* mutation	Disease progression on fulvestrant or other SERD
Progression on an AI plus palbociclib or ribociclib as the first hormonal treatment	Known inactivating *RB1* mutations or deletions
No disease progression for ≥6 months on AI-CDK4/6i combination for aBC	CDK4/6i within <14 days or radiotherapy <30 days before randomization
≤1 line of cytotoxic chemotherapy in the advanced/metastatic and/or adjuvant setting	History of PE, DVT, or any known thrombophilia
ECOG performance score of 0 or 1	History of long QTc syndrome or QTc > 480 msec
Laboratory-confirmed, adequate organ function	Taking concomitant strong CYP3A4 inhibitors or strong/moderate CYP3A4 inducers

aBC: advanced breast cancer; AI: aromatase inhibitor; CDK4/6i: cyclin-dependent kinase 4/6 inhibitor; DVT: deep vein thrombosis; ECOG: Eastern Cooperative Oncology Group; mBC: metastatic breast cancer; PE: pulmonary embolism; SERD: selective estrogen receptor degrader.

before randomization; history of pulmonary embolism, deep vein thrombosis, or any thrombophilia; history of long QTc syndrome or QTc > 480 msec; and concomitant treatment with strong CYP3A4 inhibitors or strong/moderate CYP3A4 inducers (Table 1). Other exclusion criteria include significant comorbidities associated with malabsorption, active systemic bacterial or fungal infection, past HIV or hepatitis, other malignancy (besides basal cell/squamous cell carcinoma of the skin) within the last 5 years, and positive pregnancy test. In addition to CYP3A4 inhibitors/inducers, the concomitant use of anti-cancer agents, hormone replacement therapy, and prolonged systemic corticosteroids will be prohibited. Loperamide is permitted for the treatment of diarrhea.

2.2. Interventions

Eligible patients enrolled by the principal investigators will be randomized following stratification for presence of visceral disease (i.e., lung and/or liver metastasis) versus non-visceral disease, prior chemotherapy versus no prior chemotherapy in the metastatic setting, and prior palbociclib versus prior ribociclib. Patients who received either palbociclib or ribociclib and then switched to another CDK4/6i for reasons other than progression will be stratified according to the last CDK4/6i they were taking at the time of disease progression. Patients in each stratum will be randomized 1:1 using a sponsor-generated permuted block randomization scheme to receive either oral lasofoxifene 5 mg once a day plus oral abemaciclib 150 mg twice a day or fulvestrant 500 mg IM on days 1, 15, and 29 and every 4 weeks thereafter plus oral abemaciclib 150 mg twice a day (Figure 3) until disease progression (as per RECIST 1.1), death, unacceptable toxicity, or withdrawal from the study for any reason. All study drugs are to be taken with or without food.

At the time ELAINE 3 was designed and initiated, there was no globally accepted standard of care for the treatment of patients with mBC and an *ESR1* mutation. However, the fulvestrant/abemaciclib combination is globally approved and shown to have activity in patients with *ESR1* mutations, and was thus chosen as the comparator in the ELAINE 3 study. Most recently, the postMONARCH trial reported superior PFS (investigator-assessed) with fulvestrant/abemaciclib versus fulvestrant/placebo (6.0 vs 5.3 months; HR 0.73 [95% CI, 0.57–0.95], nominal $p = 0.02$) in a non-biomarker – selected mBC that progressed on a prior CDK4/6i and AI [29]. A similar benefit was seen in patients

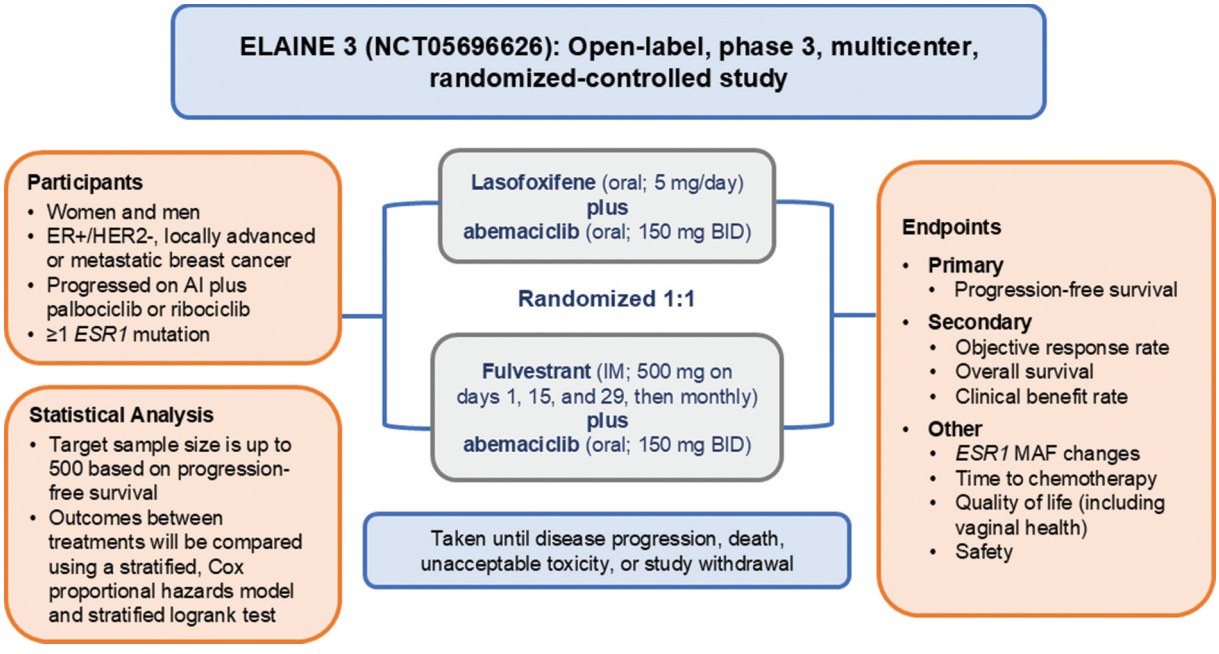

Figure 3. Design of the ELAINE 3 trial. AI, aromatase inhibitor; MAF, mutant allele fraction.

with *ESR1* mutations [29], justifying the use of the fulvestrant-abemaciclib combination in ELAINE 3.

Dose interruptions for grade 3 or 4 AEs will be permitted for lasofoxifene or fulvestrant (i.e., hold therapy and resume with resolution to grade < 2 or baseline) and for abemaciclib (i.e., two dose reductions from 150 mg BID to 100 mg, and then from 100 mg to 50 mg BID, with treatment withdrawn if 50 mg is not tolerated). Abemaciclib dose will be modified in a similar way for patients who require concomitant use of a strong/moderate CYP3A inhibitor. Doses will be modified (AEs of grade 2/3) or discontinued (AEs of grade 3/4) in cases of elevated liver enzymes, interstitial lung disease, venous thromboembolic abnormalities, and other toxicities. Patients who withdraw from treatment will be followed for 28 days for any serious adverse events (SAEs).

2.3. Outcomes and data collection

Study visits will occur at baseline and at weeks 2, 4, 8, and every 4 weeks thereafter up to the final visit or early termination. The primary endpoint is PFS per RECIST 1.1 based on blinded independent central review (BICR) for the combination of lasofoxifene and abemaciclib compared with fulvestrant and abemaciclib. Key secondary efficacy endpoints include the anti-tumor response of each drug regimen as characterized by ORR, duration of response, and time to response (in patients with an objective response), as well as CBR and OS (Table 2). Patients with measurable (≥1 lesion per RECIST 1.1 criteria) and nonmeasurable disease at baseline will be evaluated every 8 weeks according to RECIST 1.1 criteria. In patients with measurable disease, the response criteria will be complete response (CR), PR, stable disease (SD), or progressive disease (PD). If CR or PR is detected, a confirmation scan (or photograph) will be obtained at least 4 weeks after the initial observation. For subjects with non-measurable disease, the response criteria are limited to CR, non-CR/non-PD, or PD at each of the efficacy time points. Patients who withdraw from the study because of disease progression must have progression documented by RECIST 1.1 criteria. The investigator will determine progression based on clinical and radiologic assessment using RECIST 1.1, and all efficacy images will be uploaded and submitted for BICR. Local (investigator) versus BICR assessments will be compared when the study endpoint is met. Overall survival (OS) will be monitored at 6-month intervals for all patients following disease progression or discontinuation for any reason.

Safety (AEs) will be assessed at weeks 2 and 4 after enrollment and then every 4 weeks until disease progression or until early termination. Analyses will include AE collection using general questioning, clinical laboratory tests, ECGs, vital signs, and concomitant medications. AEs include (but are not limited to) worsening of conditions present at the start of the study, health deterioration due to primary illness, intercurrent illness, drug interaction, or abnormal and clinically significant laboratory values. Symptoms related to disease progression will not be considered as an AE. AEs will be summarized by system organ class and preferred term, using the Medical Dictionary for Regulatory Activities (MedDRA), for all AEs, SAEs, treatment-related AEs, AEs leading to treatment discontinuation or study withdrawal, and AEs leading to death. AEs and SAEs will be assessed for type, severity (according to Common Terminology Criteria for Adverse Events [CTCAE] version 5.0), course, duration, seriousness, and relationship to treatment throughout the study. Laboratory abnormalities will be assessed according to CTCAE version 5.0.

Quality of life will be assessed by the Functional Assessment of Cancer Therapy Breast Cancer-Endocrine Subscale (FACT B-ES) at baseline and from week 4 onward. The FACT B-ES is comprised of multiple items rated on a 5-point scale for physical well-being, social/family well-being, emotional well-being, functional well-being, additional concerns, and endocrine symptoms. It was chosen as the most appropriate questionnaire based on the tissue-selective activity of lasofoxifene, as well as its endocrine domain that includes items pertaining to vaginal and sexual health, which are of particular interest given that previous studies of lasofoxifene have demonstrated improvements in these areas in both postmenopausal [22] and oncology populations [34]. Time until cytotoxic chemotherapy will also be assessed.

Blood samples for ctDNA will be collected for genomic analyses at screening, at weeks 4 and 8, and every 8 weeks thereafter. These exploratory analyses will examine the effects of treatment in each arm on *ESR1* mutant allele fraction, as well as co-occurring mutations involving genes encoding proteins in the PI3K/PTEN/AKT pathway. Additionally, we will investigate the prognostic and predictive roles of *ESR1, PIK3CA*, *PTEN*, and *AKT* mutations.

2.4. Statistical analysis

This study is designed to test the hypothesis that lasofoxifene/abemaciclib will meaningfully increase the time to disease progression or death compared with fulvestrant/abemaciclib among patients with locally advanced or metastatic ER +/HER2- breast cancer with an *ESR1* mutation. A sample size of up to 500 (250 per treatment arm), calculated based on the

Table 2. Secondary efficacy outcome definitions (per RECIST 1.1 criteria).

Outcome	Definition
Progression-free disease (PFS)	Interval between randomization and date of first documented progression[a] or death from any cause
Objective response rate (ORR)	Percentage of patients with measurable disease at baseline whose best overall response is a confirmed CR or PR[a]
Overall survival (OS)	Time from randomization to death from any cause
Clinical benefit rate (CBR)	Percentage of patients with best overall response of confirmed CR, PR, or SD[a] for ≥24 weeks
Duration of response (DOR)	Time from first documented CR or PR[a] to the date of first documented disease progression or death
Time to response (TTR)	Time from randomization to the first documented CR or PR[a]

[a]According to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1).
CR: complete response; PR: partial; response; SD: stable disease.

primary endpoint of PFS (per RECIST 1.1) as determined by BICR, will achieve 90% power with a 1-sided, type I error rate of 0.025. PFS will be determined using Kaplan–Meier methods, with comparisons made using a stratified log-rank test, and HRs (95% CI) computed using a stratified Cox proportional hazards model. For the primary analysis, patients who discontinue treatment before disease progression will be monitored for disease progression or death, with censoring rules applied in accordance with the Food and Drug Administration guidance for industry. A non-binding, interim futility assessment will be reviewed by the data safety monitoring board; the study may be stopped for futility or safety reasons, as decided by the sponsor.

3. Conclusions

The phase 3, multicenter, randomized, open-label ELAINE 3 study will build on phase 2 findings [24,25] by evaluating the efficacy and safety of lasofoxifene/abemaciclib versus fulvestrant/abemaciclib for the treatment of locally advanced or metastatic, ER+/HER2- breast cancer with an *ESR1* mutation that progresses after AI-CDK4/6i treatment. Lasofoxifene alone [24] and when combined with abemaciclib [25] exhibited antitumor activity in ER+/HER-, *ESR1*-mutated mBC that progressed on ET and CDK4/6i, with reductions and clearance of *ESR1* MAF and no unexpected safety signals [24,25]. If the safety and efficacy of lasofoxifene/abemaciclib are confirmed in the ELAINE 3 trial, this combination will become a potentially important therapeutic option for women with ER+/HER2- mBC harboring *ESR1* mutations in the difficult-to-treat, post-CDK4/6i setting.

Acknowledgments

The authors acknowledge Miriam Portman, MD and Paul V Plourde, MD for their involvement in the conception, design, and execution of the study; protocol development; and critically reviewing the manuscript; and Laura Ninger, ELS and Kathleen Ohleth, PhD of Precise Publications, LLC, for their medical writing assistance supported by Sermonix Pharmaceuticals. This study protocol was presented at the Miami Breast Cancer Conference (MBCC), March 7–10, 2024 in Miami, FL, American Society of Clinical Oncology (ASCO), May 31-June 4, 2024 in Chicago, IL, and San Antonio Breast Cancer Symposium (SABCS), December 10–13, 2024 in San Antonio, TX.

Funding

The ELAINE 3 study and this manuscript were funded by Sermonix Pharmaceuticals who contributed to the design of the study; collected, analyzed, and interpreted the data; and were involved in drafting, reviewing, and approving the manuscript, with some employees meeting ICMJE authorship criteria.

Disclosure statement

Matthew Goetz has received research support from AstraZeneca, Atossa Genetics, Eli Lilly, Loxo, Pfizer, and Sermonix; has consulted for AstraZeneca, ARC Therapeutics, BioTheranostics, Biotheryx, Blueprint Medicines, Eli Lilly, Engage Health Media, Genzyme, Laekna Therapeutics, Novartis, RNA Diagnostics, Seagen, Sermonix, and TerSera Therapeutics; has received patents, royalties and/or other intellectual property for methods and materials for assessing chemotherapy responsiveness and treating cancer, methods and materials for using butyrylcholinesterases to treat cancer, and for the development of human tumor xenografts from women with breast cancer treated with neoadjuvant chemotherapy. **Seth Wander** has received research support from Eli Lilly, Genentech, Nuvation Bio, Pfizer/Arvinas, Regor Therapeutics, and Sermonix; has served as consultant/advisor for AstraZeneca, Biovica, Eli Lilly, Foundation Medicine, Genentech, Hologic, Menarini, Novartis, Pfizer/Arvinas, Puma Biotechnology, Regor Therapeutics, and Veracyte; and has provided educational speaking for 2nd.MD, Eli Lilly, and Guardant Health. **Thomas Bachelot** has received research support from AstraZeneca, Daiichi Sankyo/AstraZeneca, Novartis, Pfizer, Roche, and Seagen; has served on a consulting/advisory board for Daiichi Sankyo/AstraZeneca, Eli Lilly, Novartis, Pfizer, Roche, and Seagen; and has received travel and accommodation expenses from AstraZeneca, Pfizer, and Roche. **Alexandre de Nonneville** has served as a consultant/advisor for Daiichi Sankyo/AstraZeneca, Eli Lilly, Exact Sciences, Gilead Sciences, and Seagen; is on the speakers' bureau for Daiichi Sankyo/AstraZeneca, Gilead Sciences, Menarini, MSD Oncology, Novartis, and Pfizer; has received travel/accommodation expenses from Daiichi Sankyo/AstraZeneca and Gilead Sciences. **Einav Nili Gal-Yam** has served as an advisor for Astra-Zeneca, Bayer, Eli Lilly, Gilead, MSD, Novartis, Pfizer, and Roche; and has received honoraria from Astra-Zeneca, Eli Lilly, Gilead, MSD, Novartis, Pfizer, and Roche. **Sarah Sammons** has received research funding from AstraZeneca/MedImmune, Eli Lilly, Relay Therapeutics, Seagen, and Sermonix; and has served as a consultant/advisor for AstraZeneca, Daiichi Sankyo, Foundation Medicine, Loxo/Eli Lilly, Novartis, Pfizer, Relay Therapeutics, and Sermonix. **Sherry Shen** has received research funding (to institution) from Merck and Sermonix; and has received honoraria from MJH Life Sciences. **Chris Twelves** has received research funding from AstraZeneca, Avacta Life Sciences, and Pfizer; has served as a consultant/advisor for Daiichi Sankyo, Eisai, and Pfizer; is on the speakers' bureau for Daiichi Sankyo, Eisai, MSD Oncology, and Pfizer; has received travel/accommodation expenses from Eisai, Gilead Sciences, MSD Oncology, and Pfizer; and has received honoraria from Daiichi Sankyo, Eisai, MSD Oncology, Novartis, and Pfizer. **Gina Boruta** and **David Portman** are employees of Sermonix; David Portman is also a stockholder. **Senthil Damodaran** has received research funding from Daiichi Sankyo/AstraZeneca, DualityBio, EMD Serono, Guardant Health, Medilink Therapeutics, Novartis, Sermonix, and Taiho Pharma; and has served as consultant/advisor for Daiichi Sankyo/AstraZeneca.

Author contributions

Matthew Goetz participated in protocol development; and drafting, revising or critically reviewing, and approving the manuscript. **Seth Wander** participated in protocol development; and drafting, revising or critically reviewing, and approving the manuscript. **Thomas Bachelot** participated in the drafting, revising or critically reviewing, and approving the manuscript. **Alexandre de Nonneville** participated in the drafting, revising or critically reviewing, and approving the manuscript. **Einav Nili Gal-Yam** participated in protocol development; and drafting, revising or critically reviewing, and approving the manuscript. **Sarah L Sammons** participated in protocol development; and drafting, revising or critically reviewing, and approving the manuscript. **Sherry Shen** participated in the drafting, revising or critically reviewing, and approving the manuscript. **Chris Twelves** participated in the drafting, revising or critically reviewing, and approving the manuscript. **Gina Boruta** was involved in the conception, design, and execution of the study; protocol development; in revising or critically reviewing, and approving the manuscript; and is or will be participating in data acquisition and interpretation. **David Portman** was involved in the conception, design, and execution of the study; protocol development; and drafting, revising or critically reviewing, and approving the manuscript. **Senthil Damodaran** participated in protocol development; and drafting, revising or critically reviewing, and approving the manuscript.

Ethical declarations

The study will be conducted in accordance with Good Clinical Practice, the current principles of the Declaration of Helsinki, and the US Code of Federal Regulations pertaining to clinical studies, and the protocol

approved by the Institutional Review Board (IRB) and Independent Ethics Committee (IEC) local to each site (include approval numbers). The IRB/IEC and regulatory health authorities will be notified of any protocol amendments. All patients will provide written informed consent to the investigator in accordance with local IRB/IEC requirements before any study procedures begin. All patient documentation will strictly adhere to professional standards of confidentiality.

Writing disclosure

Medical writing assistance was provided by Laura Ninger, ELS and Kathleen Ohleth, PhD of Precise Publications, LLC, and supported by Sermonix Pharmaceuticals.

Data sharing statement

All data derived from the ELAINE 3 study will be shared with the authors for interpretation and conclusions.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–263. doi: 10.3322/caac.21834
2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12–49. doi: 10.3322/caac.21820
3. Gallicchio L, Devasia TP, Tonorezos E, et al. Estimation of the number of individuals living with metastatic cancer in the United States. J Natl Cancer Inst. 2022;114(11):1476–1483. doi: 10.1093/jnci/djac158
4. American Cancer Society, Inc. Breast cancer facts & figures 2022–2024. 2022 [cited 2024 Sep 17]. Available from: https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html
5. National Comprehensive Cancer Network (NCCN). NCCN guidelines version 4.2024. 2024 [cited 2024 Aug 8]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419
6. Goetz MP, Toi M, Huober J, et al. Abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy for HR+, HER2− advanced breast cancer: final overall survival results of MONARCH 3. Ann Oncol. 2024;35(8):718–727. doi: 10.1016/j.annonc.2024.04.013
7. Slamon DJ, Diéras V, Rugo HS, et al. Overall survival with palbociclib plus letrozole in advanced breast cancer. J Clin Oncol. 2024;42(9):994–1000. doi: 10.1200/JCO.23.00137
8. Prat A, Solovieff N, André F, et al. Intrinsic subtype and overall survival of patients with advanced HR+/HER2− breast cancer treated with Ribociclib and ET: correlative analysis of MONALEESA-2, -3, -7. Clin Cancer Res. 2024;30(4):793–802. doi: 10.1158/1078-0432.CCR-23-0561
9. Brett JO, Spring LM, Bardia A, et al. *ESR1* mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. Breast Cancer Res. 2021;23(1):85. doi: 10.1186/s13058-021-01462-3
10. De Santo I, McCartney A, Migliaccio I, et al. The emerging role of *ESR1* mutations in luminal breast cancer as a prognostic and predictive biomarker of response to endocrine therapy. Cancers (Basel). 2019;11(12):1894. doi: 10.3390/cancers11121894
11. Zhang K, Hong R, Xu F, et al. Clinical value of circulating ESR1 mutations for patients with metastatic breast cancer: a meta-analysis. Cancer Manag Res. 2018;10:2573–2580. doi: 10.2147/CMAR.S173193
12. Chandarlapaty S, Chen D, He W, et al. Prevalence of *ESR1* mutations in cell-free DNA and outcomes in metastatic breast cancer: a secondary analysis of the BOLERO-2 clinical trial. JAMA Oncol. 2016;2(10):1310–1315. doi: 10.1001/jamaoncol.2016.1279
13. Toy W, Shen Y, Won H, et al. *ESR1* ligand-binding domain mutations in hormone-resistant breast cancer. Nat Genet. 2013;45(12):1439–1445. doi: 10.1038/ng.2822
14. Fribbens C, O'Leary B, Kilburn L, et al. Plasma *ESR1* mutations and the treatment of estrogen receptor–positive advanced breast cancer. J Clin Oncol. 2016;34(25):2961–2968. doi: 10.1200/JCO.2016.67.3061
15. Jeselsohn R, Bergholz JS, Pun M, et al. Allele-specific chromatin recruitment and therapeutic vulnerabilities of *ESR1* activating mutations. Cancer Cell. 2018;33(2):173–186 e175. doi: 10.1016/j.ccell.2018.01.004
16. Robinson DR, Wu YM, Vats P, et al. Activating *ESR1* mutations in hormone-resistant metastatic breast cancer. Nat Genet. 2013;45(12):1446–1451. doi: 10.1038/ng.2823
17. Xi J, Ma CX. Sequencing endocrine therapy for metastatic breast cancer: what do we do after disease progression on a CDK4/6 inhibitor? Curr Oncol Rep. 2020;22(6):57. doi: 10.1007/s11912-020-00917-8
18. Sammons S, Shastry M, Dent S, et al. Practical treatment strategies and future directions after progression while receiving CDK4/6 inhibition and endocrine therapy in advanced HR+/HER2− breast cancer. Clin Breast Cancer. 2020;20(1):1–11. doi: 10.1016/j.clbc.2019.06.017
19. Andreano KJ, Baker JG, Park S, et al. The dysregulated pharmacology of clinically relevant *ESR1* mutants is normalized by ligand-activated WT receptor. Mol Cancer Ther. 2020;19(7):1395–1405. doi: 10.1158/1535-7163.MCT-19-1148
    - • **Preclincal data supporting the use of lasofoxifene for treating women with ER+/HER2-, metastatic breast cancer harboring ESR1 mutations.**
20. Lainé M, Fanning SW, Chang Y-F, et al. Lasofoxifene as a potential treatment for therapy-resistant er-positive metastatic breast cancer. Breast Cancer Res. 2021;23(1):54. doi: 10.1186/s13058-021-01431-w
    - • **Preclincal data supporting the use of lasofoxifene for treating women with ER+/HER2-, metastatic breast cancer harboring ESR1 mutations.**
21. Cummings SR, Ensrud K, Delmas PD, et al. Lasofoxifene in postmenopausal women with osteoporosis. N Engl J Med. 2010;362(8):686–696. doi: 10.1056/NEJMoa0808692
22. Kagan R, Simon JA, Goldstein SR, et al. Oral lasofoxifene's effects on moderate to severe vaginal atrophy in postmenopausal women: two phase 3, randomized, controlled trials. Menopause. 2024;31(6):494–504. doi: 10.1097/GME.0000000000002355
    - •• **Phase 3 clinical data demonstrating improvements in vaginal physiology and symptoms with lasofoxifene in postmenopausal women.**
23. Goldstein SR, Neven P, Cummings S, et al. Postmenopausal evaluation and risk reduction with lasofoxifene (PEARL) trial: 5-year gynecological outcomes. Menopause. 2011;18(1):17–22. doi: 10.1097/gme.0b013e3181e84bb4
24. Goetz MP, Bagegni N, Batist G, et al. Lasofoxifene versus fulvestrant for ER+/HER2− metastatic breast cancer with an *ESR1* mutation: results from the randomized, phase II ELAINE 1 trial. Ann Oncol. 2023;34(12):1141–1151. doi: 10.1016/j.annonc.2023.09.3104
    - •• **Phase 2 study showing the preliminary safety and anti-tumor effects of lasofoxifene monotherapy versus fulvestrant when treating women with ER+/HER2-, ESR1-mutated, metastatic breast cancer that progressed on endocrine therapy, supporting the design and initiation of the phase 3, ELAINE 3 study.**
25. Damodaran S, O'Sullivan CC, Elkhanany A, et al. Open-label, phase II, multicenter study of lasofoxifene plus abemaciclib for treating women with metastatic ER+/HER2− breast cancer and an *ESR1* mutation after disease progression on prior therapies: ELAINE 2. Ann Oncol. 2023;34(12):1131–1140. doi: 10.1016/j.annonc.2023.09.3103
    - •• **Phase 2 study showing preliminary safey and efficacy of lasofoxifene plus abemaciclib for treating women with ER+/HER2-, ESR1-mutated, metastatic breast cancer that progressed on endocrine therapy, supporting the design and initiation of the phase 3, ELAINE 3 study.**
26. Goetz MP, Wander SA, Bachelot T, et al. Open-label, randomized, multicenter, phase 3, ELAINE 3 study of the efficacy and safety of lasofoxifene plus abemaciclib for treating ER+/HER2-, locally

advanced or metastatic breast cancer with an ESR1 mutation. J Clin Oncol. 2024;42(16_suppl):TPS1127–TPS1127. doi: 10.1200/JCO.2024.42.16_suppl.TPS1127

27. Kalinsky K, Accordino MK, Chiuzan C, et al. Randomized phase II trial of endocrine therapy with or without ribociclib after progression on cyclin-dependent kinase 4/6 inhibition in hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer: MAINTAIN trial. J Clin Oncol. 2023;41(24):4004–4013. doi: 10.1200/JCO.22.02392
28. Turner N, Rugo HS, Ciruelos EM, et al. Abstract PD15–01: impact of ESR1 mutations on endocrine therapy (ET) plus alpelisib benefit in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), PIK3CA-mutated, advanced breast cancer (ABC) who progressed on or after prior cyclin-dependent kinase inhibitor (CDK4/6i) therapy in the BYLieve trial. Cancer Res. 2022;82(4_Supplement):D15–01–PD15–01.
29. Kalinsky K, Bianchini G, Hamilton EP, et al. Abemaciclib plus fulvestrant vs fulvestrant alone for HR+, HER2- advanced breast cancer following progression on a prior CDK4/6 inhibitor plus endocrine therapy: primary outcome of the phase 3 postMONARCH trial. J Clin Oncol. 2024;42(17_suppl):LBA1001–LBA1001. doi: 10.1200/JCO.2024.42.17_suppl.LBA1001
30. Mayer EL, Ren Y, Wagle N, et al. PACE: a randomized phase II study of fulvestrant, palbociclib, and avelumab after progression on cyclin-dependent kinase 4/6 inhibitor and aromatase inhibitor for hormone receptor-positive/Human epidermal growth factor receptor-negative metastatic breast cancer. J Clin Oncol. 2024;42(17):2050–2060. doi: 10.1200/JCO.23.01940
31. Llombart-Cussac A, Harper-Wynne C, Perello A, et al. Second-line endocrine therapy (ET) with or without palbociclib (P) maintenance in patients (pts) with hormone receptor-positive (Hr[+])/human epidermal growth factor receptor 2-negative (HER2[-]) advanced breast cancer (ABC): PALMIRA trial. J Clin Oncol. 2023;41(16_suppl):1001–1001. doi: 10.1200/JCO.2023.41.16_suppl.1001
32. Lindeman GJ, Fernando TM, Bowen R, et al. VERONICA: randomized phase II study of fulvestrant and venetoclax in ER-Positive metastatic breast cancer post-CDK4/6 inhibitors – efficacy, safety, and biomarker results. Clin Cancer Res. 2022;28(15):3256–3267. doi: 10.1158/1078-0432.CCR-21-3811
33. Oliveira M, Rugo HS, Howell SJ, et al. 187O capivasertib and fulvestrant for patients (pts) with aromatase inhibitor (ai)-resistant HR+/HER2– advanced breast cancer (ABC): subgroup analyses from the phase III CAPItello-291 trial. Ann Oncol. 2023;8(1):101376. doi: 10.1016/j.esmoop.2023.101376
34. Goldfarb SB, Sammons SL, Meisel JL, et al. Effects of lasofoxifene versus fulvestrant on vaginal and vulvar symptoms in patients with ESR1-mutated, ER+/HER2-, metastatic breast cancer from the ELAINE 1 study. Clin Breast Cancer. 2024;(3):1–7. doi: 10.1016/j.clbc.2024.12.002

•• **Results of the ELAINE 1 study that support positive effects of lasofoxifene on vaginal symptoms in women being treated for metastatic breast cancer.**