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ORIGINAL ARTICLE

Lasofoxifene versus fulvestrant for ER+/HER2− metastatic breast cancer with an *ESR1* mutation: results from the randomized, phase II ELAINE 1 trial

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Background: Acquired estrogen receptor alpha (ER/*ESR1*) mutations commonly cause endocrine resistance in ER+ metastatic breast cancer (mBC). Lasofoxifene, a novel selective ER modulator, stabilizes an antagonist conformation of wild-type and *ESR1*-mutated ER-ligand binding domains, and has antitumor activity in *ESR1*-mutated xenografts.

Patients and methods: In this open-label, randomized, phase II, multicenter, ELAINE 1 study (NCT03781063), we randomized women with *ESR1*-mutated, ER+/human epidermal growth factor receptor 2 negative (HER2−) mBC that had progressed on an aromatase inhibitor (AI) plus a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) to oral lasofoxifene 5 mg daily or IM fulvestrant 500 mg (days 1, 15, and 29, and then every 4 weeks) until disease progression/toxicity. The primary endpoint was progression-free survival (PFS); secondary endpoints were safety/tolerability.

Results: A total of 103 patients received lasofoxifene ($n = 52$) or fulvestrant ($n = 51$). The most current efficacy analysis showed that lasofoxifene did not significantly prolong median PFS compared with fulvestrant: 24.2 weeks (∼5.6 months) versus 16.2 weeks (∼3.7 months; $P = 0.138$); hazard ratio 0.699 (95% confidence interval 0.434-1.125). However, PFS and other clinical endpoints numerically favored lasofoxifene: clinical benefit rate (36.5% versus 21.6%; $P = 0.117$), objective response rate [13.2% (including a complete response in one lasofoxifene-treated patient) versus 2.9%; $P = 0.124$], and 6-month (53.4% versus 37.9%) and 12-month (30.7% versus 14.1%) PFS rates. Most common treatment-emergent adverse events with lasofoxifene were nausea, fatigue, arthralgia, and hot flushes. One death occurred in the fulvestrant arm. Circulating tumor DNA *ESR1* mutant allele fraction (MAF) decreased from baseline to week 8 in 82.9% of evaluable lasofoxifene-treated versus 61.5% of fulvestrant-treated patients.

Conclusions: Lasofoxifene demonstrated encouraging antitumor activity versus fulvestrant and was well tolerated in patients with *ESR1*-mutated, endocrine-resistant mBC following progression on AI plus CDK4/6i. Consistent with target engagement, lasofoxifene reduced *ESR1* MAF, and to a greater extent than fulvestrant. Lasofoxifene may be a promising targeted treatment for patients with *ESR1*-mutated mBC and warrants further investigation.

Key words: breast cancer, ctDNA, *ESR1* mutation, fulvestrant, lasofoxifene, selective estrogen receptor modulator

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer mortality in women globally.[1] In the United States, 2022 estimates for invasive breast cancer in women are 287 850 new annual cases and 43 250 deaths;[2] and 169 347 women are projected to be living with metastatic breast cancer (mBC) by 2025.[3]

Approximately 80% of breast cancers are estrogen receptor positive (ER+).[4,5] Endocrine therapy (ET), such as aromatase inhibitors (AIs) and fulvestrant, alone or combined with other agents, is the mainstay for treating ER+ mBC, with an AI plus cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) being a standard-of-care, first-line treatment.[6,7] While such therapy is often effective, endocrine resistance develops in nearly all tumors,[6] and up to 40% are due to acquired ER gene (*ESR1*) mutations in the ligand-binding domain.[8-10] *ESR1* mutations confer ligand-independent, constitutive activity[8,11] and neomorphic, metastasis-promoting properties[12] on the ER, and enrich basal-like features in ER+ breast cancer,[13] leading to endocrine resistance and subsequent tumor progression.[14-16]

Endocrine agents have a favorable safety profile, and when used sequentially, can delay the need for more toxic chemotherapy. Fulvestrant [a selective ER degrader (SERD)] monotherapy provided a median progression-free survival (PFS) of 4.6-10.2 months in patients who have advanced breast cancer that has progressed after ET alone;[17-19] however, in the post-CDK4/6i setting (mainly palbociclib), median PFS with fulvestrant monotherapy ranged from 1.9 to 4.8 months.[20-23] Moreover, fulvestrant or AIs had limited antitumor activity in patients whose tumors exhibit *ESR1* mutations, particularly the Y537S variant,[9,23-25] one of the most common *ESR1* mutations.[26] Newer endocrine agents and combinations are needed to overcome acquired resistance and delay the need for cytotoxic chemotherapy, particularly after CDK4/6i therapy.

Lasofoxifene, a novel orally administered selective ER modulator (SERM), antagonizes the ER in malignant and premalignant breast cancer cells, particularly in those harboring *ESR1* mutations, preventing estrogen-mediated tumor growth without degrading the receptor.[27,28] However, lasofoxifene is tissue selective as it is an ER agonist in bones and vaginal tissues, while being neutral on the ER in the uterus, not increasing uterine neoplasia.[29-31] In the phase III PEARL trial in postmenopausal women with osteoporosis, lasofoxifene 0.5 mg/day reduced invasive ER+ breast cancer risk by 83%.[32]

Breast cancer cells expressing *ESR1* mutations, particularly the Y537S, have shown reduced sensitivity to tamoxifen, fulvestrant, and other ER-targeting compounds,[8,11,12,28] but not to lasofoxifene.[28] Lasofoxifene disrupts and inactivates the constitutive agonist conformation of the Y537S mutation-bearing ER, and, either alone or with palbociclib, inhibits tumor suppression and metastasis significantly more than fulvestrant in mBC models harboring *ESR1* mutations.[33]

Given these intriguing data, we initiated the phase II, signal-seeking, ELAINE 1 study evaluating the safety and efficacy of lasofoxifene compared with fulvestrant in women with *ESR1*-mutated mBC after progression on an AI plus a CDK4/6i.

METHODS

Study design and patients

The ELAINE 1 study (NCT03781063) was a phase II, open-label, randomized trial evaluating lasofoxifene versus fulvestrant monotherapy, conducted at 47 sites (United States, Canada, and Israel) according to the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the institutional review board and/or independent ethics committee at each site. All patients provided written informed consent.

Eligible participants were pre- or postmenopausal women (age $\geq$18 years) with locally advanced or metastatic, ER+/human epidermal growth factor receptor 2 negative (HER2−) breast cancer that progressed on a prior AI plus CDK4/6i as their most recent ET; one or more *ESR1* mutations identified in cell-free circulating tumor DNA (ctDNA); an Eastern Cooperative Oncology Group score of 0 or 1; one or more measurable lesion per RECIST version 1.1, or if no measurable disease, lytic or mixed lytic/sclerotic bone lesions; and laboratory-confirmed, adequate organ function. *ESR1* mutations could have included Y537S, Y537C, D538G, E380Q, S463P, V534E, P535H, L536H, L536P, L536R, L536Q, or Y537N. Patient tumors must have had prior sensitivity to ET (recurrence or progression after $\geq$12 treatment months in the metastatic setting), and patients must have received one or less lines of cytotoxic chemotherapy for mBC.

Key exclusion criteria included prior use of everolimus or other mammalian target of rapamycin or phosphoinositide 3-kinase inhibitor inhibitors, prior progression on fulvestrant, brain metastasis, lymphangitic carcinomatosis involving the lung, cytotoxic chemotherapy for visceral crisis, prior radiotherapy within 30 days, significant comorbidities that would impact the study or patient's safety, a history of long QT_c syndrome or QT_c interval >480 ms, pulmonary embolus or deep vein thrombosis within the previous 6 months, any known thrombophilia, vaginal bleeding over the past year, or malignancies other than breast cancer within 5 years. Any other investigational or commercial anticancer treatments, any hormone replacement therapy, or prolonged systemic corticosteroids were not permitted during the study. Any concomitant bisphosphonate or denosumab use to prevent/manage bone metastases was documented.

Study procedures

Patients were stratified by the presence or absence of visceral metastasis and Y537S *ESR1* mutation. Each stratified group was randomized 1 : 1 to oral lasofoxifene (5 mg/day) or IM fulvestrant (500 mg on days 1, 15, and 29, then monthly) until disease progression, intolerable toxicity, or withdrawal. Crossover between treatment groups was not

allowed. Premenopausal patients were maintained on ovarian suppression.

Computed tomography of the chest, abdomen, and pelvis was carried out every 2 months, or sooner if clinically indicated or at the time of withdrawal; brain or bone were scanned if clinically indicated. Adverse events (AEs) and serious AEs (SAEs) were assessed for type, severity, course, duration, seriousness, and relationship to treatment throughout the study. Treatment-emergent AEs (TEAEs) were defined as AEs with onset or worsening on or after first-dose date. Death related to breast cancer progression was not considered an AE. Changes in *ESR1* ctDNA mutant allele fractions (MAFs; ctDNA fraction containing the mutant allele) were assessed from baseline to week 8 using the OncoBEAM or Safe-Seq assay (Sysmex Inostics Inc, Baltimore, MD), which can detect clone-specific *ESR1* MAFs at a limit of 0.05%.

Study outcomes

All efficacy endpoints were assessed according to RECIST version 1.1 criteria. The primary endpoint was PFS (time from randomization to first documented radiographic progression or death). In patients with lytic or mixed lytic/sclerotic bone lesions, disease progression was defined as one or more new lytic bone lesions or new lesions outside of the bone, or unequivocal progression of existing bone lesions. The key secondary endpoints were clinical benefit rate (CBR; patient percentage with their best overall response as complete [CR] or partial [PR] response, or stable disease for $\geq$24 weeks), objective response rate (ORR; percentage of patients with measurable disease and best overall response of CR or PR), overall survival (time from randomization to death due to any cause), and safety (AEs and mortality). The 6- and 12-month PFS rates were exploratory analyses.

Statistical analysis

The target sample size was 100 (50 per treatment arm) with total expected PFS events of 86, considering a 1-year accrual period with an additional year of follow-up at accrual completion before the primary PFS analysis. Assuming lasofoxifene would double the median PFS compared with fulvestrant for a hazard ratio (HR) of 0.5 in this patient population, the statistical power would be $\sim$0.94 for observing a positive signal (two-sided stratified log-rank $P < 0.10$) and 0.89 for a conclusive outcome (two-sided $P < 0.05$) based on 86 expected PFS events. However, the targeted 86 events were not achieved as some patients were withdrawn for clinical progression based on investigator assessment before documented radiographic progression by RECIST. The statistical analysis plan was therefore amended to have database lock on 17 May 2022, when all remaining patients ($n = 8$) had completed their 24-week assessments, which occurred when 77 progression events were documented according to RECIST and 10 clinical progression events had been determined by the investigator. A more mature analysis was conducted on 13 July 2022.

All randomized patients were included in the efficacy analysis [intention-to-treat population] and analyzed by randomized treatment assignment regardless of protocol deviations. Missing data were not imputed. The median PFS for each treatment arm was estimated by the Kaplan–Meier method and a stratified log-rank test was used to test for a statistically significant difference in PFS curves adjusting for the four randomization strata (presence or absence of visceral metastasis and Y537S *ESR1* mutation) within a single covariate. The lasofoxifene over fulvestrant HRs were estimated by a Cox proportional hazards model stratified by the four randomization strata. Safety was evaluated in patients who received one or more treatment doses (safety population) and data were summarized descriptively. AEs and SAEs were categorized using the Medical Dictionary for Regulatory Activities (MedDRA) and graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

RESULTS

Patient disposition and baseline characteristics

A total of 103 patients (intention-to-treat population) were enrolled from 201 patients screened between September 2019 and September 2021, with 52 randomized to lasofoxifene and 51 to fulvestrant; most (77.6%) of the excluded patients did not have a detectable *ESR1* mutation (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.09.3104). As of July 2022, 83 patients (lasofoxifene versus fulvestrant, $n = 42$ versus 41) discontinued study treatment due to disease progression and 13 discontinued due to consent withdrawal (2 versus 5), investigator decision (2 versus 1), AEs (1 versus 0), relocation (0 versus 1), or other causes (0 versus 1; Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.09.3104). Efficacy was assessed in all 103 patients. Safety was evaluated in 99 patients (51 lasofoxifene-treated and 48 fulvestrant-treated); one and three patients in the lasofoxifene and fulvestrant arms, respectively, did not receive any study drug.

Baseline characteristics were generally balanced between the two treatment arms (Table 1 and Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.09.3104). Patients' race included Asian (6.8%), Black (10.7%), and White (82.5%); Hispanic ethnicity was reported by 6%. The mean age was 60.8 years (range 33-84 years); 70.9% had measurable disease and 62.1% had visceral metastasis. The mean duration of prior AI-CDK4/6i therapy was 30.0 and 26.4 months in the lasofoxifene and fulvestrant arms, respectively. The majority (92.2%) of patients received palbociclib as their first-line CDK4/6i treatment; two patients (randomized to the fulvestrant arm) switched from either palbociclib or ribociclib to abemaciclib before study initiation. At baseline, 54.4% of patients had tumors with polyclonal *ESR1* mutations. Commonly detected *ESR1* mutations at baseline (incidence >10%) were D538G (56.3%), Y537S (41.7%), Y537N (29.1%), E380Q (22.3%), and Y537C (10.7%).

Table 1. Baseline characteristics

Parameter	Lasofoxifene (n = 52)	Fulvestrant (n = 51)
Age (years)		
Mean ± standard deviation	60.3 ± 11.6	61.2 ± 10.4
Range	33-84	38-82
Race, *n* (%)		
Asian	3 (5.8)	4 (7.8)
Black or African American	6 (11.5)	5 (9.8)
White	43 (82.7)	42 (82.4)
Ethnicity, *n* (%)		
Hispanic or Latino	2 (3.8)	4 (7.8)
Not Hispanic or Latino	50 (96.2)	47 (92.2)
ECOG score, *n* (%)		
0	30 (57.7)	26 (51.0)
1	21 (40.4)	22 (43.1)
Measurable disease, *n* (%)	38 (73.1)	35 (68.6)
Disease location, *n* (%)		
Metastatic bone disease only	13 (25.0)	11 (21.6)
Visceral disease only	13 (25.0)	10 (19.6)
Both	18 (34.6)	23 (45.1)
Prior AI-CDK4/6i, *n* (%)	52 (100)	51 (100)
Mean duration, months	30.0	26.4
First-line CDK4/6i, *n* (%)		
Palbociclib	48 (92.3)	47 (92.2)
Ribociclib	3 (5.8)	3 (5.9)
Abemaciclib	1 (1.9)	1 (2.0)
Chemotherapy in mBC, *n* (%)	3 (5.8)	3 (5.9)
Prior radiotherapy, *n* (%)	36 (69.2)	36 (70.6)

AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG, Eastern Cooperative Oncology Group; mBC, metastatic breast cancer.

Efficacy

At the prespecified PFS analysis (database lock on 17 May 2022), lasofoxifene did not significantly improve the median PFS compared with fulvestrant [HR 0.705, 95% confidence interval (CI) 0.431-1.153; P = 0.164]. The median PFS for lasofoxifene was 22.2 weeks (5.1 months, 95% CI 14.1-36.8 weeks) compared with 14.8 weeks (3.4 months, 95% CI 10.8-22.2 weeks) for fulvestrant (log-rank P = 0.162). At that time, 87 patients had breast cancer that had progressed (according to RECIST version 1.1 or investigator-assessed) and the remaining 8 patients had completed a 24-week assessment. In an updated analysis (13 July 2022), the overall censored median PFS was similar; 24.2 weeks (5.6 months, 95% CI 11.3-32.1 weeks) for lasofoxifene versus 16.2 weeks (3.7 months, 95% CI 11.7-24.1 weeks) for fulvestrant (log-rank P = 0.138), with an HR of 0.699 (95% CI 0.434-1.125; P = 0.140; Figure 1). The Kaplan–Meier curves showed quick drops during the initial treatment period in both arms, but with a clear separation between the two arms after 16 weeks (Figure 1). Exploratory analyses showed that the PFS rate was higher with lasofoxifene than with fulvestrant at 6 months (53.4%, 95% CI 38.6% to 66.2% versus 37.9%, 95% CI 23.9% to 51.8%) and 12 months (30.7%, 95% CI 18.0% to 44.3% versus 14.1%, 95% CI 4.6% to 28.5%). Other exploratory subgroup analyses of patients with the Y537S *ESR1* mutation and visceral metastasis showed that lasofoxifene numerically improved median PFS relative to fulvestrant [24.2 weeks (5.6 months) with lasofoxifene and 14.2 weeks (3.3 months) with fulvestrant; Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.09.3104].

The CBR was 36.5% (19/52) with lasofoxifene and 21.6% (11/51) with fulvestrant (P = 0.117; Figure 2). Among patients with measurable disease, 5 of 38 lasofoxifene-treated patients achieved a confirmed objective response (1 CR and 4 PRs), while only 1 of 35 fulvestrant-treated patients

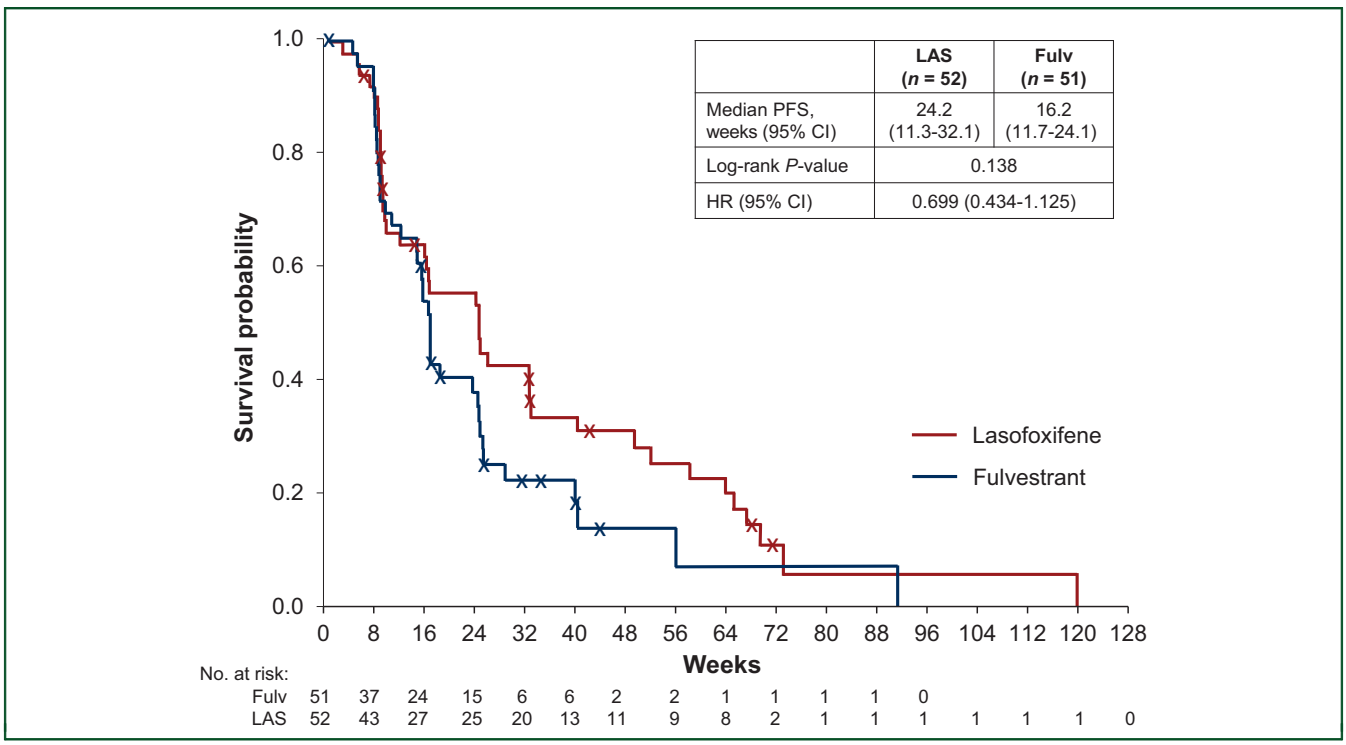

Figure 1. Kaplan–Meier estimates of progression-free survival (PFS) for lasofoxifene versus fulvestrant. Crosses indicate censored patients.
CI, confidence interval; Fulv, fulvestrant; HR, hazard ratio; LAS, lasofoxifene.

achieved a confirmed PR (Figure 3), yielding an ORR of 13.2% versus 2.9% ($P = 0.124$), respectively. The median time to response for the five objective response events with lasofoxifene was 15.8 weeks, with a median duration of response (DoR) of 52.4 weeks; DoR for the CR was 72 weeks. In the one patient who achieved a confirmed PR with fulvestrant, the time to response was 36.6 weeks and the DoR was 55.0 weeks. Of note, 4 of 9 (44.4%) lasofoxifene-treated patients who achieved a confirmed/unconfirmed response had the Y537S mutation, while 1 of 3 (33.3%) fulvestrant-treated patients with a confirmed response had the Y537S mutation (Figure 3).

Safety

Both treatments were generally well tolerated. TEAEs occurred in 48 (94.1%) lasofoxifene-treated patients and 46 (95.8%) fulvestrant-treated patients; grade 3/4 toxicities were 19.6% with lasofoxifene and 20.8% with fulvestrant; no grade 5 TEAEs were noted (Table 2). The most common TEAEs (all-grade incidence $\geq$20%) with lasofoxifene were nausea, fatigue, arthralgia, and hot flushes, and those with fulvestrant were fatigue, arthralgia, and increased aspartate aminotransferase; most were grade 1/2 (Table 2). TEAEs were considered treatment related in 64.7% of lasofoxifene-treated patients and 56.3% of fulvestrant-treated patients (Table 2). Other AEs of interest are summarized in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.09.3104. Grade 2 vaginal dryness was reported by one (2.1%) fulvestrant-treated patient, but no lasofoxifene-treated patients. Grade 1 vaginal discharge was reported by five (9.8%) patients receiving lasofoxifene, but none receiving fulvestrant. No venous thromboembolic events (VTEs), neutropenia, bradycardia, QT-interval changes, or ocular changes were observed. SAEs were reported in four (7.8%) lasofoxifene-treated patients and two (4.2%) fulvestrant-treated patients (Table 2). One death occurred in the fulvestrant arm (Table 2) due to fulminant disease progression (not considered a grade 5 AE as it was disease related).

Changes in ESR1 MAF

Among the 61 patients with evaluable baseline and week 8 ctDNA, 35 lasofoxifene-treated patients had a total of 68 different *ESR1* mutations with the most commonly detected baseline *ESR1* mutations being D538G, Y537S, Y537N, E380Q, and Y537C. For the 26 fulvestrant-treated patients, 61 different *ESR1* variants were observed. *ESR1* MAF from baseline to week 8 decreased in 82.9% (29/35) of lasofoxifene-treated patients and 61.5% (16/26) of fulvestrant-treated patients [undetectable in 31.4% (11/35) versus 23.1% (6/26), respectively; Figure 4A]. *ESR1* MAF increased in 17.1% (6/35) of patients with lasofoxifene versus 38.5% (10/26) with fulvestrant. For each of the commonly detected *ESR1* mutations, decreases in MAF were observed in 71.4%-100% of lasofoxifene-treated patients and 38.9%-75.0% of fulvestrant-treated patients (Figure 4A). In particular, lasofoxifene decreased Y537S MAF in 86.7% (13/15) of patients; in marked contrast, fulvestrant decreased the Y537S MAF in 38.9% (7/18).

The median percent changes in *ESR1* MAF were substantially different between lasofoxifene and fulvestrant (−87.1% versus −14.7%; Figure 4B). In evaluable patients with the Y537S mutation, the median percent changes in Y537S MAF were −89.1% with lasofoxifene and +82.3% with fulvestrant. Moreover, Y537S decreased to an undetectable level in 33.3% (5/15) of evaluable patients who received lasofoxifene versus 5.5% (1/18) of fulvestrant-treated patients.

Lasofoxifene also decreased MAF for numerically more variants than fulvestrant [85.3% (58/68) versus 49.2% (30/61)] after 8 weeks of treatment.

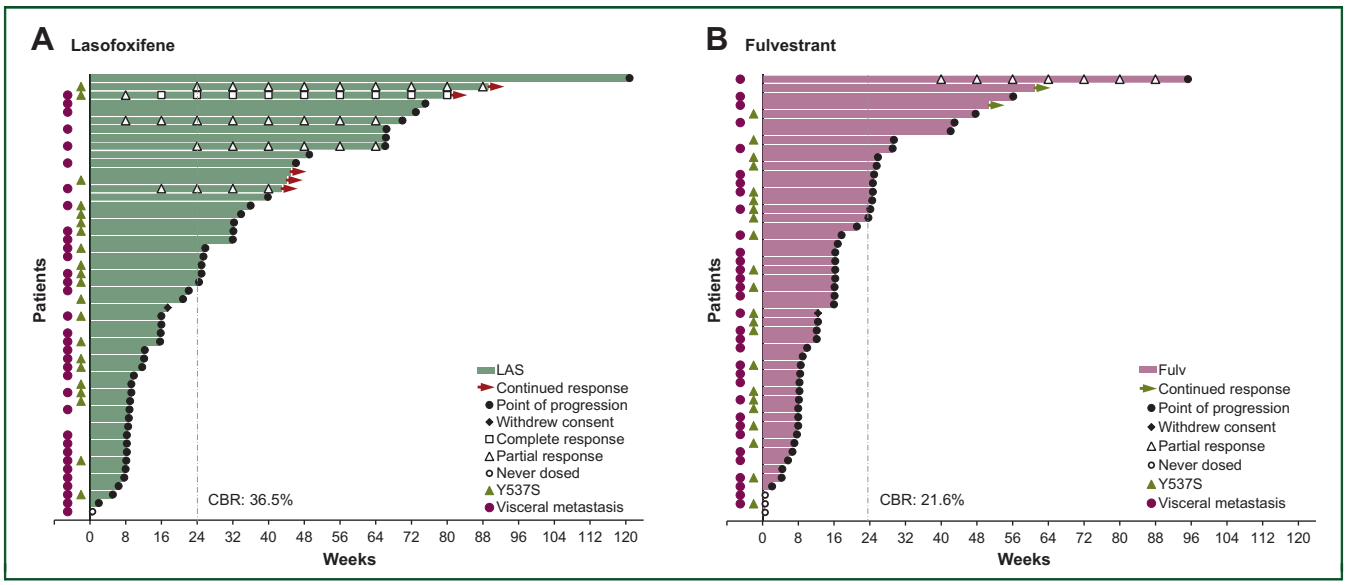

Figure 2. Time to response and duration of response for all patients treated with (A) lasofoxifene and (B) fulvestrant.
CBR, clinical benefit rate; Fulv, fulvestrant; LAS, lasofoxifene.

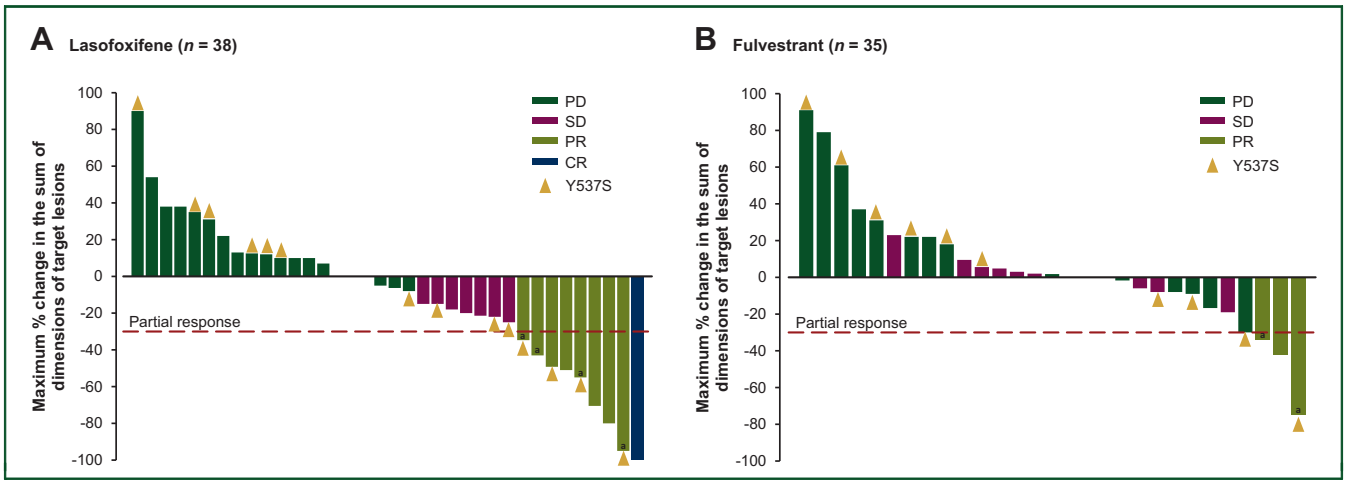

Figure 3. Maximum response for target lesions according to RECIST version 1.1 in patients with measurable lesions who were treated with (A) lasofoxifene and (B) fulvestrant. Response was measured as a change in the sum of dimensions of target lesions. Patients with Y537S detected at baseline are marked with gold arrowheads.

CR, complete response; Fulv, fulvestrant; LAS, lasofoxifene; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Unconfirmed.

DISCUSSION

ELAINE 1 is the first study to demonstrate the antitumor activity of lasofoxifene, a novel SERM, compared with the ER degrader fulvestrant, in patients with *ESR1*-mutated mBC in the post-CDK4/6i setting. Although the primary endpoint was not met, lasofoxifene provided a clinically meaningfully improvement in PFS relative to fulvestrant (~5.6 versus 3.7 months; $P = 0.138$), resulting in a CBR ~70% greater than with fulvestrant (37% versus 22%; $P = 0.117$), with an ORR over fourfold greater [13% for

Table 2. Incidence of TEAEs in the safety population

TEAE, *n* (%)	Lasofoxifene (*n* = 51)		Fulvestrant (*n* = 48)	
Total number of TEAEs	419		304	
Patients with				
Any TEAE	48 (94.1)		46 (95.8)	
Any treatment-related TEAE	33 (64.7)		27 (56.3)	
Any CTCAE grade 3/4 TEAE	10 (19.6)		10 (20.8)	
Any grade 5 TEAE	0 (0)		0 (0)	
TEAE leading to study drug discontinuation	0 (0)		1 (2.1)	
Any SAE	4 (7.8)		2 (4.2)	
Any treatment-emergent SAEs	4 (7.8)		2 (4.2)	
Death	0 (0)		1 (2.1)	
TEAEs ≥10% of patients in either arm	**All Grades**	**Grade 3/4/5**	**All Grades**	**Grade 3/4/5**
Nausea	14 (27.5)	0 (0)	9 (18.8)	0 (0)
Fatigue	12 (23.5)	1 (2.0)	18 (37.5)	0 (0)
Arthralgia	11 (21.6)	0 (0)	11 (22.9)	0 (0)
Hot flush	11 (21.6)	0 (0)	5 (10.4)	0 (0)
Constipation	8 (15.7)	0 (0)	6 (12.5)	0 (0)
Dizziness	8 (15.7)	0 (0)	2 (4.2)	0 (0)
Hypertension	8 (15.7)	2 (3.9)	7 (14.6)	1 (2.1)
Cough	8 (15.7)	0 (0)	5 (10.4)	0 (0)
Anemia	7 (13.7)	2 (3.9)	7 (14.6)	2 (4.2)
Myalgia	7 (13.7)	0 (0)	7 (14.6)	0 (0)
Diarrhea	7 (13.7)	1 (2.0)	6 (12.5)	0 (0)
Back pain	7 (13.7)	0 (0)	6 (12.5)	1 (2.1)
Muscle spasm	6 (11.8)	1 (2.0)	4 (8.3)	0 (0)
Dyspnea	6 (11.8)	1 (2.0)	3 (6.3)	1 (2.1)
Aspartate aminotransferase increased	5 (9.8)	0 (0)	10 (20.8)	1 (2.1)
Decreased appetite	5 (9.8)	0 (0)	5 (10.4)	0 (0)
Headache	4 (7.8)	0 (0)	7 (14.6)	0 (0)
Pain in extremity	1 (2.0)	0 (0)	6 (12.5)	0 (0)
Injection site pain	0 (0)	0 (0)	6 (12.5)	0 (0)
Alanine aminotransferase increased	0 (0)	0 (0)	7 (14.6)	0 (0)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious AE; TEAE, treatment-emergent adverse event.

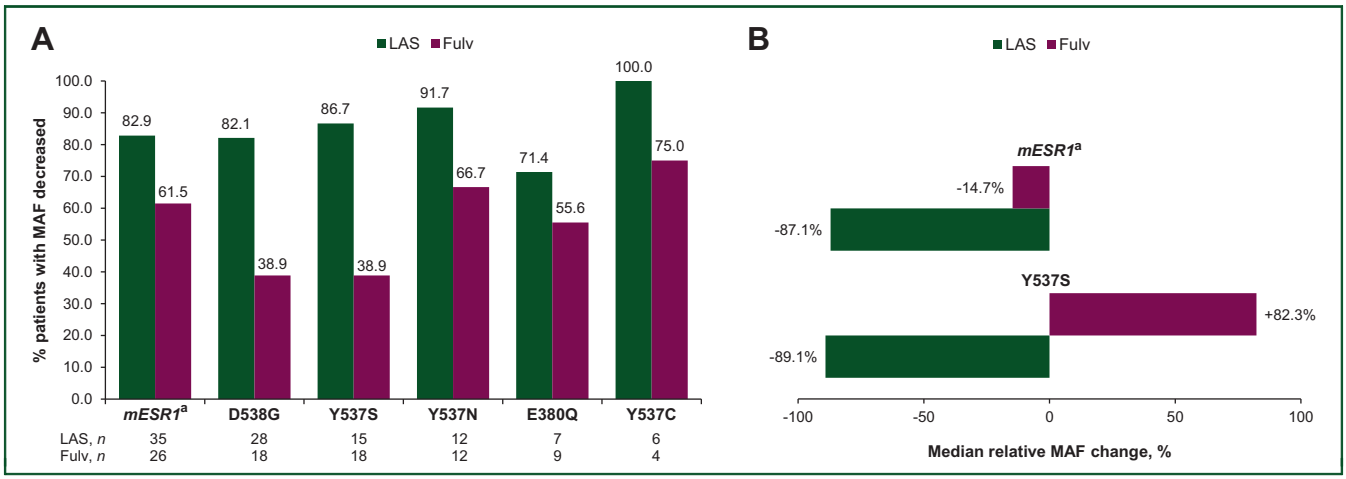

Figure 4. Changes of *ESR1* mutant allele fraction (MAF) from baseline to week 8. (A) Proportions of patients with *ESR1* MAF decreased. n is the number of patients with evaluable baseline and week-8 circulating tumor DNA and the respective *ESR1* mutation. (B) Median percent changes in *ESR1* MAF.
Fulv, fulvestrant; LAS, lasofoxifene; *mESR1*, *ESR1* mutations.
[a]Percent change was calculated for the overall MAF of all detected *ESR1* mutations in patients with tumors harboring polyclonal *ESR1* mutations.

lasofoxifene versus 3% for fulvestrant ($P = 0.124$)]. One patient experienced a durable CR on lasofoxifene. All efficacy endpoints numerically favored lasofoxifene over fulvestrant. Moreover, the significant decrease or clearance of *ESR1*-mutated ctDNA with lasofoxifene suggests its target engagement. Lasofoxifene also had a favorable safety profile, with few grade 3/4 TEAEs and no unexpected safety signals.

In this signal-seeking, phase II study, although with small patient numbers, lasofoxifene improved PFS in those with and without visceral metastasis, including those with visceral metastases and resistant *ESR1* Y537S mutation, clinical and genomic factors both associated with more severe disease.[12,26,34] Although a subset of patients in both arms exhibited initial rapid progression of their disease, consistent with endocrine resistance, the PFS curves diverged after ∼16 weeks, with numerically higher PFS rates for lasofoxifene at 6 and 12 months.

Clinically, fulvestrant monotherapy has been associated with a short median PFS (∼2-4 months) in patients with *ESR1* mutations.[9,21,23,24] The emergence of the Y537S mutation with fulvestrant or fulvestrant plus palbociclib in the PALOMA-3 study also suggests limited activity of fulvestrant against the Y537S mutant.[35] In line with this finding, our ctDNA analysis found that Y537S MAF decreased more frequently with lasofoxifene than with fulvestrant. Collectively, these clinical and previous preclinical data[28,33] suggest that lasofoxifene more effectively targets the mutant ER than fulvestrant, especially the Y537S mutant, even without the need for ER degradation of fulvestrant or an oral SERD. While both ER antagonism and degradation are thought to account for fulvestrant's activity, it has been suggested that the ability to induce ER degradation may not be correlated with the antitumor activity of fulvestrant and other SERDs in *ESR1*-mutated breast cancer cells.[36-38]

Newer ER degrading agents under clinical development for ER+ mBC are elacestrant, giredestrant, imlunestrant, and camizestrant,[39,40] while several others, such as amcenestrant,[41] rintodestrant,[42] brilanestrant,[43] and Zn-C5[44] have been withdrawn from development. Elacestrant is the first ER degrader to be Food and Drug Administration (FDA) approved for the treatment of patients with *ESR1*-mutated advanced BC or mBC.[45] In the subgroup of patients with *ESR1*-mutated advanced breast cancer who had prior CDK4/6i treatment in the EMERALD study, elacestrant improved efficacy compared with standard-of-care AI or fulvestrant (median PFS 3.8 versus 1.9 months; CBR 24% versus 12%; ORR 7% versus 5%).[25] The PFS rate with elacestrant was 41% and 27% at 6 and 12 months, respectively, compared with 21% and 8%, respectively, with fulvestrant.[25] Reports on imlunestrant (phase Ia/Ib EMBER),[46] camizestrant (phase II SERENA-2),[23] giredestrant (phase II acelERA Breast Cancer),[47] and amcenestrant (phase I/II AMEERA-1)[48] have shown that the median PFS with these newer ER degraders ranged from 3.7 to 5.5 months and the CBR from 27% to 50%; most of these patients (61%-100%) had prior CDK4/6i exposure. In subgroups of patients with tumors harboring *ESR1* mutations (with or without prior CDK4/6i), camizestrant, giredestrant, and amcenestrant were associated with a median PFS of 5.3-9.2 months and a CBR of 21%-26%.[23,47,48] Our median PFS (5.6 months), 6-month (53%) and 12-month (31%) PFS rates, CBR (37%), and ORR (13%) with lasofoxifene compare favorably with those seen with elacestrant or other SERDs under investigation in an *ESR1* mutation, post-CDK4/6i setting.

Both lasofoxifene and fulvestrant were well tolerated with no significant differences in their safety profiles, and a similar incidence of grade 3/4 TEAEs. In addition, patients treated with lasofoxifene 5 mg/day did not have a higher frequency/severity of AEs than previously reported for lower lasofoxifene doses.[29] Lasofoxifene TEAEs were not unexpected, as nausea, arthralgia, and hot flushes have been previously observed with lower doses in non-oncology populations.[29,49,50] Nausea is a known side-effect of tamoxifen (5%-26%),[51] fulvestrant (11%-28%),[17,18,52,53] and elacestrant (35%).[25] In ELAINE 1, 28% of lasofoxifene-

treated patients versus 19% of fulvestrant-treated patients had nausea, and few (<10%) patients experienced vomiting. Dizziness (grade 1 only) was also reported more often with lasofoxifene versus fulvestrant (16% versus 4%), but no syncope occurred with either agent. Injection site pain was reported only with intramuscular fulvestrant, as expected. VTE is a known class effect for ER modulators including lasofoxifene, raloxifene, and tamoxifen,[54-59] and tamoxifen is also associated with increased cataract incidence.[60] ELAINE 1 study results are reassuring regarding these potential toxicities with no VTEs, ocular toxicity, cardiac events, or neutropenia reported.

In addition to its once-daily, oral dosing without food, lasofoxifene may confer quality-of-life benefits, including improved vulvovaginal and bone health, with its tissue-selective properties. Lower lasofoxifene doses (0.25 and 0.5 mg/day) have been shown to improve symptoms of vulvovaginal atrophy.[30] Here, one vaginal dryness AE occurred in the fulvestrant arm, while no vaginal dryness events were reported in the lasofoxifene arm. However, five patients treated with lasofoxifene experienced vaginal discharge, suggesting a potential lubricant benefit of lasofoxifene (5 mg/day). Moreover, lasofoxifene (0.5 mg/day) has been shown to reduce fracture risk in postmenopausal women with osteoporosis,[29] unlike AIs, which suppress estrogen activity potentially leading to poor bone preservation.[61,62] Potential tissue-selective benefits of lasofoxifene at 5 mg/day in patients with breast cancer will be explored in future studies.

While this signal-seeking study is limited by its small sample size, especially in subgroup analyses, and not reaching the targeted 86 PFS events, ELAINE 1 demonstrated promising antitumor activity of lasofoxifene monotherapy for women with endocrine-resistant mBC after prior CDK4/6i exposure. Furthermore, this is the first study demonstrating the antitumor activity of a nondegrading SERM in patients with mBC that had ligand-independent, constitutively active *ESR1* mutations and progressed on an AI-CDK4/6i combination. In addition to ELAINE 1, a single-arm, phase II study (ELAINE 2) evaluated the safety and efficacy of lasofoxifene plus abemaciclib and demonstrated encouraging PFS of ∼13 months in heavily pretreated patients with *ESR1*-mutated mBC and prior CDK4/6i exposure, as recently reported.[63] A phase III, ELAINE 3 trial (NCT05696626) has been initiated to evaluate the combination of lasofoxifene plus abemaciclib versus fulvestrant plus abemaciclib in patients with *ESR1*-mutated mBC.

Conclusions

In the ELAINE 1 study, lasofoxifene resulted in promising, preliminary, antitumor activity compared with fulvestrant in patients with *ESR1*-mutated mBC with prior CDK4/6i exposure, and a favorable safety profile. While the study did not statistically meet the primary endpoint given the small sample size, attrition, and censoring from patients discontinuing for clinical rather than RECIST progression, lasofoxifene did provide numerical and clinical improvement in median PFS, CBR, and ORR compared with fulvestrant. Importantly, lasofoxifene demonstrated 'on-target' effects, with reductions in the difficult-to-treat Y537S MAF in most (87%) patients (median percent change in MAF of −89%), while Y537S MAF increased in more than half (61%) of fulvestrant-treated patients. Lasofoxifene may be a new targeted, endocrine treatment option for patients with *ESR1*-mutated mBC after disease progression on endocrine plus CDK4/6i therapies.

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