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ORIGINAL ARTICLE

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

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Background: Acquired *ESR1* mutations in estrogen receptor-positive (ER+) metastatic breast cancer (mBC) drive treatment resistance and tumor progression; new treatment strategies are needed. Lasofoxifene, a next-generation, oral, endocrine therapy and tissue-specific ER antagonist, provided preclinical antitumor activity, alone or combined with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) in *ESR1*-mutated mBC.

Patients and methods: In the open-label, phase II, ELAINE 2 trial (NCT04432454), women with *ESR1*-mutated, ER+/human epidermal growth factor receptor 2-negative (HER2−) mBC who progressed on prior therapies (including CDK4/6i) received lasofoxifene 5 mg/day and abemaciclib 150 mg b.i.d until disease progression/toxicity. The primary endpoint was safety/tolerability. Secondary endpoints included progression-free survival (PFS), clinical benefit rate (CBR), and objective response rate (ORR).

Results: Twenty-nine women (median age 60 years) participated; all but one were previously treated with a CDK4/6i (median duration 2 years). The lasofoxifene—abemaciclib combination was well tolerated with primarily grade 1/2 treatment-emergent adverse events (TEAEs), most commonly diarrhea, nausea, fatigue, and vomiting. One patient (with no prior CDK4/6i) discontinued treatment due to grade 2 diarrhea. No deaths occurred during the study. Median PFS was 56.0 weeks [95% confidence interval (CI) 31.9 weeks-not estimable; ∼13 months]; PFS rates at 6, 12, and 18 months were 76.1%, 56.1%, and 38.8%, respectively. CBR at 24 weeks was 65.5% (95% CI 47.3% to 80.1%). In 18 patients with measurable lesions, ORR was 55.6% (95% CI 33.7% to 75.4%). *ESR1*-mutant circulating tumor DNA (ctDNA) allele fraction decreased from baseline to week 4 in 21/26 (80.8%) patients.

Conclusions: Lasofoxifene plus abemaciclib had an acceptable safety profile, was well tolerated, and exhibited meaningful antitumor activity in women with *ESR1*-mutated, ER+/HER2− mBC after disease progression on prior CDK4/6i. Observed decreases in *ESR1*-mutant ctDNA with lasofoxifene concordant with clinical response suggest target engagement. If the ELAINE 2 findings are confirmed in the initiated, phase III, ELAINE 3 trial, these data could be practice-changing and help address a critical unmet need.

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

INTRODUCTION

Breast cancer is the most common female cancer in the United States, and 287 850 new cases were estimated in 2022.[1] Approximately three-quarters of breast cancers express estrogen receptor alpha (ERα); endocrine therapy (ET) alone or combined with other targeted agents is presently the mainstay of treatment for ER+, metastatic breast cancer (mBC).[2-4] Acquired mutations in the ER

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(*ESR1*) ligand-binding domain have been described in patients with mBC who are estrogen deprived with aromatase inhibitors (AIs).[5-7] These *ESR1* mutations confer ligand-independent constitutive ER activity and drive allele-specific transcriptional network reprogramming, leading to endocrine resistance, cancer metastasis, and poor outcomes.[8-10] Moreover, breast cancers with *ESR1* mutations may gain basal-like features with increased expression of basal subtype markers.[11]

Three cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6is), palbociclib, ribociclib, and abemaciclib, are Food and Drug Administration and European Medicines Agency approved for treating ER+/human epidermal growth factor receptor 2-negative (HER2−) mBC, alone or combined with ET, in first- and second-line settings.[3,4,12-17] Although progression-free survival (PFS) among the CDK4/6is is similar, differences in overall survival and efficacy in the adjuvant setting are emerging.[18,19] Further, differences in the biology, mechanisms of action and resistance, and safety profiles of these agents are clear.[19-21] In contrast to palbociclib and ribociclib, abemaciclib is dosed continuously and has been shown to inhibit other kinases such as CDK2/cyclin A/E, CDK1/cyclin B, glycogen synthase kinase 3α/β, and calcium/calmodulin-dependent protein kinase type IIγ/δ, which have been implicated in CDK4/6i resistance.[22] Data from the MAINTAIN study[23] and a multicenter retrospective analysis[24] suggest that ribociclib and abemaciclib could have meaningful clinical activity in patients with ER+/HER2− mBC that developed disease progression on prior palbociclib; and others suggest a potential benefit switching to an alternate CDK4/6i at progression.[22,25,26]

Currently, systemic treatment options for patients with ER+/HER2−, *ESR1*-mutated mBC after disease progression on a CDK4/6i alone or combined with ET are limited, with no established best standard of care.[25,27] The phase III, PADA-1 study showed that switching from first-line AI plus palbociclib to the selective estrogen receptor degrader (SERD), fulvestrant, plus palbociclib before clinical disease progression, prolonged PFS in patients with advanced breast cancer and a rising blood *ESR1* mutation.[28] However, fulvestrant as monotherapy or in combination with other targeted therapies has limited clinical activity in patients with *ESR1*-mutated tumors following ET and/or CDK4/6i progression.[23,29-32] Although another SERD, elacestrant, was recently approved as a treatment option for patients with *ESR1*-mutated, ER+/HER2− mBC,[33] its activity as a single agent in the post-CDK4/6i setting was limited (median PFS 3.8 months).[32] Other novel SERDs, including giredestrant, imlunestrant, and camizestrant, are under clinical development for the treatment of ER+/HER2− mBC,[34,35] while several others including amcenestrant,[36] rintodestrant,[37] brilanestrant,[38] and Zn-C5[39] have been withdrawn from development. Recent smaller studies of SERDs combined with a CDK4/6i for *ESR1*-mutated, ER+/HER2− mBC after CDK4/6i progression have shown modest clinical responses; for example, the median PFS was 3 months for fulvestrant plus ribociclib,[23] and the clinical benefit rate (CBR) for camizestrant plus palbociclib or abemaciclib was 10%-38%, with no objective responses observed.[40,41] Thus, novel therapeutic strategies, especially those targeting acquired *ESR1* mutations, are critically needed.

Lasofoxifene is a next-generation breast ER antagonist that inactivates the receptor by modifying it from a constitutive to antagonist conformation.[42] Lasofoxifene significantly reduced the incidence of invasive ER+ breast cancer in the Postmenopausal Evaluation and Risk Reduction with Lasofoxifene (PEARL) osteoporosis trial (n = 8556),[43] consistent with preclinical results.[44] In *ESR1*-mutated mBC xenograft models, lasofoxifene exhibited superior antitumor activity compared with fulvestrant, either alone or combined with palbociclib.[42] Lasofoxifene also maintained its antagonist activity in breast cancer cells that had greater relative levels of mutant over wild-type *ESR1*, unlike fulvestrant and other ER modulators or degraders.[45] A recent report from the signal-seeking, phase II, ELAINE 1 trial showed that lasofoxifene monotherapy exhibited encouraging antitumor activity versus fulvestrant monotherapy, with numerically improved PFS (5.6 versus 3.7 months; $P = 0.138$) and higher CBR (37% versus 22%; $P = 0.117$) and objective response rate (ORR; 13% versus 3%; $P = 0.124$), in women with *ESR1*-mutated mBC that progressed on an AI-CDK4/6i combination.[46]

The ELAINE 2 study was initiated to evaluate the safety and efficacy of lasofoxifene combined with abemaciclib in women with ER+/HER2− mBC and *ESR1* mutations who had progressed on CDK4/6i-based regimens.

PATIENTS AND METHODS

Study design and patients

The ELAINE 2 study (NCT04432454) is an open-label, phase II, multicenter, single-arm trial conducted at 16 USA sites according to the ethical principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by each participating site's institutional review board and/or independent ethics committee. All participants provided written informed consent.

Eligible participants were pre- and postmenopausal women (aged ≥18 years) who had locally advanced and/or metastatic ER+/HER2− breast cancer that progressed after one or two lines of ET, ≥1 *ESR1* mutation identified in cell-free circulating tumor DNA (ctDNA) by central testing using the SafeSeq assay (Sysmex Inostics Inc., Baltimore, MD), an Eastern Cooperative Oncology Group score of 0 or 1, and adequate organ function confirmed by laboratory testing. *ESR1* mutations included Y537S, Y537C, D538G, E380Q, S463P, V534E, P535H, L536H, L536P, L536R, L536Q, and/or Y537N variants. Patients must have shown no evidence of disease progression for ≥6 months during their first ET-based treatment for advanced breast cancer. Prior use of CDK4/6i and/or one chemotherapy regimen for metastatic disease was allowed.

Key exclusion criteria included lymphangitic carcinomatosis; visceral crisis in need of immediate cytotoxic chemotherapy; radiotherapy within 30 days of study entry; known inactivating *RB1* mutations or deletions; a history of

long QT syndrome or a QT_c of >480 mc; pulmonary embolism (PE) or deep vein thrombosis (DVT) within 6 months; any known thrombophilia; or other malignancy (excluding basal or squamous cell carcinoma of the skin) in the past 5 years. Patients were not allowed to take any other investigational or commercial anticancer treatments, hormone replacement therapy, prolonged courses of systemic corticosteroids, or strong CYP3A4 inhibitors or moderate or strong CYP3A4 inducers. Concomitant bisphosphonate therapy or denosumab for the management of bone metastases was allowed.

Study procedures

Patients took oral lasofoxifene 5 mg/day and abemaciclib (supplied by Eli Lilly and Co., Indianapolis, IN) 150 mg twice a day (b.i.d) until evidence of disease progression, death, unacceptable toxicity, or withdrawal from the study. Safety was assessed at every visit (weeks 2, 4, 6, and 8, and then monthly until disease progression). Adverse events (AEs) were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA), and their severity graded as per the Common Terminology Criteria for Adverse Events version 5.0. The course, duration, seriousness, and causal relationship to study treatment were evaluated for all AEs. Treatment-emergent AEs (TEAEs) were defined as any AEs with onset or worsening of pre-existing events on or after the first-dose date. Tumor response was determined using RECIST version 1.1 (RECIST v1.1). Magnetic resonance imaging (MRI) or computed tomography (CT) of the chest, abdomen, and pelvis was carried out every 8 weeks or sooner if clinically indicated or at withdrawal; MRI or CT of the brain or bone scan were also carried out if clinically indicated. Testing of ctDNA for *ESR1*-mutant allele fractions (MAF; percentage of cell-free DNA that contains the mutant allele) was carried out at baseline, week 4, and disease progression using the SafeSeq assay, which detects clone-specific *ESR1* mutations at low MAF levels (limit of detection 0.05%).

Abemaciclib dose reductions or dose interruptions were allowed as per approval label.[12] Concurrent lasofoxifene dose interruption during the time of abemaciclib interruption was not required, but some investigators opted to do so. If a patient was unable to tolerate 50 mg abemaciclib b.i.d, treatment with lasofoxifene alone could be continued until disease progression at the discretion of the treating physician. Dose reductions for lasofoxifene were not permitted; however, lasofoxifene could be suspended if a related, grade 3/4 AE occurred, and then resumed at the assigned dose after the toxicity resolved to a level <grade 2 or baseline. Patients who could not tolerate lasofoxifene or had not taken lasofoxifene for 3 consecutive weeks were withdrawn from the study; continuing abemaciclib alone was not allowed.

Outcomes

The primary endpoint was the safety and tolerability of the lasofoxifene—abemaciclib combination as assessed by the incidence and severity of AEs and mortality due to AEs. Secondary endpoints included PFS (time from study entry to earliest date of first documented progression or death), CBR [percentage of patients with best overall response being a complete response (CR), partial response (PR), or stable disease for ≥24 weeks according to RECIST v1.1], ORR (percentage of patients with best overall response being a confirmed CR or PR according to RECIST v1.1), duration of response (DoR; time from the date of first documented CR or PR to that of first documented progression or death), time to response (TTR; time from the first treatment dose to time of first documented CR or PR), and steady-state pharmacokinetics. For patients with measurable disease, disease progression was based on assessment by the investigator according to RECIST v1.1. In patients without measurable disease at baseline, disease progression was defined as ≥1 new lytic lesion in the bone, ≥1 new lesion outside of the bone, or unequivocal progression of existing bone lesions.

Statistical analysis

Since the primary objective of this open-label, single-arm study was to evaluate safety and tolerability, no formal sample size was calculated and the planned sample size was considered adequate to assess initial safety and tolerability of the treatment. Data were summarized descriptively with no formal hypothesis tested. PFS is presented in a Kaplan—Meier curve with an estimated median PFS. CBR in the intent-to-treat population (all patients who received treatment) and ORR in patients with measurable disease are reported as percentages of patients with 95% confidence interval (CI).

RESULTS

Patient disposition and baseline demographics

A total of 29 women were enrolled from October 2020 to June 2021. As of January 2023, 8 patients remained on treatment; 15 had developed disease progression; and 6 discontinued because of AEs ($n = 1$), patient withdrawal ($n = 3$), and other causes ($n = 2$; Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.09.3103).

The median age was 60 years; 86.2% of patients were White, and 62.1% had measurable disease at baseline (Table 1). Before study entry, patients had received a median of two lines of ET in the metastatic setting, and >70% had tumors that progressed on two prior ET-based regimens. All but one patient (96.6%) had prior CDK4/6i exposure with tumor progression on their most recent CDK4/6i; five (17.2%) received two prior CDK4/6i-based regimens (Table 1). Twenty-three (79.3%) patients had received prior fulvestrant, and 14 (48.3%) prior chemotherapy in the metastatic setting (Table 1). The median duration of prior CDK4/6i treatment was 2 years. Of the most common baseline *ESR1* mutations, the Y537S mutation was seen in 65.5% of patients and the D538G mutation

Table 1. Baseline demographics and characteristics

	N = 29
Age, years	
Mean	58.3
Median (range)	60 (35-79)
Menopause, *n* (%)	
Premenopausal	4 (13.8)
Postmenopausal	25 (86.2)
Race, *n* (%)	
Black	2 (6.9)
White	25 (86.2)
Unknown	2 (6.9)
Ethnicity, *n* (%)	
Non-Hispanic	27 (93.1)
Hispanic	2 (6.9)
Measurable disease, *n* (%)	18 (62.1)
Visceral disease, *n* (%)	16 (55.2)
Bone only, *n* (%)	10 (34.5)
Commonly detected (≥10%) *mESR1*, *n* (%)	
Y537S	19 (65.5)
D538G	13 (44.8)
Y537N	8 (27.6)
Y537C	3 (10.3)
Polyclonal *mESR1*, *n* (%)	14 (48.3)
Prior breast cancer therapy, *n* (%)	
Chemotherapy in the metastatic setting	14 (48.3)
CDK4/6i	28 (96.6)
Palbociclib	26 (89.7)
Abemaciclib	4 (13.8)
Ribociclib	2 (6.9)
Unknown	1 (3.4)
≥2 CDK4/6i therapies	5 (17.2)
Endocrine therapy, *n* (%)	29 (100)
Aromatase inhibitor	28 (96.6)
Fulvestrant	23 (79.3)
Tamoxifen	12 (41.4)
Everolimus, *n* (%)	4 (13.8)
Alpelisib, *n* (%)	3 (10.3)

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *mESR1*, *ESR1* mutation.

in 44.8%; 48.3% of patients had polyclonal *ESR1* mutations (Table 1).

Safety

The combination of lasofoxifene and abemaciclib was well tolerated, with the most common TEAEs of any grade being diarrhea, nausea, fatigue, and vomiting (Table 2). Other AEs of special interest with an incidence of ≥10% were anemia ($n = 8$; 27.6%), decreased white blood cell count ($n = 8$; 27.6%), neutropenia/decreased neutrophil count ($n = 6$; 20.7%), muscle spasms ($n = 5$; 17.2%), hot flushes ($n = 4$; 13.8%), myalgia ($n = 4$; 13.8%), urinary tract infections ($n = 4$; 13.8%), and DVT/PE ($n = 3$; 10.3%). Grade 3/4 TEAEs occurred in 15 (51.7%) patients, most commonly neutropenia/decreased neutrophil count ($n = 4$; 13.8%), anemia ($n = 3$; 10.3%), PE ($n = 3$; 10.3%), hypokalemia ($n = 3$; 10.3%), and decreased lymphocyte counts ($n = 3$; 10.3%; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.09.3103). Three of these patients experienced grade 4 TEAEs, including decreased lymphocyte count ($n = 1$) and neutropenia/decreased neutrophil count ($n = 2$). The one (3.4%) patient who had not received a prior CDK4/6i discontinued study treatment after 4 weeks due to grade 2 diarrhea, attributed to abemaciclib. No deaths occurred on study treatment.

Three (10.3%) of the 29 patients developed a DVT and/or PE (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.09.3103). One patient had a spontaneous, symptomatic PE, which occurred at week 64 of the study, and subsequently withdrew from the study due to anticoagulation-related complications. In the second patient, a symptomatic DVT was diagnosed after elective knee surgery and an asymptomatic PE was noted on a surveillance scan. In the third patient, a DVT and PE (both asymptomatic) were found incidentally on surveillance scans. Both patients were treated with anticoagulants and were able to continue study treatment. All three patients achieved a clinical benefit as described in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.09.3103.

While the lasofoxifene dose was not reduced per protocol, abemaciclib dose was reduced (from 150 mg to 100 mg b.i.d) in six (20.7%) patients (all due to AEs; Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.09.3103). TEAEs led to abemaciclib interruption in 15 (51.7%) patients and lasofoxifene interruption in 12 (41.4%) patients (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2023.09.3103). Lasofoxifene was interrupted along with abemaciclib largely due to interruptions for abemaciclib-related AEs.

Efficacy

Among 18 patients with measurable target lesions, 10 experienced a confirmed PR, yielding an ORR of 55.6% (95% CI 33.7% to 75.4%; Figure 1). Median TTR was 24.6 weeks (5.7 months), and median DoR was 27.8 weeks (6.4 months). Seven of the 10 patients with a PR remained on treatment for >1 year. In all patients, the CBR at 24 weeks was 65.5% (95% CI 47.3% to 80.1%), with 10 patients achieving a PR and 9 having stable disease for ≥24 weeks (Figure 2). The censored median PFS was 56.0 weeks (95% CI 31.9 weeks-not estimable), ∼13 months (Figure 3). The PFS rate (95% CI) was 76.1% (54.4% to 88.5%) at 6 months, 56.1% (34.9% to 72.8%) at 12 months, and 38.8% (20.0% to 57.3%) at 18 months.

Among the four patients with prior tumor progression on abemaciclib-based treatment, two achieved clinical benefit (one with a confirmed PR and one with stable disease ≥24 weeks), and one experienced RECIST progression at week 16 but remained on study through week 40 at the discretion of the investigator given marked clinical benefit (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2023.09.3103). Clinical benefit was also observed in two of three other patients who previously received alpelisib combined with fulvestrant.

Changes in *ESR1* MAF

In 26 patients with evaluable baseline and week 4 ctDNA data, *ESR1* MAF decreased from baseline to week 4 in 21 (80.8%) patients [including 14 (53.8%) whose *ESR1* MAF

Table 2. Most common (all-grade incidence ≥12%) TEAEs ($N = 29$)

TEAEs, *n* (%)	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Diarrhea	19 (65.5)	5 (17.2)	0	0	24 (82.8)
Nausea	10 (34.5)	5 (17.2)	0	0	15 (51.7)
Fatigue	7 (24.1)	3 (10.3)	1 (3.4)	0	11 (37.9)
Vomiting	6 (20.7)	2 (6.9)	1 (3.4)	0	9 (31.0)
Anemia	4 (13.8)	1 (3.4)	3 (10.3)	0	8 (27.6)
Dyspnea	4 (13.8)	4 (13.8)	0	0	8 (27.6)
White blood cell count decreased	2 (6.9)	6 (20.7)	0	0	8 (27.6)
Blood creatinine increased	3 (10.3)	4 (13.8)	0	0	7 (24.1)
Constipation	5 (17.2)	0	1 (3.4)	0	6 (20.7)
Cough	5 (17.2)	1 (3.4)	0	0	6 (20.7)
Decreased appetite	4 (13.8)	2 (6.9)	0	0	6 (20.7)
Neutropenia/neutrophil count decreased	0	2 (6.9)	2 (6.9)	2 (6.9)	6 (20.7)
Hypokalemia	2 (6.9)	0	3 (10.3)	0	5 (17.2)
Muscle spasm	5 (17.2)	0	0	0	5 (17.2)
Alopecia	4 (13.8)	0	0	0	4 (13.8)
Dehydration	2 (6.9)	2 (6.9)	0	0	4 (13.8)
Dizziness	2 (6.9)	2 (6.9)	0	0	4 (13.8)
Fall	1 (3.4)	1 (3.4)	2 (6.9)	0	4 (13.8)
Hot flush	3 (10.3)	1 (3.4)	0	0	4 (13.8)
Hypoalbuminemia	4 (13.8)	0	0	0	4 (13.8)
Myalgia	4 (13.8)	0	0	0	4 (13.8)
Edema peripheral	4 (13.8)	0	0	0	4 (13.8)
Pain in extremity	4 (13.8)	0	0	0	4 (13.8)
Pruritus	3 (10.3)	1 (3.4)	0	0	4 (13.8)
Stomatitis	3 (10.3)	1 (3.4)	0	0	4 (13.8)
Urinary tract infection	0	4 (13.8)	0	0	4 (13.8)

Patients with maximum grade counts. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) versions 23.0. Severity of TEAEs were scored from grades 1 (least severe) to 4 (most severe).
TEAEs, treatment-emergent adverse events, defined as adverse events that started or worsened after the first dose.

became undetectable] and increased in 3 (11.5%) patients. The change was equivocal in two (7.7%) patients who had tumors with polyclonal (>1) *ESR1* mutations (*ESR1* MAF increased or decreased for various mutants). In 47 *ESR1*-mutant variants detected at baseline, *ESR1* MAF decreased for 43 [91.5%; undetectable for 32 (68.1%)] and increased for 4 (8.5%). In the two patients with disease progression on prior abemaciclib-based therapies who experienced clinical benefit in this study, *ESR1* MAF was not detectable at week 4 (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2023.09.3103).

DISCUSSION

The ELAINE 2 trial demonstrated that lasofoxifene plus abemaciclib exhibited an acceptable safety and tolerability profile and robust antitumor activity in women who had ER+/HER2− mBC with acquired *ESR1* mutations and progression on a prior CDK4/6i. Lasofoxifene plus abemaciclib was associated with a clinically meaningful PFS (median ∼13 months), ORR (56%), and CBR (66%), and reduced or cleared *ESR1* MAF ctDNA, concordant with target engagement.

No new safety signals were observed for the combination of lasofoxifene plus abemaciclib, and TEAE incidence with the combination was consistent with the previously reported individual safety profiles of each agent, including those reported for lasofoxifene in ELAINE 1.[46] The most frequently reported TEAEs in our study were abemaciclib-related toxicities,[12,47] including diarrhea (83%), nausea (52%), fatigue (38%), and vomiting (31%). While cross-trial comparisons have their limitations, especially given the low number of patients in ELAINE 2 and different study populations among other studies, the rates of these events with the lasofoxifene−abemaciclib combination were within the range previously reported with abemaciclib monotherapy [diarrhea (67%-90%), nausea (33%-64%), fatigue (27%-65%), and vomiting (25%-35%)],[47,48] suggesting that lasofoxifene does not increase the incidence of these abemaciclib-associated TEAEs. Neutropenia and leukopenia are known side-effects of CDK4/6i that were previously reported in 42%-88% and 22%-91% of patients receiving abemaciclib monotherapy or combined with ET, respectively.[47-53] Incidence of neutropenia/decreased neutrophil count in ELAINE 2 was 21% and incidence of decreased white blood cell count was 28%. Furthermore, abemaciclib did not appear to increase the incidence or severity of certain known lasofoxifene-related AEs; the observed muscle spasms (17%) and hot flushes (14%) in our study were reported as some of the most common events with a similar incidence in previous lasofoxifene studies (16%-25% and 13%-29%, respectively).[54-56]

A particular toxicity that will require further investigation is thromboembolism. Given that venous thromboembolism (VTE) is a known risk associated with mBC,[57] selective estrogen receptor modulators,[58-63] and CDK4/6is (abemaciclib in particular),[64] the VTE rate with the combination of lasofoxifene plus abemaciclib in this phase II study is pertinent. The PEARL osteoporosis study showed that the risk of VTE increased by approximately twofold to threefold

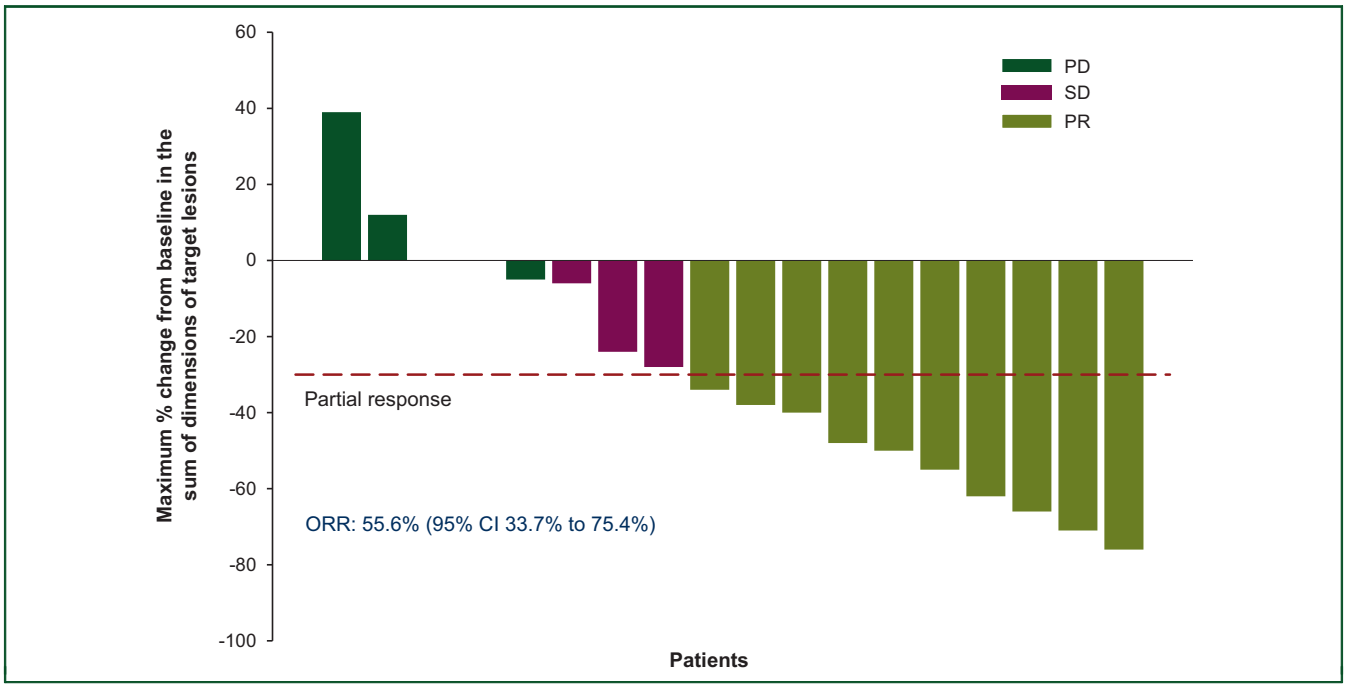

Figure 1. Maximum response for target lesions according to RECIST v1.1 in patients with measurable lesions ($n = 18$).
Response was measured as changes in the sum of dimensions of target lesions. ORR was based on confirmed response events. CI, confidence interval; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

with lasofoxifene at 0.25 mg/day and 0.5 mg/day versus placebo in postmenopausal women with osteoporosis, for an absolute increase of 2.35 and 1.49 cases per 1000 person-years, respectively,[63] similar to that reported for tamoxifen and raloxifene.[58-62] VTE events at a rate of 2%-10% for patients treated with abemaciclib alone or combined with ET have been reported across several clinical trials and observational cohorts in different patient populations.[12,24,48-52,65] It should be noted too that most of these previous trials on abemaciclib-based therapies were conducted in the adjuvant setting or early-line ($\leq$2) setting for mBC,[47,49-52] whereas in ELAINE 2, most patients were on their third line of therapy. Further, >50% of ELAINE 2 patients had visceral disease, which may have contributed to their VTE risk. Notably, no thrombotic events were reported with lasofoxifene monotherapy in the ELAINE 1 study.[46] Here in ELAINE 2, the VTE rate was 10% and it will be important to more fully assess the relative risk of thromboembolism with this combination in larger trials, such as the phase III, ELAINE 3 study.

Among the three patients who experienced VTE, all had evidence of treatment benefit. One had a confirmed PR at

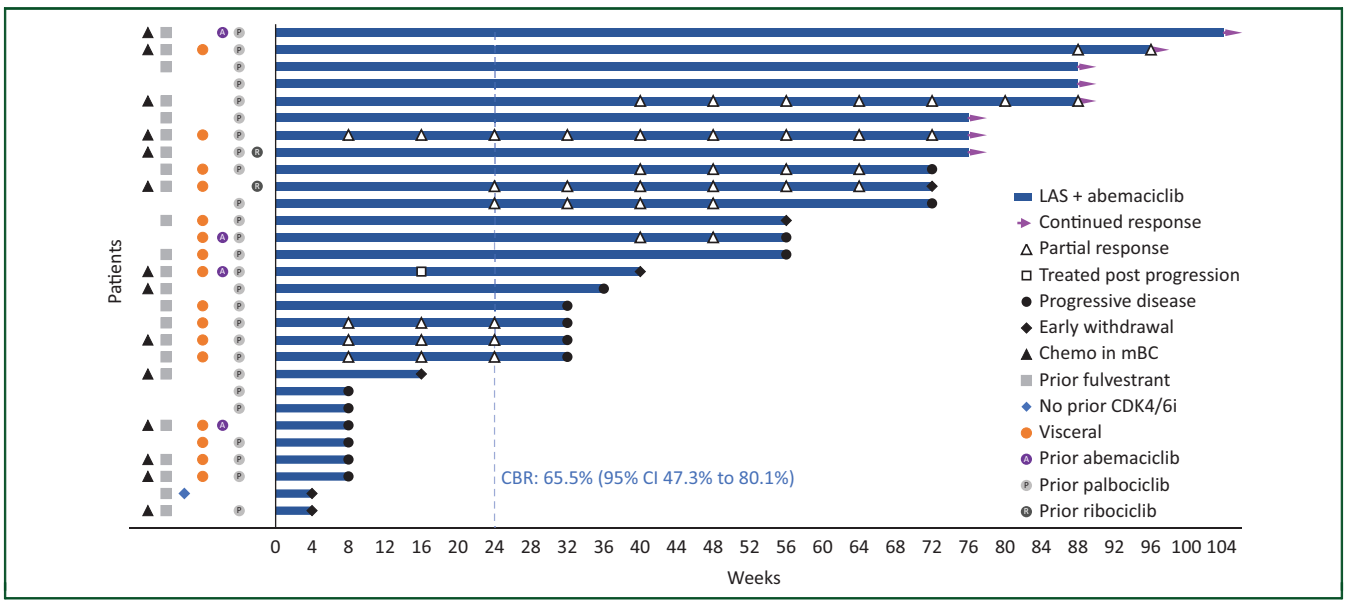

Figure 2. Time to response and duration of response for all patients ($n = 29$).
CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; LAS, lasofoxifene; mBC, metastatic breast cancer.

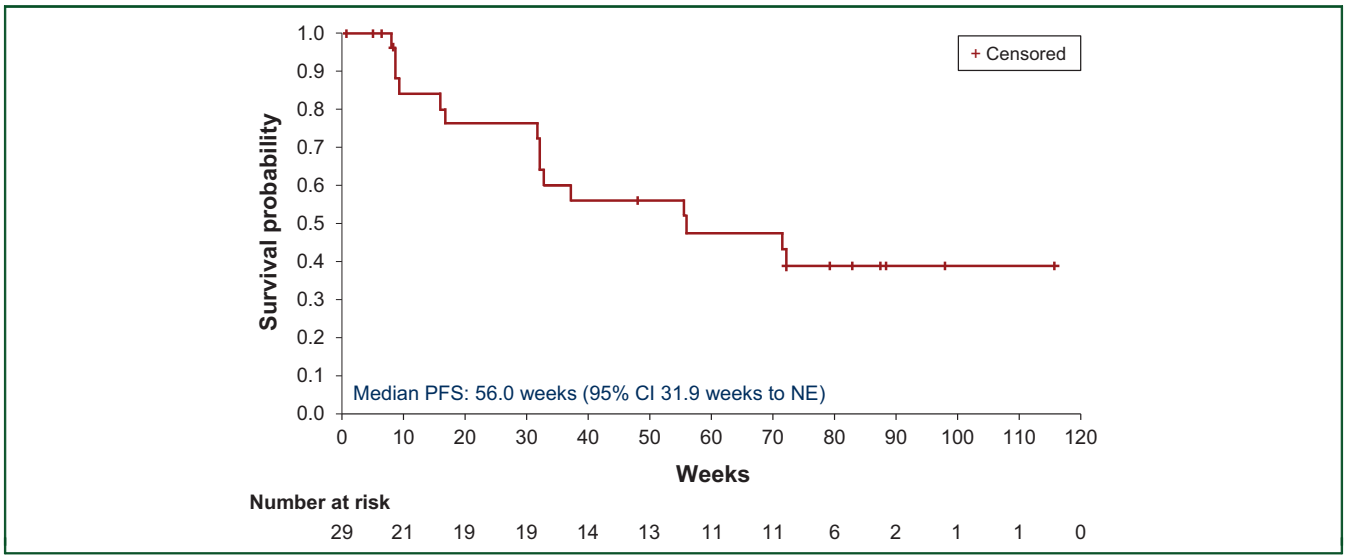

Figure 3. Kaplan–Meier analysis of progression-free survival.
CI, confidence interval; NE, not estimable; PFS, progression-free survival.

the time of the PE but withdrew later because of anticoagulation-related complications, and the other two patients achieved meaningful clinical benefit after treatment with anticoagulants (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.09.3103). Collectively, results suggest that these known thrombotic risks with lasofoxifene and abemaciclib may be acceptable and manageable, especially considering the magnitude of clinical benefit in the overall study population, as well as in those with VTEs.

The relative infrequency of abemaciclib dose reductions further supports a manageable safety profile of the lasofoxifene–abemaciclib combination. In ELAINE 2, the abemaciclib dose was reduced from 150 mg to 100 mg b.i.d in six (21%) patients due to AEs; no reductions from 100 mg to 50 mg b.i.d were required, though one patient did discontinue therapy due to abemaciclib-related toxicity (diarrhea). Additionally, dose interruptions for abemaciclib occurred in 52% of patients, while those for lasofoxifene mostly occurred when abemaciclib was suspended. In other studies of abemaciclib-based therapy in breast cancer patients, abemaciclib dose reductions due to AEs were made in 28%-52% of patients, dose interruption/omissions in 47%-68%, and treatment discontinuations due to AEs in 16%-25%.[48-53]

Consistent with the preclinical finding that lasofoxifene alone or with palbociclib was effective in reducing tumor growth and metastasis in mBC xenografts harboring *ESR1* mutations,[42] lasofoxifene plus abemaciclib exhibited promising clinical benefit in *ESR1*-mutated mBC in our phase II study. Several ET-based regimens have been previously evaluated in the post-CDK4/6i setting in other early-phase studies. In the phase II, VERONICA trial, the median PFS for fulvestrant plus the B-cell lymphoma 2 inhibitor, venetoclax, was 2.7 months compared with 1.9 months for fulvestrant alone.[66] In the phase II, BYLieve study of fulvestrant combined with the α-specific phosphoinositide 3-kinase inhibitor, alpelisib, in patients with *PIK3CA*-mutated, advanced, ER+/HER2− breast cancer that progressed on an AI-CDK4/6i combination, a median PFS of 7.3 months was observed.[67] However, alpelisib-based therapy was associated with significant toxicity, requiring frequent dose modifications and discontinuations.[68-70] While the addition of ribociclib to fulvestrant after CDK4/6i prolonged the median PFS (8.3 versus 2.8 months) in ER+/HER2− mBC patients with wild-type *ESR1* in the phase II, MAINTAIN study, no significant improvement in PFS was noted in patients with *ESR1* mutations (3.0 versus 3.0 months).[23] The phase II, PACE trial also showed no further improvement in PFS when palbociclib was added to fulvestrant (median PFS 4.6 versus 4.8 months) in the post-AI-CDK4/6i setting.[71] The phase II, PALMIRA and BioPER trials did not demonstrate any benefit of rechallenging patients with palbociclib plus a different ET over ET alone[72] or in patients with *ESR1* mutations[73] after progression on palbociclib plus ET. Additionally, a recent report from the phase I, SERENA-1 study of camizestrant plus palbociclib cited a CBR of 28% in patients with advanced breast cancer (80% had prior CDK4/6i), and the rate was even lower (10%) in the subgroup with *ESR1* mutations and prior CDK4/6i exposure.[40]

Prospective clinical trials evaluating the combination of abemaciclib and ET after palbociclib are limited. Wander et al. reported a retrospective analysis of patients with advanced breast cancer and prior progression on ET plus palbociclib, and observed a median PFS of 5.4 months for abemaciclib alone and 5.1 months for abemaciclib with ET (47% fulvestrant).[24] Camizestrant plus abemaciclib was associated with a CBR of 67% in the overall SERENA-1 study population (75% had prior CDK4/6i); however, in patients with *ESR1* mutations and prior CDK4/6i exposure, the CBR was much lower (38%), with no objective responses observed.[41] The clinically meaningful PFS (median ∼13 months), ORR (56%), and CBR (66%) with the lasofoxifene–abemaciclib combination in ELAINE 2 suggest its potentially

favorable efficacy over other ET-based treatments. However, caution should be observed as the differences across trials may be due to the variation in patient populations; the small number of patients in the ELAINE 2 study also limits the ability to draw firm conclusions.

All patients in ELAINE 2 had baseline *ESR1* mutations, which are associated with a less favorable prognosis. Two of the four patients who developed rapid disease progression after 3-4 months on prior abemaciclib-based treatment experienced durable clinical benefit with lasofoxifene plus abemaciclib in ELAINE 2, suggesting that lasofoxifene contributes substantially to PFS outcomes, and may synergistically interact with abemaciclib in modulating ER- and CDK-signaling cross-talk.

Changes in *ESR1* MAF from ctDNA may be associated with disease response to targeted therapy.[74,75] Timely switching from AI to fulvestrant, which is relatively more effective on *ESR1*-mutated tumors, before clinical disease progression was shown to improve PFS in PADA-1, suggesting the usefulness of monitoring ctDNA *ESR1* mutations in patients with ER+/HER2−, advanced breast cancer.[28] Analyses of ctDNA from ELAINE 2 revealed decreased levels in *ESR1* MAF after 4 weeks of treatment in most patients. It is noteworthy that the MAF was cleared/undetected in the two patients who had disease progression on prior abemaciclib, but achieved clinical benefit on the lasofoxifene−abemaciclib combination. The relationship between MAF changes and tumor responses suggests target engagement of lasofoxifene. Additional evaluations in larger studies are needed to confirm a predictive role of *ESR1* MAF for clinical response to lasofoxifene plus abemaciclib.

Our study is limited by its small sample size and single-arm, open-label design. The safety and efficacy results should be interpreted with caution given the small numbers of patients and the differences in patient populations between our study and other studies discussed. Nevertheless, the preliminary efficacy of this treatment strategy is promising in patients with ER+/HER2− mBC and *ESR1* mutations following disease progression on prior lines of therapy including ET, CDK4/6is, chemotherapy, and other targeted therapies. Further, serial analysis of the *ESR1* MAF corroborates target engagement with lasofoxifene and could be a potential surrogate for clinical response.

Conclusions

In ELAINE 2, the combination of lasofoxifene and abemaciclib was well tolerated with a manageable safety profile. Further, treatment with lasofoxifene plus abemaciclib provided promising clinical antitumor activity in patients with ER+/HER2− mBC and *ESR1* mutations in the post-CDK4/6i setting. The preliminary efficacy observed in ELAINE 2 will be further evaluated in the initiated phase III, randomized, controlled, multinational, ELAINE 3 study (NCT05696626) that compares lasofoxifene plus abemaciclib with fulvestrant plus abemaciclib in patients with *ESR1*-mutated, ER+/HER2−, advanced breast cancer whose tumors had progressed on a first-line AI plus palbociclib or ribociclib.

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