Open-Label, Phase 2, Multicenter Study of Lasofoxifene (LAS) Combined with Abemaciclib (Abema) for Treating Pre- and Postmenopausal Women with Locally Advanced or Metastatic ER+/HER2− Breast Cancer and an *ESR1* Mutation After Progression on Prior Therapies

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Introduction

- Endocrine therapy (ET), particularly with aromatase inhibitors (AIs), reduces estrogen receptor (ER) activity and has been the mainstay for treating ER+ breast cancer.
- Long-term ET often leads to treatment resistance caused by acquired *ESR1* mutations.[1,2]
  - *ESR1* mutations result in a constitutively active (ligand independent) ER leading to AI resistance, tumor progression, and overall poor prognosis.[3,4]
- LAS, a novel endocrine therapy and next generation selective estrogen receptor modulator (SERM), has shown potent activity against *ESR1* mutants alone or in combination with a CDK4/6 inhibitor (CDK4/6i) compared with fulvestrant ([Fulv], a selective estrogen degrader [SERD]) in metastatic breast cancer (mBC) xenograft models expressing *ESR1* mutations.[5,6]
- LAS modifies the constitutive conformation of the mutated *ERα* to an antagonist conformation, thereby inactivating the receptor.[6]
- Single-agent activity of LAS in patients progressing after CDK4/6i and AIs was shown in the ELAINE 1 trial (NCT03781063). In ELAINE 1, LAS demonstrated numerical superiority over Fulv for all primary and secondary clinical endpoints (ESMO 2022).
- Abema, a CDK4/6i, has been shown to have meaningful clinical activity after disease progression on prior CDK4/6i with mBC.[7]
- Treatment options for mBC patients with an *ESR1* mutation are limited, creating an unmet clinical need for new treatment strategies, particularly in the post-CDK4/6i setting.[4,8,9]
- Here, we describe the results of the ELAINE 2 study. This poster provides updates on data originally presented at ASCO 2022.

Objective

The ELAINE 2 study (NCT04432454) is an open-label, phase 2, multicenter, single-arm trial, and one of the first studies,[4,9] whose objective was to evaluate the safety and efficacy of LAS combined with Abema in a post-CDK4/6i setting

Methods

- Women ≥18 years with ER+/HER2- mBC and acquired *ESR1* mutation(s) identified in circulating tumor DNA (ctDNA)
- Progressed on one or two lines of ET for mBC (prior Abema allowed); could have received one line of chemotherapy
- Patients took oral LAS 5 mg/day and Abema 150 mg twice a day (BID) (Abema provided by Eli Lilly and Co.) until progression, death, toxicity, or withdrawal
- **Primary endpoint:** safety and tolerability as assessed by CTCAE (V.5)
- **Secondary endpoints:** progression-free survival (PFS), clinical benefit rate (CBR), objective response rate (ORR), duration of response (DoR), and time to response (TTR)
- Response was determined using RECIST 1.1; staging scans were performed every 8 weeks
- ctDNA was screened for *ESR1* mutant allele fractions at baseline and week 4 using SafeSEQ NGS technology (Sysmex Inostics Inc)

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Results

Patient disposition and baseline characteristics

- 29 women were enrolled at 16 US sites from October 2020 to June 2021.
  - 5 patients discontinued for reasons other than disease progression (2 for adverse events [AEs], 2 investigator withdrawals, 1 patient withdrawal).
- Patients had a median age of 60 years; 86% were Caucasian (**Table 1**).
- 97% had a prior CDK4/6i, 79% received prior Fulv, and 48% received prior chemotherapy in the metastatic setting (Table 1).
- Patients had a median of 2 prior lines of therapy in the metastatic setting.
- 48% of patients had polyclonal *ESR1* mutations; 66% had Y537S and 48% D538G.

Table 1. Baseline demographics and characteristics

	N=29
Median age (range), y	60 (35–79)
Race	
White	25 (86.2)
Black	2 (6.9)
Not reported	2 (6.9)
Measurable disease	18 (62.1)
Visceral disease	16 (55.2)
Bone only	10 (34.5)
Prior breast cancer therapy	
Chemotherapy (total)	25 (86.2)
Chemotherapy in metastatic setting	14 (48.3)
CDK4/6i	28 (96.6)
Palbociclib	25 (86.2)
Abemaciclib	4 (13.8)
Ribociclib	2 (6.9)
Unknown	1 (3.4)
Endocrine therapy	29 (100)
Aromatase inhibitor	28 (96.6)
Fulvestrant	23 (79.3)
Tamoxifen	12 (41.4)
Everolimus	4 (13.8)
Alpelisib	3 (10.3)

Data expressed as n (%), unless stated otherwise. CDK4/6, Cyclin-dependent kinase 4/6 inhibitor.

Safety

- The most common AEs reported to date were diarrhea, nausea, fatigue, and white blood cell decrease; most AEs were grade 1 or 2 (**Table 2**).
- The most likely treatment-emergent AEs due to LAS were muscle spasms and hot flashes.
- Three patients developed deep vein thrombosis (DVT)/pulmonary embolism (PE): one DVT was diagnosed after knee surgery; Another asymptomatic PE/DVT was found incidentally on surveillance scan. The only symptomatic PE occurred in a patient at 72 weeks with a 10-month objective response. All three patients had clinical benefit.
- LAS dose was not reduced per protocol; Abema dose was reduced to 100 mg BID in 5 patients (4 due to AEs, 1 due to investigator discretion).

Table 2. Frequency of most common AEs (in ≥12% of patients)* (N=29)

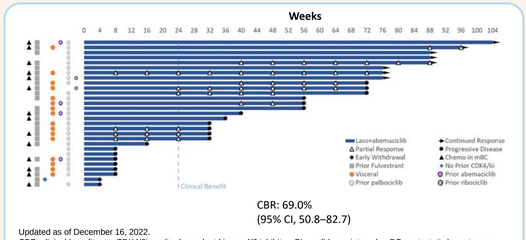
AE	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	20 (69.0)	4 (13.8)	0	0
Nausea	9 (31.0)	4 (13.8)	0	0
Fatigue	6 (20.7)	3 (10.3)	1 (3.4)	0
Cough	7 (24.1)	2 (6.9)	0	0
White blood cell decrease	3 (10.3)	6 (20.7)	0	0
Vomiting	5 (17.2)	2 (6.9)	1 (3.4)	0
Dyspnea	4 (13.8)	2 (6.9)	0	0
Anemia	4 (13.8)	1 (3.4)	1 (3.4)	0
Lymph decreased	1 (3.4)	2 (6.9)	3 (10.3)	
Muscle spasm	5 (17.2)	0	0	0
Constipation	5 (17.2)	0	0	0
Increased creatinine	3 (10.3)	2 (6.9)	0	0
Myalgia	4 (13.8)	0	0	0
Hyperglycemia	4 (13.8)	0	0	0
Decreased albumin	4 (13.8)	0	0	0
Decreased appetite	3 (10.3)	1 (3.4)	0	0
Stomatitis	3 (10.3)	1 (3.4)		
Dehydration	2 (6.9)	2 (6.9)	0	0
Dizziness	2 (6.9)	2 (6.9)	0	0
Hypokalemia	1 (3.4)	1 (3.4)	2 (6.9)	0

*Patients with maximum grade counts. Severity of adverse events (AEs) were scored from grades 1 (least severe) to 4 (most severe).

Efficacy

- 16 patients had disease progression and 8 continue treatment (**Figure 1**), with a CBR at 24 weeks of 69.0% (95% CI, 50.8–82.7).
- The median PFS was 55.7 weeks (13 months), 95% CI, 32.0–NE (**Figure 2**).
- Among patients with measurable target lesions (n=18), 10 had a confirmed partial response (PR), resulting in an ORR of 55.6% (95% CI, 29.0 – 71.0; **Figure 3**).
- Patients achieved PR at a median of 169 days, with a median response duration of 164 days.
- Of 4 enrolled patients who previously progressed while taking Abema, 3 had significant clinical responses (1 PR, 2 with stable disease; **Table 3**).
- 2 of 3 patients who took prior Fulv/alpelisib had clinical benefit.
- In patients with evaluable ctDNA, 47 *ESR1* mutant variants were detected at baseline; after 4 weeks of treatment, 91% were undetectable or reduced (68% undetectable), while only 9% increased.

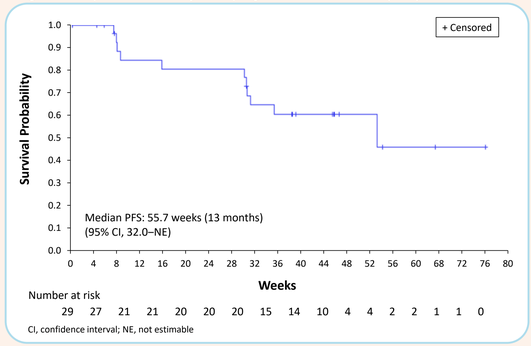
Figure 1. Time on treatment and response in all patients



CBR: 69.0%
(95% CI, 50.8–82.7)

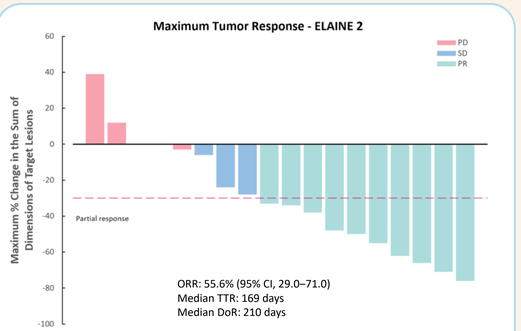
Updated as of December 16, 2022.
CBR, clinical benefit rate; CDK4/6i: cyclin-dependent kinase 4/6 inhibitor; CI: confidence interval; mBC: metastatic breast cancer.

Figure 2. Kaplan–Meier analysis of progression-free survival (PFS)



CI, confidence interval; NE, not estimable

Figure 3. Best response in patients with measurable lesions



Updated as of Dec 16, 2022. ORR is based on confirmed response events.
CI: confidence interval; DoR: duration of response; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease; TTR: time to response.

Table 3. Patients enrolled with post-Abema progression

Patient Age	*ESR1* Mut, MAF baseline/wk 4	Baseline disease Status	Prior mBC treatment	Current disease status
40 y	D538G, 6.855%/ND	Bone metastases	LTZ/PAL (3 yrs); **Fulv/Abema (12 wks);** CAPE (7 mos)	At **104 wks** with SD
42 y	Y537S, 0.248%/ND	24 mm liver lesion	LTZ/PAL (2.7 yrs); **Abema (16 wks)**	**Stable until 56 wks** with confirmed PR (liver lesion decreased 71% at 40 wks)
78 y	D538G, 0.3%/ND	18 mm liver lesion, pleural, and bone metastases	LTZ/PAL (2.2 yrs); **Fulv/Abema (1.3 yrs);** CAPE (1 mo)	SD up to **40 wks** (target lesion decreased 6%)
59 y	D538G, 1.28%/1.926%	35 mm liver metastases	**Fulv/Abema (2 yrs);** CAPE (1 mo)	Progressed at **8 wks** (liver lesion stable, but new lesion noted)

Abema, abemaciclib; CAPE, capecitabine; Fulv, fulvestrant; MAF, mutant allele fraction; mBC, metastatic breast cancer; ND, not detected; LTZ, letrozole; PAL, Palbociclib; PR, partial response; SD, stable disease.

Key Takeaways

- ELAINE 2 showed acceptable tolerability with a favorable benefit-to-risk ratio and promising efficacy, with LAS/Abema achieving a PFS of 13 mos, ORR of 55.6%, and CBR of 69% in mBC patients harboring *ESR1* mutations who had progressed on CDK4/6is and ETs.
- Consistent evidence from a larger, randomized trial would support LAS/Abema as a potential therapy to help fulfill the unmet clinical need in this population.

Conclusions

- LAS plus Abema had acceptable safety and tolerability. As with other CDK4/6i-ET combinations, most toxicity was considered related to the CDK4/6i component.
- This is one of the first clinical trials to prospectively observe a meaningful PFS (55.7 weeks/13 months), ORR (56%), and CBR (69%) of ET-CDK4/6i combination in CDK4/6i pre-treated mBC population with acquired *ESR1* mutations.
  - Considering limitations of cross-study comparisons, PFS with LAS/Abema is 2.5 times the ~5-month PFS and nearly double the 37% CBR reported with Abema alone or combined with Fulv after progression on prior palbociclib and ET.[7]
- Although VTE is a known risk with the use of Abema and SERMs alone, the reported incidence in ELAINE 2 was in line with previous findings of nextMONARCH, in which the incidence of VTE was 7.1% with tamoxifen/ Abema and 3.9% with Abema alone[10]. No VTEs were seen on lasofoxifene monotherapy in ELAINE 1.
- Undetectable and reduced levels of *ESR1* MAF with LAS/Abema is consistent with target engagement and may correlate with clinical response.
- The clinically meaningful efficacy of >12 mos PFS with LAS/Abema combination may offer a significantly greater benefit than currently available therapies in this setting, with a differentiated profile from intra-muscular and oral SERD monotherapy, particularly in this patient population, and warrants further study and large randomized trial of LAS/Abema compared to fulvestrant/Abema in patients with an ESR1 mutation following progression on an AI/CDK4/6i has been initiated.

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