Lasofoxifene (LAS) Plus Abemaciclib (Abema) for Treating *ESR1*-mutated ER+/HER2- Metastatic Breast Cancer (mBC) after Progression on Prior Therapies: ELAINE 2 Study Update

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Introduction

- Endocrine therapy (ET), particularly aromatase inhibitors (AIs), for estrogen receptor (ER)-positive breast cancer can lead to acquired *ESR1* mutations (*mESR1*), which drive endocrine resistance and tumor progression[1-4]
- Current therapies have limited activity for mBC with *mESR1*, especially in the post CDK4/6 inhibitor (CDK4/6i) setting[5,6]
- LAS is a next-generation ET and breast ER antagonist that prolonged progression-free survival (PFS; median 5.6 vs 3.7 mos; *P*=0.138) compared with fulvestrant (Fulv) and provided a greater clinical benefit rate (CBR, 37% vs 22%; *P*=0.117) and objective response rate (ORR, 13% vs 3%; *P*=0.124), in patients with *mESR1* mBC that progressed on an AI plus CDK4/6i, in the phase 2, ELAINE 1 study[7]
- Results from the phase 2, ELAINE 2 study showed that LAS plus Abema had a median PFS of ~13 mos, ORR of 33%, and CBR of 62%, with a well tolerated safety profile in patients with endocrine-resistant *mESR1* mBC[8]
- Here, we report ELAINE 2 data with longer patient follow up

Objective

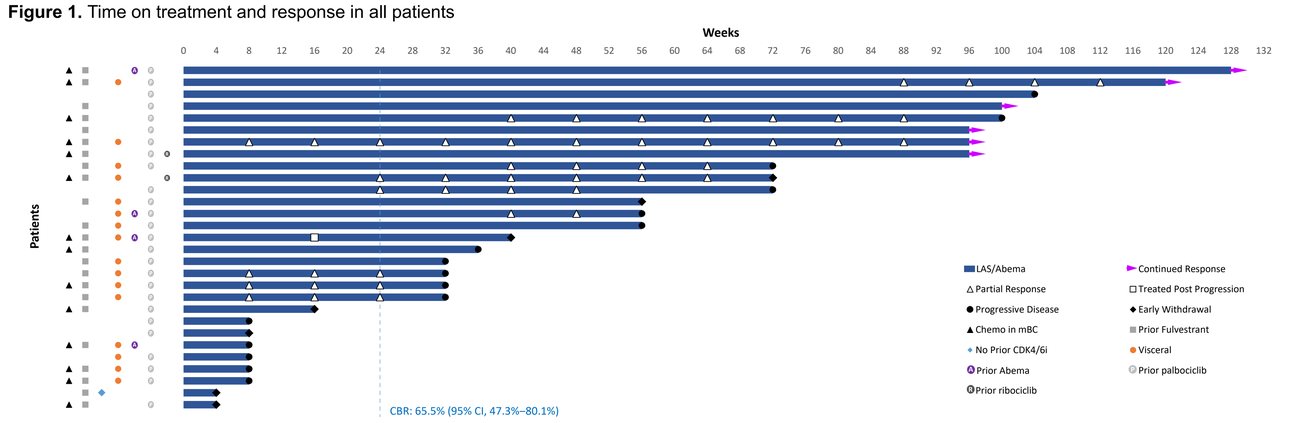
The objective of the ELAINE 2 study was to evaluate the safety and efficacy of LAS combined with Abema in patients with *ESR1*-mutated, ER+/HER2- mBC in the post-CDK4/6i setting

Methods

- The open-label, phase 2, single-arm ELAINE 2 study (NCT04432454) enrolled women (≥18 years) with ER+/HER2- mBC and acquired *mESR1* identified in circulating tumor DNA (ctDNA) who had disease progression on prior ET for mBC (≤2 lines)
  - Prior CDK4/6i and/or one line of chemotherapy for mBC was allowed
- Patients took oral LAS 5 mg/day and Abema (supplied by Eli Lilly and Co) 150 mg BID until disease progression, death, toxicity, or withdrawal
- **Primary endpoint:** safety and tolerability (AEs)
- **Secondary endpoints:** PFS, CBR, ORR, duration of response, and time to response
  - Staging scans were performed every 8 weeks
- *ESR1* mutant allele fractions (MAF) were analyzed in ctDNA at baseline and wk 4 using the Sysmex-Inostics SafeSeq assay
  - Guardant 360 ctDNA analysis was utilized to identify other genomic alterations
- Data were summarized descriptively with no formal hypothesis testing

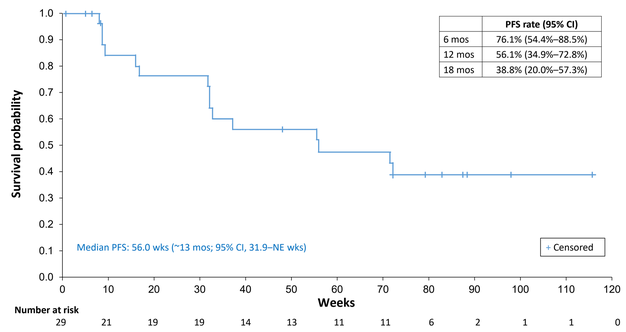
Results

Figure 1. Time on treatment and response in all patients



Data as of April 2023. Abema, abemaciclib; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; LAS, lasofoxifene.

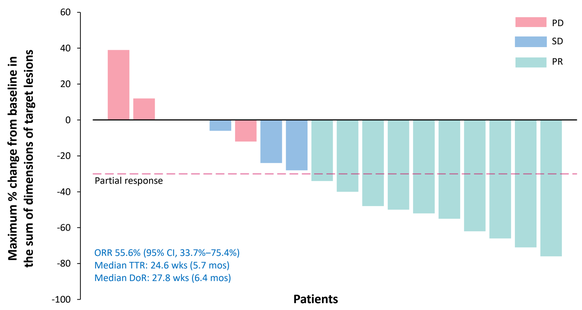
Figure 2. Kaplan-Meier analysis of progression-free survival



	PFS rate (95% CI)
6 mos	76.1% (54.4%–88.5%)
12 mos	56.1% (34.9%–72.8%)
18 mos	38.8% (20.0%–57.3%)

Data as of January 2023. CI, confidence interval; NE, not estimable; PFS, progression-free survival.

Figure 3. Best response in patients with measurable lesions (n=18)



Data as of April 2023. CI, confidence interval; DoR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.

Patient disposition and baseline characteristics

- As of April 2023, 6 of 29 enrolled patients were continuing treatment (**Figure 1**); 17 had disease progression; and discontinuations were due to AEs (n=1), patient withdrawal (n=3), and other causes (n=2)
- Patients had a median age of 60 yrs and received a median of 2 prior lines of ET for mBC; 55.2% had visceral disease; all but one (96.6%) received prior CDK4/6i (median duration 2 yrs), 79.3% prior Fulv, and 48.3% prior chemotherapy for mBC
- The most frequently detected *ESR1* mutations at baseline were Y537S (65.5%), D538G (44.8%), Y536N (27.6%), and Y537C (10.3%); 48.3% of patients had tumors with polyclonal *ESR1* mutations

Safety

- LAS/Abema was well tolerated with primarily grade 1/2 treatment-emergent AEs (TEAEs), most commonly diarrhea, nausea, fatigue, and vomiting (**Table 1**); 3 patients (10.3%) had scan-identified venous thromboembolism
- One patient discontinued treatment due to grade 2 diarrhea
- No deaths on treatment occurred
- Abema dose was reduced to 100 mg BID in 6 (20.7%) patients; LAS dose was not reduced per protocol

Efficacy

- Median PFS was 56.0 wks (~13 mos; **Figure 2**), CBR was 65.5% (**Figure 1**), and ORR was 55.6% (**Figure 3**); median overall survival could not be estimated at the time
- Eight (27.6%) patients achieved PFS over 96 wks (**Figure 1**)
- Of the 4 patients who had prior Abema exposure, two achieved clinical benefit, and one experienced RECIST progression at wk 16 but remained on study through wk 40
- In 26 patients with evaluable baseline and wk 4 ctDNA, *ESR1* MAF decreased at wk 4 in 21 (80.8%) patients, including 14 (53.8%) whose *ESR1* MAF was undetectable
- Antitumor activity of LAS/Abmea was not compromised by baseline genomic alterations concurrent with *mESR1* (**Table 2**)

Table 1. Most frequently reported TEAEs (incidence ≥15%; N=29)*

TEAE, n (%)	Grade 2	Grade 3	Grade 4	All grades
Diarrhea	5 (17.2)	0	0	24 (82.8)
Nausea	5 (17.2)	0	0	15 (51.7)
Fatigue	3 (10.3)	1 (3.4)	0	11 (37.9)
Vomiting	2 (6.9)	1 (3.4)	0	9 (31.0)
Anemia	1 (3.4)	3 (10.3)	0	8 (27.6)
Dyspnea	4 (13.8)	0	0	8 (27.6)
White blood cell count decreased	6 (20.7)	0	0	8 (27.6)
Blood creatinine increased	4 (13.8)	0	0	7 (24.1)
Constipation	0	1 (3.4)	0	6 (20.7)
Cough	1 (3.4)	0	0	6 (20.7)
Decreased appetite	2 (6.9)	0	0	6 (20.7)
Neutropenia/neutrophil count decreased	2 (6.9)	2 (6.9)	2 (6.9)	6 (20.7)
Hypokalemia	0	3 (10.3)	0	5 (17.2)
Muscle spasm	0	0	0	5 (17.2)

*Patients' TEAE of maximum grade was counted.
TEAEs, treatment-emergent adverse events, defined as adverse events that started or worsened after the first dose.

Table 2. Treatment response by baseline genomic alterations concurrent with *mESR1* (N=26)

Alteration	Baseline n (%)	CBR	Median PFS
***TP53* mutation**	11 (42%)	64%	36 wks
***PIK3CA* mutation**	8 (31%)	63%	34 wks
CCND1* amplification	6 (23%)	100%	72 wks
FGFR1* amplification	5 (19%)	100%	72 wks

*3 of the 6 patients with baseline CCND1 amplification also had FGFR1 amplification.
Data as of May 2023. CBR, clinical benefit rate; PFS, progression-free survival.

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Key Takeaways

- In ELAINE 2, LAS/Abema was well tolerated with an acceptable safety profile
- LAS/Abema was associated with a clinically meaningful PFS (median ~13 mos), ORR (56%), and CBR (66%) in women with ER+/HER2- mBC and acquired *mESR1*
- *ESR1* MAF decreased with LAS/Abema, consistent with target engagement

Conclusions

- With longer ELAINE 2 follow up, LAS/Abema continued to be well tolerated; no new safety signals were noted
  - Incidence of venous thromembolism in ELAINE 2 was within the range previously reported for Abema-based therapies[9-11]
- LAS/Abema exhibited meaningful antitumor activity in patients with *mESR1*, ER+/HER2- mBC that had progressed on ET and CDK4/6i
- Observed decreases in *mESR1* ctDNA suggest target engagement with LAS
- Other genomic alterations associated with resistance that were detected concurrently with *mESR1* at baseline did not appear to compromise the efficacy of LAS/Abema
- A confirmatory, phase 3 study (ELAINE 3; NCT05696626) will compare LAS/Abema with Fulv/Abema. If ELAINE 2 results are corroborated, the combination of LAS and Abema may provide a practice-changing option for treating *mESR1* mBC

Disclosures

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