

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 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 ER α to an antagonist conformation, thereby inactivating the receptor⁶
- The ELAINE 1 study (NCT03781063) comparing LAS and Fulv in patients progressing after CDK4/6i and AIs has recently been completed (submitted to ESMO 2022)
- Abema, a CDK4/6i, has been shown to have meaningful clinical activity after disease progression on prior CDK4/6i with mBC⁷
- 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

Objective

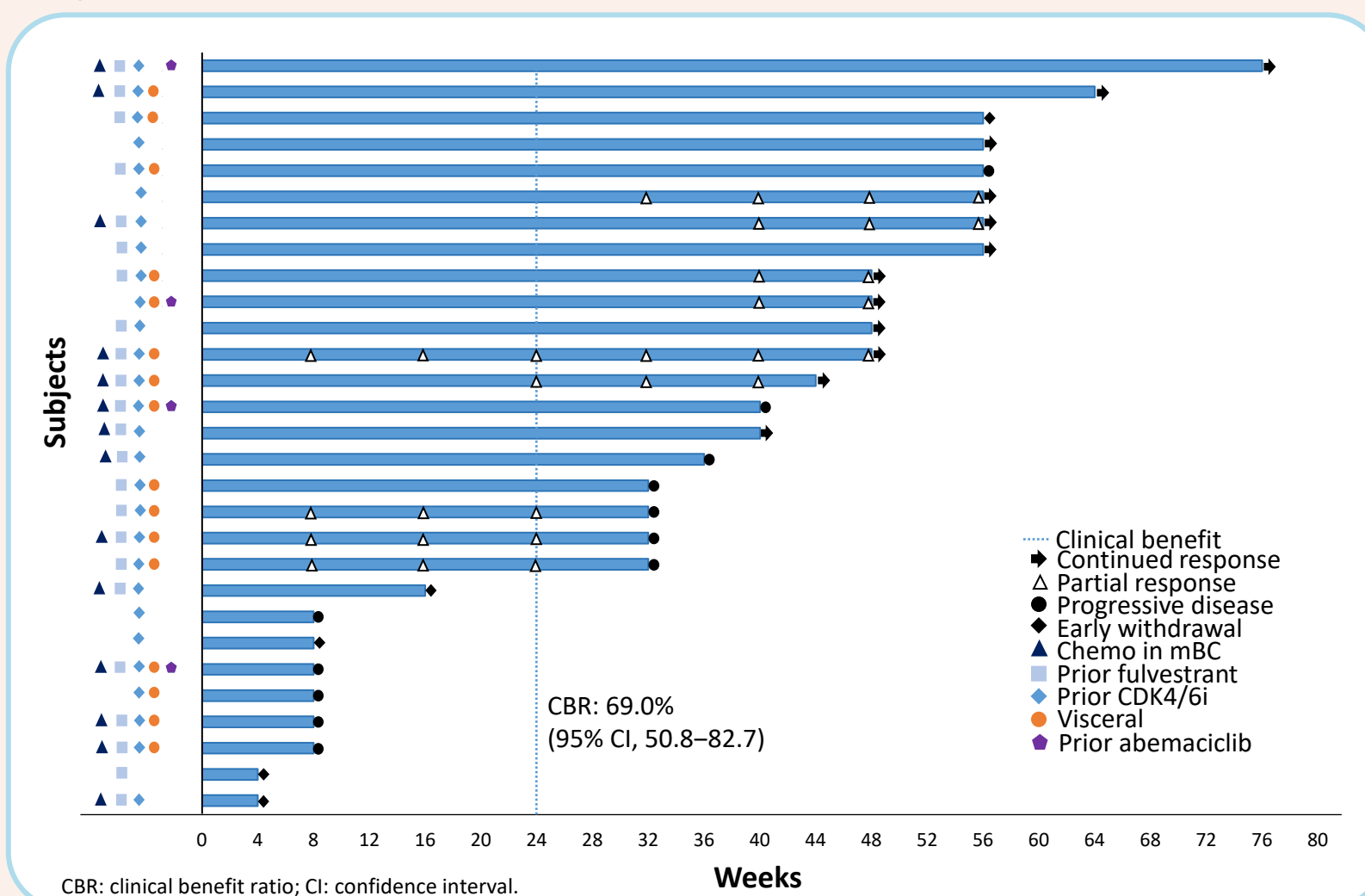
The ELAINE 2 study (NCT04432454) is an open-label, phase 2, multicenter, single-arm trial, and one of the first studies^{4,9} whose objective was to evaluate the safety and efficacy of LAS combined with Abema in a post-CDK4/6i setting

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) 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)

Results

Figure 1. Time on treatment and response in all patients



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 lines of therapy in the metastatic setting and the median duration on prior CDK4/6i was 2 years
- 48% of patients had polyclonal *ESR1* mutations; 66% had Y537S and 48% D538G

Table 1. Baseline demographics and characteristics

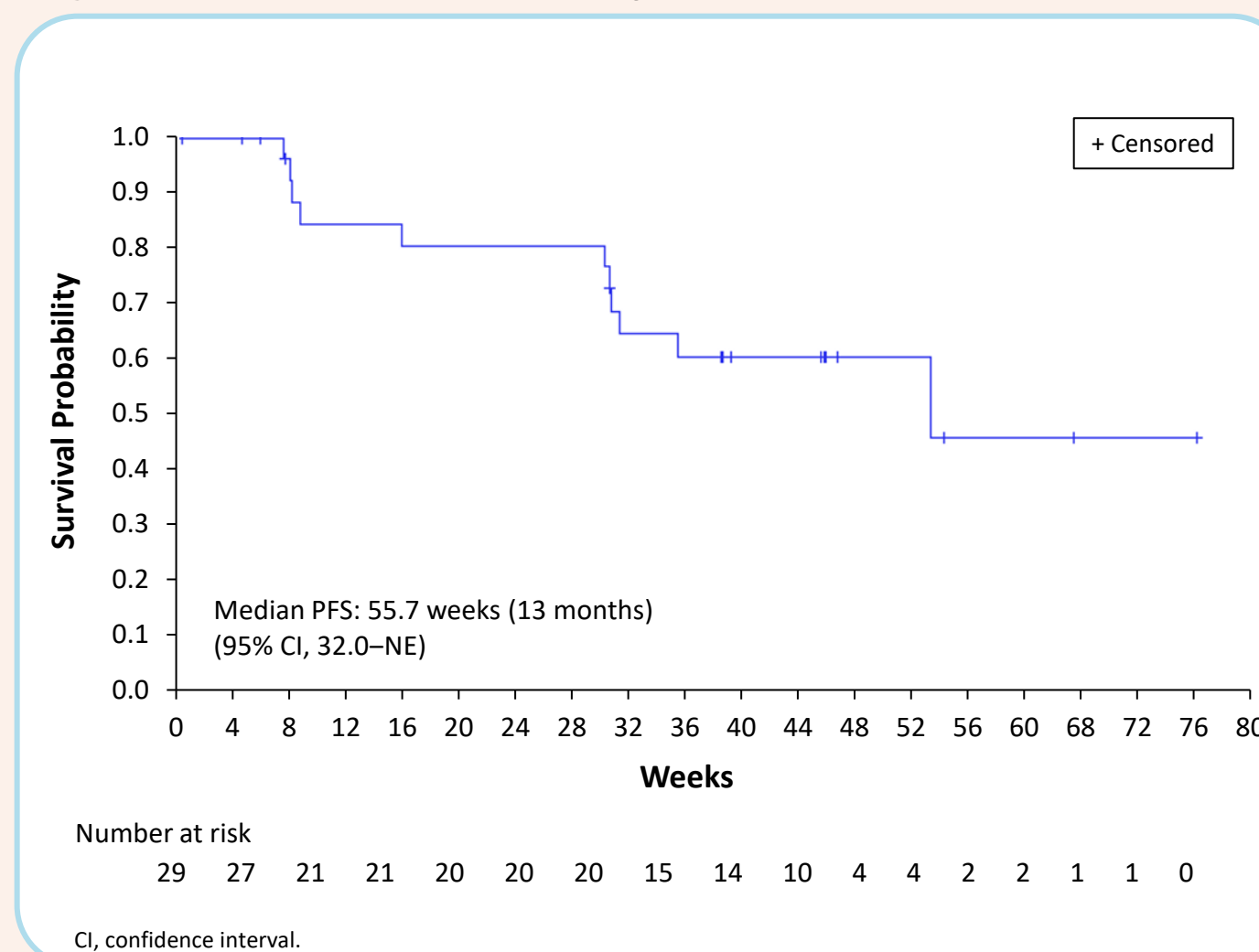
	N=29
Median age (range), y	60 (35-79)
Race	
White	25 (86.2)
Black	2 (6.9)
Not reported	2 (6.9)
Measurable disease	18 (62.1)
Visceral disease	16 (55.2)
Bone only	10 (34.5)
Prior breast cancer therapy	
Chemotherapy (total)	25 (86.2)
Chemotherapy in metastatic setting	14 (48.3)
CDK4/6i	28 (96.6)
Palbociclib	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. CDK4/6i, Cyclin-dependent kinase 4/6 inhibitor.

References

- Fan P, et al. *Cancer Drug Resist.* 2019;2:198-209.
- De Santo I, et al. *Cancers (Basel).* 2019;11:1894.
- Brett JO, et al. *Breast Cancer Res.* 2021;23:85.
- Herzog SK, et al. *Br J Cancer.* 2022;126:174-186.
- Andreano KJ, et al. *Mol Cancer Ther.* 2020;19:1395-1405.
- Lainé M, et al. *Breast Cancer Research.* 2021;23:54.
- Wander SA, et al. *J Natl Compr Canc Netw.* 2021;1-8.
- Xi J, et al. *Curr Oncol Rep.* 2020;22:57.
- Sammons S, et al. *Clin Breast Cancer.* 2020;20:1-11.
- Hamilton E, et al. *Clin Breast Cancer.* 2021;21:181-190.e182.

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



Safety

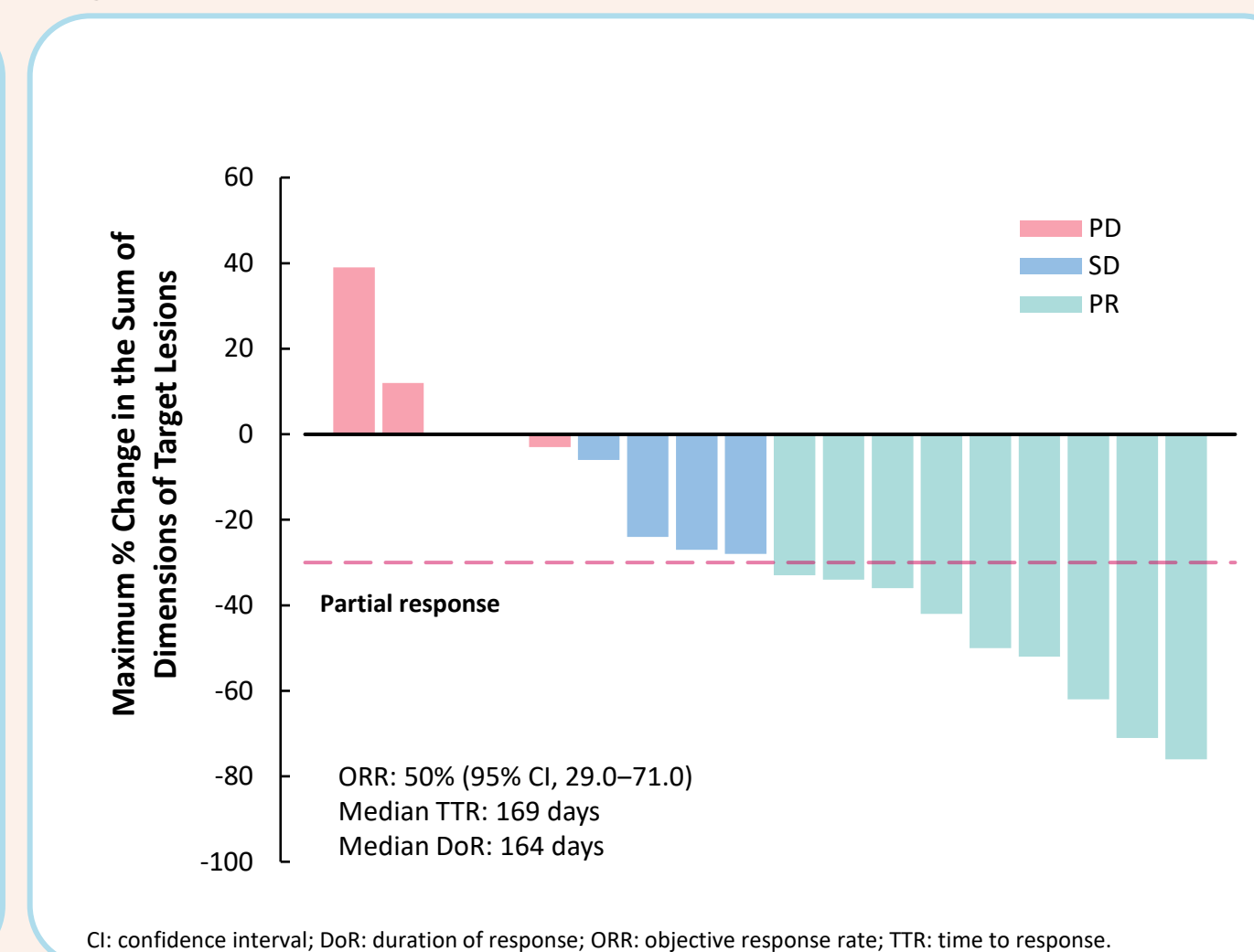
- The most common AEs reported to date were diarrhea, nausea, fatigue, and white blood cell decrease; most AEs were grade 1 or 2 (Table 2)
- The most likely treatment-emergent AEs due to LAS were muscle spasms and hot flashes
- Two patients developed a deep vein thrombosis (DVT) and pulmonary embolism (PE): one DVT was diagnosed after knee surgery; PEs and other DVT were found incidentally on surveillance scan. Both patients were successfully treated with anticoagulants and continued the study.
- 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 $\geq 12\%$ 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)	0
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)	0	0
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).

Figure 3. Best response in patients with measurable lesions



Efficacy

- 12 patients had disease progression and 12 continue treatment (Figure 1), with a CBR at 24 weeks of 69.0% (95% CI, 50.8-82.7)
- The censored median PFS was 55.7 weeks (13 months), 95% CI, 32.0-NE (Figure 2)
- Among patients with measurable target lesions (n=18), 9 had a partial response (PR), resulting in an ORR of 50% (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

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 76 wks with SD
42 y	Y537S, 0.248%/ND	24 mm liver lesion	LTZ/PAL (2.7 yrs); Abema (16 wks)	At 48 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 stable, but new lesion noted)
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 50%, 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
 - Although VTE is a known risk with the use of SERMs alone and Abema, 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 alone¹⁰
- This is one of the first clinical trials to prospectively observe a meaningful PFS (55.7 weeks/13 months), ORR (50%), 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 almost triple the ~5-month PFS and double the 37% CBR reported with Abema alone or combined with Fulv after progression on prior palbociclib and ET⁷
- The clinically meaningful efficacy of LAS/Abema combination may offer a significantly greater benefit than currently available therapies, with a differentiated profile from intra-muscular and oral SERDs, particularly in this patient population, and warrants further study
- Undetectable and reduced levels of *ESR1* MAF with LAS/Abema is consistent with target engagement and may correlate with clinical response
- Single-agent LAS in the ELAINE 1 trial will inform the activity of LAS alone relative to Fulv in the post-CDK4/6i AI setting (abstract submitted to ESMO 2022)

Disclosures

- SD has received research funding from EMD Serono, Guardant Health, Taiho Pharmaceuticals, Novartis, and Sermonix Pharmaceuticals. ICA has received research funding from AbbVie, Apollomics, AstraZeneca, EMD Serono, Hutchison MediPharma, Merck, Seattle Genetics, and Turning Point Therapeutics. HCFM has received research funding from Daiichi Sankyo, Roche, AstraZeneca, and Sermonix Pharmaceuticals. DJP and PVP are employees and stockholders of Sermonix Pharmaceuticals. DJP is also a consultant for Agile Therapeutics and Sebela Pharmaceuticals.
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