Open-label, randomized study of lasofoxifene (LAS) vs fulvestrant (Fulv) for women with locally advanced/metastatic ER+/HER2- breast cancer (mBC), an estrogen receptor 1 (ESR1) mutation, and disease progression on aromatase (AI) and cyclin-dependent kinase 4/6 (CDK4/6i) inhibitors

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Introduction

- Acquired *ESR1* mutations result in endocrine resistance, metastases, and poor prognosis in ER+/HER2- metastatic breast cancer (mBC) patients (pts)[1-4]
- Selective estrogen receptor degraders, including fulvestrant (Fulv), exhibit limited efficacy in this population
- Lasofoxifene (LAS), a novel endocrine agent and next-generation oral selective estrogen receptor modulator (SERM), was more effective than Fulv in preclinical models at inhibiting tumor growth and reducing metastases, as monotherapy or with a CDK4/6i in WT and ESR1 mutated cell lines[5,6]
- In ELAINE 2, LAS plus abemaciclib resulted in an objective response rate of 56% and median progression-free survival (PFS) of 13 months in ER+/HER2- mBC pts with *ESR1* mutations and prior progression on CDK4/6i[7]
- Here we describe ELAINE 1, a signal-seeking randomized trial of LAS vs Fulv, in the post-CDK4/6i second-line setting
- This report provides updates on data presented at ESMO 2022.

Methods

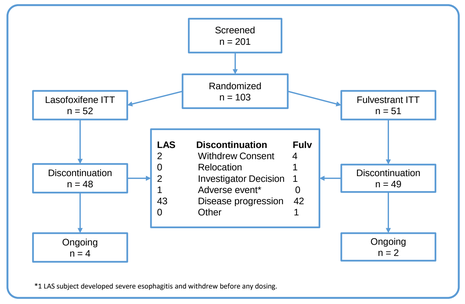
- Women with ER+/HER2- mBC and *ESR1* mutation(s) identified in circulating tumor DNA (ctDNA)
- Progressed on prior (≥12 months) aromatase inhibitors plus CDK4/6i
- Patients were randomized to oral LAS 5 mg daily or IM Fulv 500 mg days 1, 15, and 29, then every 4 weeks, until disease progression, death, toxicity, or withdrawal; Imaging occurred every 2 months (or if clinically indicated)

Endpoints	
Primary	Progression-free survival (PFS)
Secondary	Clinical benefit rate (CBR) Objective response rate (ORR) Overall survival (OS) Safety and tolerability as assessed by CTCAE (V.5)

- **Statistical analysis:** For the primary endpoint of PFS, a log-rank test stratifying on (a) visceral metastasis status (yes/no) and (b) Y537S mutation status (yes/no) was used for the primary comparison. A two-sided p<0.05 provided a power of 0.90 to detect a HR of 0.5

Miami Breast Cancer Conference (MBCC)
March 2-5, 2023, Miami Beach, Florida

Results



*1 LAS subject developed severe esophagitis and withdrew before any dosing.

- Mean patient age was 60.8 years; most were white (83%) and 66% had visceral disease

Parameter	LAS (n=52)	Fulv (n=51)
Age, y Mean Range	 61.6 33–84	 60.1 38–82
Measurable disease, n (%)	38 (73.1)	33 (64.7)
Visceral disease, n (%)	35 (67.3)	33 (64.7)
Chemotherapy in mBC, n (%)	3 (5.8)	3 (5.9)
AI/CDK4/6 inhibitor, n (%)	52 (100)	51 (100)
Mean duration on AI/CDK, y	2.5	2.2
ESR1 mutation Y537S	52 (100) 21 (40)	51 (100) 24 (47)

AI, aromatase inhibitor; Fulv, fulvestrant; ITT, intent-to-treat; LAS, lasofoxifene; mBC, metastatic breast cancer.

Safety

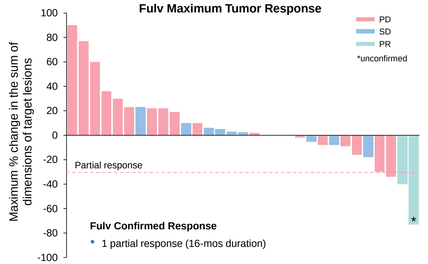
- Most AEs were Grade 1/2
- No thrombotic events occurred

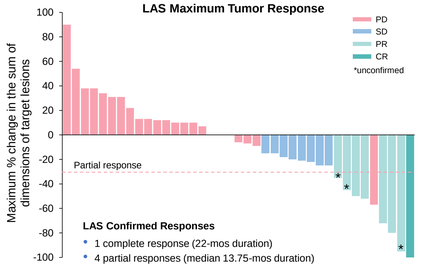
Most common TEAEs	LAS (n=52)	Fulv (n=51)
Nausea	14 (27.5)	9 (18.8)
Fatigue	12 (23.5)	18 (37.5)
Arthralgia	11 (21.6)	11 (22.9)
Hot flush	11 (21.6)	5 (10.4)
Constipation	8 (15.7)	6 (12.5)
Dizziness	8 (15.7)	2 (4.2)
Hypertension	8 (15.7)	7 (14.6)
Cough	8 (15.7)	5 (10.4)

AE, adverse event; TEAE, treatment-emergent adverse event.

Maximum tumor response

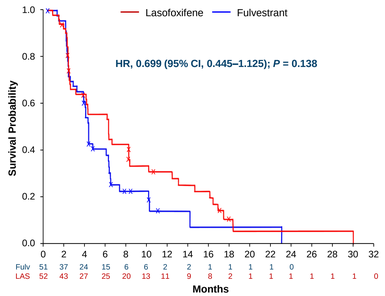
- Objective response rate for LAS vs Fulv was 13.2% vs 2.9% (*P*=0.12)
- Clinical benefit rate (≥24 weeks) for LAS vs Fulv was 36.5% vs 21.6% (*P*=0.12)





*Include stable disease, confirmed PR, CR.
CR, complete response; PD, progressive disease; PR, partial response.

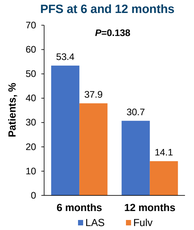
Progression-free survival (PFS)



Crosses indicate censored subjects; 1 month = 4 weeks.
Fulv, fulvestrant; LAS, lasofoxifene; PFS, progression-free survival.

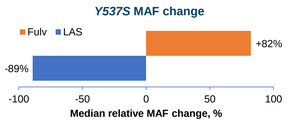
Median PFS

- LAS: 6.04 mos (2.82–8.04)
- Fulv: 4.04 mos (2.93–6.04)



Exploratory ctDNA analyses

- In 61 patients with evaluable baseline and 8-week ctDNA samples, *ESR1* mutant allele fraction (MAF) was assessed
  - LAS median relative change for all variants
    - ↓ 87.1%
  - Fulv median relative change for all variants
    - ↓ 14.7%
- In patients with Y537S mutations



ctDNA, circulating tumor DNA.

References

1. Fan P, et al. Cancer Drug Resist. 2019;2:198-209. **2.** De Santo I, et al. Cancers (Basel). 2019;11:1894. **3.** Brett JO, et al. Breast Cancer Res. 2021;23:85. **4.** Herzog SK, et al. Br J Cancer. 2022;126:174-186. **5.** Andreano KJ, et al. Mol Cancer Ther. 2020;19:1395-1405. **6.** Lainé M, et al. Breast Cancer Research. 2021;23:54. **7.** Damodaran S, et al. J Clin Oncol. 2021;40:1022.

Conclusions

- ELAINE 1 is the first trial comparing LAS with Fulv in *ESR1*-mutated mBC patients with progression on CDK4/6 inhibitors, with LAS being the first and only SERM to demonstrate antitumor activity in this setting.
- Although LAS did not statistically improve PFS compared with Fulv (HR, 0.699; 95% CI, 0.445–1.125; *P*=0.138), LAS was numerically superior to Fulv for all primary and secondary clinical outcomes and was well tolerated with no unexpected safety concerns. No thrombotic events were observed.
- LAS versus Fulv decreased *ESR1*-mutated MAF, including the difficult-to-treat Y537S, consistent with target engagement.
  - Analysis of clinical outcomes according to clearance of *ESR1* mutations are ongoing.
- LAS may be a monotherapy option for *ESR1*-mutated mBC, if efficacy is confirmed in a larger clinical study.
- A phase 3, combination study of LAS and abemaciclib is being initiated based on encouraging efficacy/safety from the ELAINE 1 and 2 studies.

Disclosures & Contact Information

- P.V.P. and D.J.P. are employees and stockholders of Sermonix Pharmaceuticals. M.P.G. discloses: CME activities from Research to Practice, Clinical Education Alliance, and Medscape; panelist for Total Health Conferencing; a moderator for Curio Science; consulting for AstraZeneca, Biovica, Biotheranostics, Blueprint Medicines, Eagle, Eli Lilly, Novartis, Pfizer, Sanofi Genzyme, and Sermonix; and has received research support from Eli Lilly, Pfizer, and Sermonix. D.G.S. has served on an advisory board for Novartis. N.A.B has received research support from Ambrx, AstraZeneca, Biovica International AB, Daiichi Sankyo, Novartis, Pfizer, Sarah Cannon Development Innovations, Seattle Genetics, Sermonix, and Xcovery Holdings Company LLC. G.V. has consulted for Roche/Genentech, Novartis, Eli Lilly, Gilead, Puma, Pfizer, AstraZeneca, Biotheranostics, Daiichi Sankyo, Concerto AI; received fees for CME services from Eli Lilly; received research support from Roche/Genentech, Puma, Celcuity, Merck, Bristol Myers Squibb, Eli Lilly, AstraZeneca, Pfizer, Gilead, GlaxoSmithKline; has ownership with Oncodisc. A.B. has served as a consultant for AstraZeneca, Pfizer, Novartis, Eli Lilly, Genentech/Roche, SeaGen, Daiichi Sankyo, Merck, Agendia, Sanofi, Puma; has received research support from Agendia and AstraZeneca. H.S.R. has received research support from Pfizer, Merck, Novartis, Eli Lilly, Roche, Daiichi, Seattle Genetics, Macrogenics, Sermonix, Boehringer Ingelheim, Polyphor, AstraZeneca, Ayala, Astellas and Gilead; honoraria from Puma, Samsung, and NAPO.
- Sermonix Pharmaceuticals sponsored the study and provided support for the medical writing assistance of Kathleen Ohleth, PhD (Precise Publications, LLC) and Nicole Neuman (MJH Life Sciences).
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