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Estrogen receptor 1 (*ESR1*) mutations in circulating tumor DNA (ctDNA) from patients with ER+/HER2- metastatic breast cancer (mBC) treated with lasofoxifene or fulvestrant in the ELAINE 1 study

Matthew P Goetz[1]; Einav Nili Gal-Yam[2]; Daniel G Stover[3]; Sarah L Sammons[4]; Stephanie L Graff[5]; Grace Wang[6]; Massimo A Cristofanilli[7]; Gary Riordan[8]; Hillary S Sloane[9]; Dominic Carroll[10]; Paul V Plourde[10]; David J Portman[10]

[1]Mayo Clinic Rochester, Rochester, MN; [2]Breast Oncology Institute Sheba Medical Center, Ramat Gan, Israel; [3]Ohio State University, Columbus, OH; [4]Dana Farber Cancer Institute, Harvard Medical School, Boston, MA; [5]Lifespan Cancer Institute/Legorreta Cancer Center at Brown University, Providence, RI; [6]Miami Cancer Institute at Baptist Health, Inc, Miami, FL; [7]Weill Cornell Medicine, New York, NY; [8]Reg Pro1, LLC, Tucson, AZ; [9]Sysmex Inostics, Baltimore, MD; [10]Sermonix Pharmaceuticals, Columbus, OH

Introduction

- Acquired *ESR1* mutations (*mESR1*) during endocrine therapy drive treatment resistance, metastasis, and poor prognosis in ER+/HER2- mBC patients[1-4]
- ELAINE 1 (NCT03781063) is a phase 2, randomized trial of lasofoxifene (LAS), a SERM, versus fulvestrant (Fulv), a SERD, in *mESR1* mBC patients with disease progression on an AI plus a CDK4/6i
  - Preliminary median PFS was 6.04 months (LAS) vs 4.04 months (Fulv; *P*=0.138), with a CBR of 36.5% vs 21.6% (*P*=0.12), respectively, and a favorable safety profile[5]
  - Numerically more commonly detected *mESR1* variants decreased with LAS vs Fulv, regardless of baseline *ESR1* mutant allele fraction (MAF; percentage of cell-free DNA that contains the mutant allele), in preliminary analyses[6]
- Changes in MAF from ctDNA may correlate with clinical response to targeted therapies[7,8]

Objectives

- To evaluate the association between changes in ctDNA *ESR1* MAF with clinical responses to LAS or Fulv in ELAINE 1
- To assess the Y537S ctDNA kinetics and its association with clinical outcomes in both treatment arms

Methods

- Women with ER+/HER2- mBC and *mESR1* ctDNA whose disease progressed on prior AI plus CDK4/6i (≥12 mos) were randomized to oral LAS 5 mg daily or IM Fulv 500 mg on days 1, 15, and 29, then every 4 weeks, until disease progression or severe toxicity
- Efficacy measures were PFS (primary endpoint) and CBR (secondary endpoint; clinical benefit: CR, PR, or SD for ≥24 weeks). Patients were stratified by visceral disease (y/n) and the Y537S mutation (y/n).
- ctDNA was analyzed at baseline and week 8 using the Sysmex Inostics OncoBeam or SafeSeq assays, which detect clone-specific *mESR1* at low MAFs (limit of detection 0.05%)
- *ESR1* MAF changes from baseline were characterized as **decreased** (decreased or cleared [*mESR1* not detected]), **increased** (increased), or **equivocal** (some increased and decreased MAF trends in polyclonal patients [>1 *mESR1*])
  - Patients with equivocal MAF changes were excluded from analyses of associations between MAF changes and clinical benefit

Results

- 103 patients were randomized to LAS (n=52) or Fulv (n=51) in the ITT population
- As of October 2022, 4 patients (LAS vs Fulv: 2 vs 2) remain in the study
  - 86 discontinuations due to disease progressions (45 vs 41);
  - 13 discontinuations due to consent withdrawal (2 vs 5), relocation (0 vs 1), investigator decision (2 vs 1), adverse event (1 vs 0), and others (0 vs 1)
- Patient demographics and characteristics are shown in Table 1
- Most commonly detected *mESR1* variants (>10%) were D538G (56%), Y537S (39%), Y537N (29%), E380Q (22%), and Y537C (11%)
- 61 patients (59%) had evaluable baseline and week 8 ctDNA and unequivocal *ESR1* MAF changes

Table 1. Baseline demographics and characteristics (ITT population)

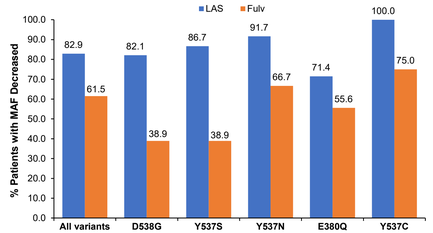
	Lasofoxifene (n=52)	Fulvestrant (n=51)
Mean age (range), yrs	**61.6 (33–84)**	**60.1 (38–82)**
Race		
White	**43 (82.7)**	**42 (82.4)**
Black or African American	**6 (11.5)**	**5 (9.8)**
Asian	**3 (5.8)**	**4 (7.8)**
Measurable disease, n (%)	38 (73.1)	33 (64.7)
Visceral disease, n (%)	**35 (67.3)**	**33 (64.7)**
Chemotherapy in mBC, n (%)	3 (5.8)	3 (5.9)
AI/CDK4/6i, n (%)	52 (100)	51 (100)
Mean duration on AI/CDK4/6i, yrs	**2.5**	**2.2**
ESR1 mutation, n (%)	52 (100)	51 (100)
D538G	34 (65.4)	24 (47.1)
Y537S	18 (34.6)	22 (43.1)
Y537N	14 (26.9)	16 (31.4)
E380Q	9 (17.3)	14 (27.5)
Y537C	7 (13.5)	4 (7.8)
Polyclonal ESR1 mutation, n (%)	**29 (55.8)**	**27 (52.9)**

Table 2. Change from baseline to week 8 in *ESR1* MAF

ESR1 MAF	Lasofoxifene (n=35)	Fulvestrant (n=26)
Cleared, n (%)	11 (31)	6 (23)
Decreased only (excluding cleared), n (%)	18 (51)	10 (38)
Increased, n (%)	6 (17)	10 (38)

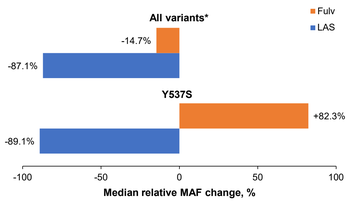
- *mESR1* MAF decreased in numerically more patients with LAS vs Fulv (Table 2, Figure 1)
- In patients with the Y537S variant, complete clearance of Y537S was observed in 5/15 (33%) with LAS vs 1/18 (6%) with Fulv
- Median percent changes in *mESR1* MAF were substantially different between LAS and Fulv for all variants and Y537S (Figure 2)
- PFS was numerically greater with LAS than with Fulv in patients with increased and decreased *ESR1* MAF (Table 3)
- CBR was 55% (16/29) on LAS and 25% (4/16) on Fulv in patients with decreased *ESR1* MAF (Table 3)
- In patients with *mESR1* clearance, 10 of 11 on LAS experienced clinical benefit (PPV 90.9%), in contrast to 2 of 6 on Fulv (PPV 33.3%)
- Figure 3 shows changes in *mESR1* variants for individual patients

Figure 1. Proportion of patients with decreased *ESR1* variants from baseline to week 8



n: number of patients having evaluable baseline and week-8 ctDNA results and respective *ESR1* mutation.

Figure 2. Median % changes in *ESR1* MAF from baseline to week 8



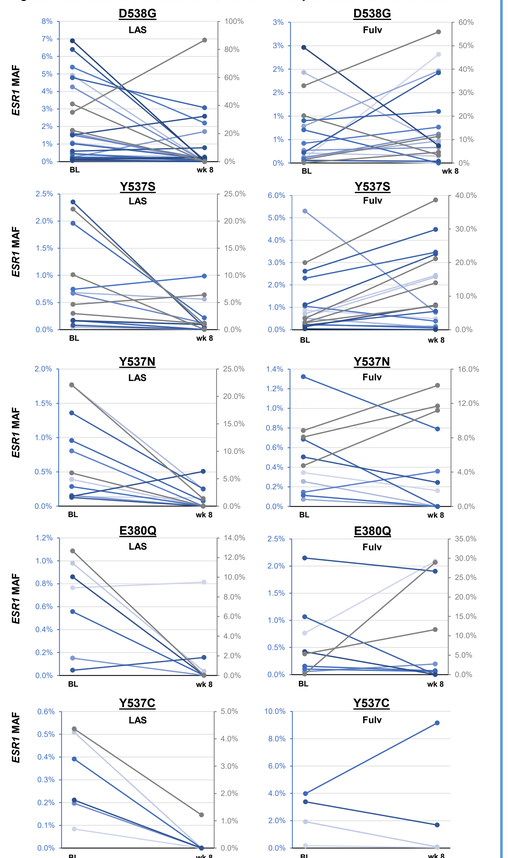
*In polyclonal patients, % change was calculated for aggregate *ESR1* MAF

Table 3. Change from baseline to week 8 in *ESR1* MAF and efficacy outcomes

	Lasofoxifene (n=35)		Fulvestrant (n=26)	
	Decreased/ND MAF	Increased MAF	Decreased/ND MAF	Increased MAF
Median PFS (95% CI), mos	8 (2–11)	4 (2–16.5)	4.5 (3–10)	2.8 (0.5–6)
Clinical benefit at week 24				
Yes, n (%)	16 (45.7)	1 (2.9)	4 (15.4)	1 (3.9)
No, n (%)	13 (37.1)	5 (14.3)	12 (46.2)	9 (34.6)
Sensitivity (95% CI), %	94.1 (73.0–99.0)		80.0 (29.9–98.9)	
Specificity (95% CI), %	27.8 (11.8–48.8)		42.9 (22.6–65.6)	

Clinical benefit: CR, PR, or ≥24 weeks of SD or non-CR/Non-PD as the patient's best overall response during the study

Figure 3. Individual MAF kinetics for the most commonly detected *mESR1* variants



Variants with low MAF (any blue) utilize the left vertical axis and those with high MAF (gray) utilize the right vertical axis.

Abbreviations

AI: aromatase inhibitor; BL: baseline; CBR: clinical benefit rate; CDK4/6i: cyclin-dependent kinase 4/6 inhibitor; CR: complete response; ctDNA: circulating tumor DNA; Fulv: fulvestrant; ITT: intent to treat; LAS: lasofoxifene; MAF: mutant allele fraction; *mESR1*: *ESR1* mutation; ND: none detected (clearance); PFS: progression-free survival; PPV: positive predictive value; PR: partial response; SERM: selective estrogen receptor modulator; SERD: selective estrogen receptor degrader; SD: stable disease.

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.** Goetz MP, et al. *Annals of Oncology.* 2022;33:S1387-S1388. **6.** Cristofanilli MA, et al. Poster presented at *the 4th Congress of the International Society of Liquid Biopsy*; Miami, FL. Poster PP. 38. **7.** Gerratana L, et al. *JCO Precis Oncol.* 2021;5:943-952. **8.** Garcia-Saenz JA, et al. *BMC Cancer.* 2017;17:210.

Key Takeaways

- Treatment with LAS effectively decreased or cleared *mESR1* from ctDNA, including the difficult-to-treat Y537S variant
- Decreased/cleared *mESR1* was associated with numerically prolonged PFS and higher CBR in the LAS arm but not the Fulv arm

Conclusions

- Our ctDNA data show that *mESR1* levels decreased or cleared in numerically more patients treated with LAS than with Fulv in women with ER+/HER-, *mESR1* mBC, including the Y537S mutant, which is known to be resistant to Fulv[3]
- Decreased/cleared *ESR1* MAF was associated with a prolonged PFS and higher CBR in the LAS arm but not the Fulv arm
- Our results demonstrate target engagement of LAS with *mESR1*
- These data suggest that *ESR1* MAF could potentially be a liquid biomarker for predicting response to LAS monotherapy in *mESR1*, endocrine-resistant mBC patients previously treated with an AI plus CDK4/6i
- The association between ctDNA *ESR1* MAF changes and clinical response to LAS plus abemaciclib was also explored in the ELAINE 2 study (see poster **P5-05-02**)

Disclosures

- **MPG** has CME activities from Research to Practice, Clinical Education Alliance, and Medscape; was a panelist for Total Health Conferencing; a moderator for Curio Science; has done consulting for AstraZeneca, Biovica, Biotheranostics, Blueprint Medicines, Eagle Pharmaceuticals, Eli Lilly, Novartis, Pfizer, Sanofi Genzyme, and Sermonix; has received research support from Eli Lilly, Pfizer, and Sermonix. **ENG** has received honoraria from Eli Lilly, Novartis, Pfizer, Roche, AstraZeneca, and MSD. **DGS** is on the advisory board for Novartis. **SLS** has received research funding (paid to institution) from Astra Zeneca, Abbvie, Bristol Myers Squibb, Eli Lilly, Seagen, and Sermonix; consults for Foundation Medicine, AstraZeneca, Daichii Sankyo, Eli Lilly, Pfizer, Sermonix, and Novartis. **SLG** is an advisor for Daiichi Sankyo, AstraZeneca, Novartis, Pfizer, Genentech, Seagen, Eli Lilly and Gilead Sciences. **GW** has received research support from Daiichi Sankyo, Esai, Eli Lilly, Gilead Sciences, Pfizer, and Seagen. **MAC** has done consulting for Menarini, Eli Lilly, AstraZeneca, Ellipses, Celcuity, Olaris, and Sermonix; has received research support from Pfizer, Eli Lilly and AstraZeneca; and honoraria from Pfizer, Eli Lilly, Foundation Medicine, and Guardant. **GR** is a consultant and stock holder of Sermonix, NuProbe, and Arcadia Medicine. **HSS** is a former employee of Sysmex Inostics. **DC** consults with Sermonix. **PVP** and **DJP** are employees and stockholders of Sermonix.
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