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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 plus abemaciclib in the ELAINE 2 study

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Introduction

- Endocrine therapy (ET) for ER+ metastatic breast cancer (mBC) frequently leads to acquired and often polyclonal *ESR1* mutations (*mESR1*), causing endocrine resistance, tumor progression, and poor prognosis[1-4]
- Preliminary data from the ELAINE 1 study in mBC patients with *mESR1* showed that monotherapy with lasofoxifene (LAS), a selective estrogen receptor modulator, numerically prolonged median PFS (6.04 vs 4.04 months; *P*=0.138) and improved clinical benefit rate (CBR) (36.5% vs 21.6%; *P*=0.12), compared with fulvestrant (Fulv), a selective estrogen receptor degrader[5]
  - ctDNA analyses showed that LAS was associated with numerically more frequent decrease/clearance of all commonly detected *mESR1* variants than Fulv, regardless of baseline *ESR1* mutant allele fraction (MAF; percentage of cell-free DNA that contains the mutant allele)[6]
- ELAINE 2 (NCT04432454) is an open-label, phase 2, multicenter trial evaluating the safety and efficacy of LAS plus the CDK4 and 6 inhibitor (CDK4/6i) abemaciclib (Abema, provided by Eli Lilly and Co) in *mESR1* mBC patients whose disease progressed on prior ET
  - Preliminary data with LAS plus Abema showed meaningful median progression-free survival (PFS 55.7 wks), objective response (OR) rate (50%), and 24-wk CBR (69%; Figure 1), with a favorable safety profile[7]
- Changes in MAF in circulating tumor DNA (ctDNA) on treatment may correlate with clinical response[8,9]

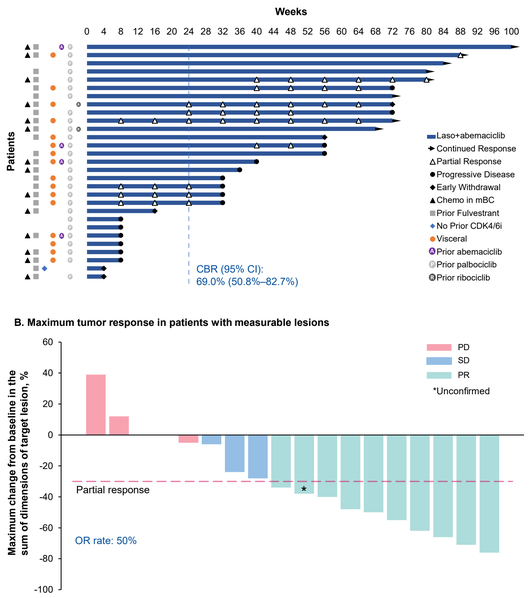
Objective

To assess the association of changes in *mESR1* levels measured in ctDNA with OR and clinical benefit in patients receiving LAS plus Abema in ELAINE 2

Methods

- Women with ER+/HER2- mBC and detectable *mESR1* from ctDNA whose disease progressed on 1 or 2 lines of ET for mBC with a CDK4/6i (prior Abema allowed) were enrolled
- Patients took oral LAS 5 mg/day and oral Abema 150 mg BID until disease progression, death, toxicity, or withdrawal
- The primary endpoint was safety and tolerability and secondary endpoints included PFS, OR rate, and CBR
- ctDNA was analyzed at baseline, every 4 weeks, and end of treatment using the Sysmex-Inostics SafeSeq assay, which detects clone-specific *mESR1* at low MAFs (limit of detection 0.05%)
  - *ESR1* MAF changes from baseline to week 4 were characterized as **decreased** (decrease in MAF or clearance [*mESR1* not detected), **increased** (increase in MAF), or **equivocal** (in polyclonal patients [>1 *mESR1*] with some MAF increasing and decreasing trends)

Figure 1. Preliminary results from ELAINE 2 as of October 2022 (n=29)



Clinical benefit: CR, PR, or ≥24 weeks of SD or non-CR/Non-PD as the patient's best overall response during the study. OR: CR or PR as the patient's best overall response during the study. OR rate is based on confirmed responses.
CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; CR, complete response; OR, objective response; PD, progressive disease; PR, partial response; SD, stable disease.

Results

Patient disposition and baseline characteristics

- 29 patients were enrolled from October 2020 to June 2021
  - 26 patients had evaluable baseline and week-4 ctDNA
- Patients had a median of 2 lines of prior metastatic therapies; 97% had received a prior CDK4/6i, 79% fulvestrant, and 48% chemotherapy (Table 1)
- Commonly detected ctDNA *mESR1* (baseline prevalence ≥10%): Y537S (66%), D538G (45%), Y537N (28%), and Y537C (10%)
  - 48% (14/29) of patients had polyclonal *mESR1*

Table 1. Baseline demographics and characteristics

	N=29
Mean age (range), yrs	58.3 (35–79)
Median prior lines of treatment in mBC	2
Race, n (%)	
White	25 (86.2)
Black or African American	2 (6.9)
Not reported	2 (6.9)
Measurable disease, n (%)	18 (62.1)
Visceral disease, n (%)	16 (55.2)
Bone only, n (%)	10 (34.5)
Prior breast cancer therapy, n (%)	
Chemotherapy (total)	25 (86.2)
Chemotherapy in mBC	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)

CDK4/6i, Cyclin-dependent kinase 4/6 inhibitor.

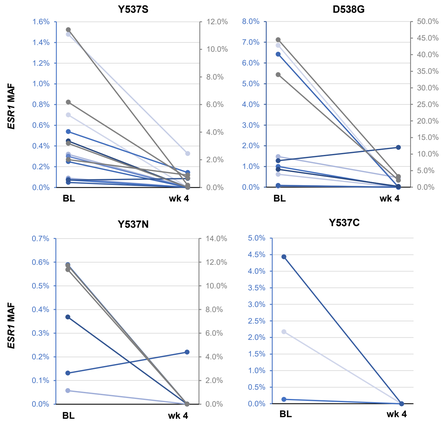
Changes in *ESR1* MAF from baseline to week 4

- In patients who had evaluable baseline and week-4 ctDNA
  - *ESR1* MAF decreased in 21 (81%; clearance in 14 [54%]), increased in 3 (12%), and was equivocal in 2 (8%) after 4 weeks of LAS plus Abema
  - *mESR1* clearance at week 4 was observed in 3 of the 4 patients who previously progressed while taking prior Abema-based therapies with all 3 achieving clinical benefit
- Decreased/cleared MAF was frequently observed for all the commonly detected *mESR1* variants, including the Y537S variant, after 4 weeks of LAS plus Abema (Figure 2)

Association of *ESR1* MAF changes with clinical response

- Clinical benefit at week 24 was observed in 17 patients with decreased *ESR1* MAF and 2 patients with increased *ESR1* MAF, yielding a sensitivity of 89% and a positive likelihood ratio (LR+) of 1.1 for predicting clinical benefit based on *ESR1* MAF changes (Table 2)
  - The positive predictive value (PPV) for clinical benefit was 81% with decreased MAF and the negative predictive value (NPV) was 33% with increased MAF
- *mESR1* clearance at week 4 had a similar sensitivity (87%) for predicting clinical benefit and a higher PPV (93%) compared with decreased MAF (Table 2), with a LR+ of 1.7
- All 9 patients with an OR showed complete *mESR1* clearance (n=5) or 50%–93% decreases in *ESR1* MAF (n=4) at week 4

Figure 2. Individual MAF kinetics for the most commonly observed *mESR1* variants



Variants with low baseline MAF (any blue) utilize the left vertical axis and those with high baseline MAF (gray) utilize the right vertical axis.
BL, baseline; MAF, mutant allele fraction.

Table 2. Change from baseline to week 4 in *ESR1* MAF and clinical benefit at week 24

Clinical benefit at week 24	MAF change at week 4 (n=26)		
	Decreased*/ND only	Increased	Equivocal
Yes, n (%)	17 (65.4)/13 (50.0)	2 (7.7)	1 (3.8)
No, n (%)	4 (15.4)/1 (3.8)	1 (3.8)	1 (3.8)
	Decreased*/Increased		
Sensitivity (95% CI),# %	89.5 (65.5–98.2)		
Specificity (95% CI),# %	20.0 (1.05–70.1)		
Positive predictive value (95% CI), %	81.0 (57.4–93.7)		
Negative predictive value (95% CI), %	33.3 (1.80–87.5)		
	ND only/Increased		
Sensitivity (95% CI),# %	86.7 (58.4–97.7)		
Specificity (95% CI),# %	50.0 (9.50–90.5)		
Positive predictive value (95% CI), %	92.9 (64.2–99.6)		
Negative predictive value (95% CI), %	33.3 (1.80–87.5)		

Clinical benefit: CR, PR, or ≥24 weeks of SD or non-CR/Non-PD as the patient's best overall response during the study.
*Defined as a decrease in MAF or clearance (ND).
#Sensitivity and specificity analyses do not include equivocal results.
CI, confidence interval; CR, complete response; MAF, mutant allele fraction; mPFS, median progression-free survival; ND, none detected (clearance); PR, partial response; SD, stable disease.

Key Takeaways

- Decreasing levels and clearance of *mESR1* in ctDNA, including the difficult-to-treat Y537S variant, was consistently observed in patients treated with LAS plus Abema
- Decreased levels and clearance of *ESR1* ctDNA was associated with clinical benefit and OR, with a high sensitivity and PPV for clinical benefit

Conclusions

- Analyses of ctDNA data in ELAINE 2 demonstrated that *mESR1* variants, including the difficult-to-treat Y537S,[3] were decreased/cleared in most (81%) patients after 4 weeks of LAS plus Abema
- Decreased/cleared *ESR1* MAF was associated with clinical benefit and OR, with a high sensitivity (89%) and favorable PPV (81%) for predicting clinical benefit
  - PPV was higher with *mESR1* clearance (93%)
  - An increase in MAF was less specific and not as predictive of treatment failure
- Our results indicate robust target engagement of LAS plus Abema with *mESR1*
- Overall, ctDNA *ESR1* MAF changes appear predictive of response in ELAINE 2 and could serve as a potential non-invasive biomarker for monitoring treatment response to this very active novel LAS/Abema combination, which will be further assessed in a large, phase 3, registrational trial planned for early 2023
- The association between ctDNA *ESR1* MAF changes and clinical response to LAS vs Fulv monotherapy was also explored in ELAINE 1 (see poster **P5-05-04**)

Disclosures

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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.** Damodaran S, et al. *Journal of Clinical Oncology.* 2022;40:1022-1022. **8.** Gerratana L, et al. *JCO Precis Oncol.* 2021;5:943-952. **9.** Garcia-Saenz JA, et al. *BMC Cancer.* 2017;17:210.