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Baseline Genomic Alterations and the Activity of Lasofoxifene (LAS) Plus Abemaciclib (Abema) in Patients with ER+/HER2- Metastatic Breast Cancer (mBC): The ELAINE 2 Study

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Introduction

- Estrogen receptor-positive (ER+)/HER2-negative (HER2-) breast cancers treated with endocrine therapy (ET) often acquire constitutively active mutations in the ERα-encoding gene (*ESR1*), resulting in ET resistance[1,2]
- Alterations or expression changes in other genes (eg, *RB1*, *FGFR1*, *CCND1*, *ERBB2*, *TP53*, *CCNE1*) are also implicated in ET or cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) resistance[3-5]
- Novel therapies are needed for *ESR1*-mutated, metastatic breast cancer (mBC), especially after progression on a CDK4/6i
- Lasofoxifene (LAS), a next-generation selective ER modulator (SERM) and potent, breast ER antagonist, prolonged progression-free survival (PFS) vs fulvestrant in the phase 2, ELAINE 1 study in women with *ESR1*-mutated, ER+/HER2- mBC who had disease progression on an aromatase inhibitor plus a CDK4/6i (median PFS 5.6 vs 3.7 months; *P*=0.138)[6]
- In the single-arm, phase 2, ELAINE 2 study, LAS combined with abemaciclib (Abema) resulted in a median PFS of 56.0 weeks (95% CI, 31.9 weeks–NE; ~13 months), clinical benefit rate (CBR) of 65.5%, and objective response rate of 56% in women with *ESR1*-mutated, ER+/HER2- mBC that progressed on ET and CDK4/6is[7]
  - Changes in *ESR1* mutant allele fraction (MAF) appear predictive of response in ELAINE 2; the positive predictive value (PPV) for clinical benefit after 4 weeks of treatment was 81% when *ESR1* MAF decreased and 93% when cleared[8]

Objective

To describe baseline genomic alterations co-occurring with *ESR1* mutations in the ELAINE 2 study and treatment responses to LAS plus Abema in patients with these genomic co-alterations

Methods

- In ELAINE 2 (NCT04432454), women (age ≥18 yrs) with ER+/HER2- mBC that progressed after prior ET and CDK4/6i and an *ESR1* mutation detected using the Sysmex-Inostics SafeSeq circulating tumor DNA (ctDNA) test received oral LAS 5 mg/day and Abema (provided by Eli Lilly and Co) 150 mg BID until disease progression, death, unacceptable toxicity, or withdrawal
- Baseline genomic alterations in ctDNA (including *ESR1* mutations) were identified with the Guardant360 CDx test
- Median PFS and CBR were assessed in patients with *ESR1* mutations and co-existing baseline genomic alterations
  - For patients who withdrew before disease progression, their last observation time was used as the progression time for PFS estimation
- Data were summarized descriptively with no formal hypothesis testing

Results

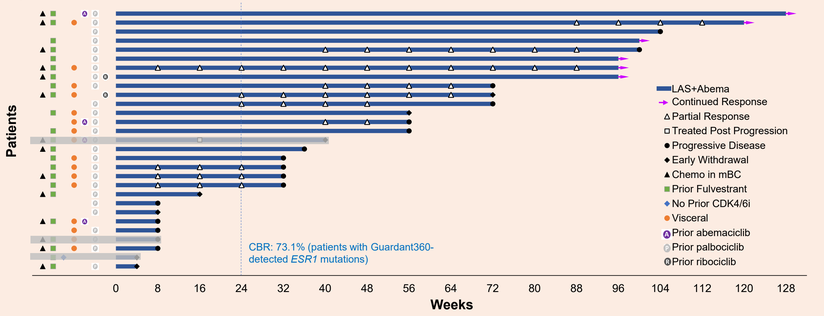
- In 26 of the 29 patients (median age 60 yrs) enrolled, *ESR1* mutations were identified at baseline by the Guardant360 CDx test; all 26 (100%) received prior CDK4/6i, 20 (76.9%) prior fulvestrant, 2 (7.7%) prior PIK3CA inhibitor, and 12 (46.2%) prior chemotherapy for mBC (**Figure 1**)
  - In the biomarker subset (n=26), the median PFS and CBR of LAS plus Abema were 12.9 mos and 73.1%, respectively, similar to the overall parent trial (12.9 mos and 65.5%) (**Table**)
- Alterations in 39 genes co-occurred with *ESR1* mutations at baseline
  - *TP53* mutations were identified in 11 (42.3%) patients, *PIK3CA* mutations in 8 (30.8%), *CCND1* amplifications in 6 (23.1%), and *FGFR1* amplifications in 5 (19.2%); 3 (11.5%) patients had both *CCND1* and *FGFR1* amplifications (**Figure 2**; **Table**)
- In patients who had co-occurring *TP53* mutations, the CBR was 64% and median PFS was 8.3 mos; corresponding values for patients with co-occurring *PIK3CA* mutations were 63% and 7.8 mos, respectively (**Table**)
- All patients in the *CCND1* and *FGFR1* amplification subgroups achieved clinical benefit, with a median PFS of 16.6 mos in both subgroups (**Table**)
- For patients with co-alterations in ≥2 other genes of interest, the CBR was 83.3% and median PFS was 14.7 mos (**Table**)

Table. Treatment response by genomic alterations of interest that were concurrently detected with *ESR1* mutations at baseline (n=26)

Genomic alteration	Baseline n (%)	mPFS,[a] mos	CBR, %
ESR1 mutation	26 (100)	12.9	73.1
+ *TP53* mutation	11 (42.3)	8.3	63.6
+ *PIK3CA* mutation	8 (30.8)	7.8	62.5
+ *CCND1* amplification	6 (23.1)	16.6	100
+ *FGFR1* amplification	5 (19.2)	16.6	100
+ *ERBB2* mutation	3 (11.5)	12.9	66.7
+ *CCNE1* amplification or mutation	3 (11.5)	23.0	100
+ *RB1* mutation	1 (3.8)	11.0	100
+ *CCND1* and *FGFR1* amplification	3 (11.5)	7.6	100
+ ≥2 co-alterations in other genes of interest	12 (46.2)	13.8	83.3

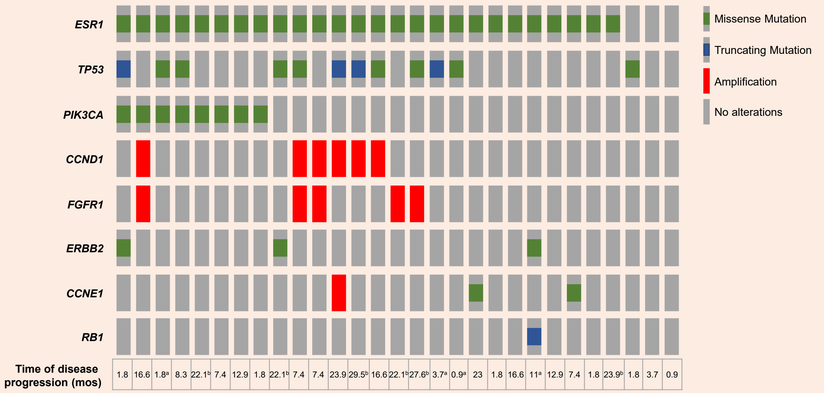
[a]For patients who withdrew before disease progression, the last observation time was used as the progression time for PFS estimation.
[b]Other genes of interest include *PIK3CA*, *FGFR1*, *CCND1*, *TP53*, *ERBB2*, *CCNE1*, or *RB1*.
CBR, clinical benefit rate; mPFS, median progression-free survival.

Figure 1. Time on treatment and response to treatment in ELAINE 2



Data as of April 2023. Bars shaded in gray represent patients with *ESR1* mutations detected in the Sysmex-Inostics SafeSeq ctDNA test but not in the Guardant360 CDx test, who were excluded from the analysis of treatment response with genomic co-alterations.
Abema, abemaciclib; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; LAS, lasofoxifene.

Figure 2. Distribution of genomic alterations detected by the Guardant360 CDx test



Three patients with *ESR1* mutations found by Sysmex-Inostics SafeSeq but not Guardant360 were excluded from the treatment response with gene co-alteration analysis.
[a]Early withdrawal, time of last assessment or withdrawal. [b]Continued response, time of last assessment.

Key Takeaways

- Genomic alterations concurrent with *ESR1* mutations were frequent in mBC that has progressed on ET and CDK4/6is
- Co-alterations in *ESR1* and other genes associated with treatment resistance did not appear to compromise the efficacy of LAS plus Abema in ELAINE 2

Conclusions

- Guardant360 ctDNA profiling from patients in ELAINE 2 demonstrates that other genomic alterations are frequently detected concurrently with *ESR1* mutations in the endocrine-resistant setting, in line with previous findings among patients with hormone receptor-positive mBC[3,5]
- While mutations in *TP53* and *PIK3CA* and amplifications in *CCND1* and *FGFR1* are associated with poor prognosis and CDK4/6i resistance,[4,9,10] the efficacy of LAS plus Abema in ELAINE 2 appeared similar in those with or without their co-occurrence with *ESR1* mutations
- The current analysis is limited by its exploratory nature and the small sample size of the study; results should be interpreted with caution
- With the ELAINE 2 data suggesting the potential of LAS plus Abema for treating *ESR1*-mutated, ER+/HER2- mBC in the post-CDK4/6i setting, the ongoing, registrational, phase 3, ELAINE 3 study (NCT05696626) will further evaluate the safety and efficacy of LAS plus Abema compared with fulvestrant plus Abema in a larger patient population

Disclosures

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