Lasoxifene (LAS) Plus Abemaciclib (Abema) for Treating ESR1-mutated ER+/HER2- Metastatic Breast Cancer (mBC) after Progression on Prior Therapies: ELAINE 2 Study Update

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Introduction
- Endocrine therapy (ET), particularly aromatase inhibitors (AIs), for estrogen-receptor (ER)-positive breast cancer can lead to acquired ER mutations (mERs), which drive endocrine resistance and tumor progression. 
- Current therapies have limited activity for mBC with CDK4/6i setting.

Objective
- The objective of the ELAINE 2 study was to evaluate the safety and efficacy of LAS combined with AIs in patients with ER+,HER2- mBC in the post-CDK4/6i setting.

Methods
- The open-label, phase 2, single-arm ELAINE 2 study (NCT04422542) enrolled women (118 years) with ER+/HER2- mBC who had received prior ET and mCDK4/6i and were identified in circulating tumor DNA (ctDNA) who had progressed on prior ET for mBC (32 line).
- Prior CDK4/6i and/or one line of chemotherapy for mBC was allowed.
- Patients took LAS and AI reg and Abema (supplied by Eli Lilly and Co) 150 mg BID until disease progression, death, toxicity, or withdrawal.

Primary endpoint: safety and tolerability (AEs)
Secondary endpoints: PFS, CBR, ORR, duration of response, and time to response
- Safety and tolerability were analyzed in all evaluable patients. Patients were available for efficacy analysis from cycle 1.
- ESR1-mutant allele fractions (hAF) were analyzed in ctDNA baseline and wk 4 using Sysmex-Inostics SafeSeq assay.
- Guardant 360 ctDNA analysis was utilized to identify other genetic alterations.
- Data were summarized descriptively with no formal hypothesis testing.

Results
- Prior palbociclib.
- ESR1
- Primary endpoint:
- Here, we report ELAINE 2 data with longer patient follow up.
- Current therapies have limited activity for mBC with CDK4/6i setting.
- LAS is a next-generation ET and breast ER antagonist that prolongs progression-free survival (PFS; median 6.5 vs 3.7 mos; P=0.183) compared with fulvestrant (Fulv) in patients with mER mBC that progressed on an AI plus CDK4/6i, with a greater clinical benefit (CBR; 37% vs 22%; P=0.177) and objective response rates (ORR; 13% vs 5%; P=0.124).
- In the phase 2; ELAINE 1 study.
- Results from the phase 2; ELAINE 2 study showed that LAS plus Abema had a median PFS of 13 mos, ORR of 32%, and CBR of 62%, with a well tolerated safety profile in patients with endocrine-resistant mER mBC.
- Here, we report ELAINE 2 data with longer patient follow up.

Safety
- LAS/Abema was well tolerated with primarily grade 1/2 treatment-emergent AEs (TEAEs), most common diarrhea, nausea, fatigue, and vomiting (Table 1).
- Three patients (10.3%) had scan-identified VTEs (Table 2)
- One patient discontinued treatment due to grade 2 diarrhea.
- No deaths on treatment occurred.
- Abame dose was reduced to 10 mg BID in 6 (20.7%) patients; LAS dose was not reduced per protocol.

Efficacy
- Median PFS was 56.0 wks (~13 mos; Figure 2).
- ORR 55.6% (95% CI, 33.7%–75.4%; Table 3).
- Median DoR: 27.8 wks (6.4 mos).
- 8 (27.6%) patients achieved PFS over 96 wks (~2.5 yrs).
- The European Society for Medical Oncology (ESMO) guidelines recommend a PFS rate of 30% at 12 mos, 50% at 24 mos, and 60% at 36 mos for mBC.
- In ELAINE 2, LAS/Abema compared well to the previously reported rates (Table 3).

Disclosures
- This study was funded by Eli Lilly and Co., a member of the Lilly Research Alliance, which includes Eli Lilly and Co., Inc., and its affiliated companies (Eli Lilly), and Incyte Corporation.
- The study and manuscript were prepared under the direction of the study sponsor, and all authors had access to the data and were involved in the decision to submit the manuscript for publication.
- The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

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Key Takeaways
- In ELAINE 2; LAS/Abema was well tolerated with an acceptable safety profile.
- LAS/Abema was associated with a clinically meaningful PFS (median ~13 mos), CBR (37%), and CBR (62%) in women with ER+/HER2- mBC that had progressed on ET and CDK4/6i.
- ESR1 MAF decreased with LAS/Abema, consistent with target engagement.

Conclusions
- With longer ELAINE 2 follow up; LAS/Abema continued to be well tolerated; no new safety signals were noted.
- Incidence of mETV in ELAINE 2 was within the range previously reported for Abema-based therapies.
- LAS/Abema exhibited meaningful antitumor activity in patients with mER-,ER+/HER2- mBC that had progressed on ET and CDK4/6i.
- Observed decreases in mER1 ctDNA suggest target engagement with LAS.
- Other co-occurring genetic alterations associated with resistance did not appear to compromise the efficacy of LAS/Abema.
- A confirmatory, phase 3 study (ELAINE 3; NCT05969626) will compare LAS/Abema with Fulv/Abemaciclib (NCT03235126); NE=not estimable at the time of the analysis.
- The combination of LAS and Abema may provide a practice-changing option for treating mER+ mBC.