ESMO 2022 Abstract
Submission deadline: May 3, 2022 (21:00 CEST)
Late-breaking abstract deadline: August 9, 2022 (shell abstract required by May 3rd, to be updated by this August 9th LBA deadline)
Character limit: 2039 characters, **2035 now** (includes title, body, tables; excludes author information, spaces, and section headers [39 char; 2039 max])
Title character limit: 250 characters, **246 characters now** (excludes spaces)

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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

Background: Acquired *ESR1* mutations cause endocrine resistance, driving metastasis and poor prognosis in patients with ER+/HER2- mBC. A phase 2 trial of LAS plus abemaciclib (ELAINE 2) showed efficacy in heavily pretreated patients with *ESR1*-mutated mBC post-CDK4/6i (ASCO 2022). Here we describe ELAINE 1, a randomized trial of LAS vs Fulv in a post-CDK4/6i second-line setting.

Methods: Women with ER+/HER2-/*ESR1*-mutated mBC and progression on prior (≥12 mos) AI plus CDK4/6i (n=103) were randomized to oral LAS 5 mg (n=52) daily or IM Fulv 500 mg (n=51) days 1, 15, and 29, then every 4 weeks, until disease progression or severe toxicity. Imaging occurred every 2 mos (or if clinically indicated). Primary endpoint was progression-free survival (PFS).

Results: Mean age was 60.8 yr (33-84); 83% were white, 66% had visceral disease, 71% (n=73) had measurable disease. For LAS vs Fulv, median PFS was 6.04 mos (95% CI, 2.82–8.04) vs 4.04 mos (95% CI, 2.93–6.04), *P*=0.138 (HR, 0.699 [95% CI, 0.445–1.125]); PFS at 12 mos was 30.7% vs 14.1%; clinical benefit rate was 36.5% vs 21.6%, *P*=0.12. Objective response rate for LAS vs Fulv was 13.2% vs 2.9%, *P*=0.12, with 1 complete response (60-week duration) and 4 partial responses (PR) in the LAS arm versus 1 PR in the Fulv arm. PFS was numerically and consistently greater with LAS vs Fulv when visceral metastasis and/or Y537S *ESR1* mutation subgroups were analyzed. Clearance of ctDNA also favored LAS over Fulv. Most common

adverse events were fatigue, nausea, arthralgias, and hot flushes; most were Grade 1/2. No thrombotic events occurred.

Conclusions: ELAINE 1 is the first clinical trial comparing LAS with Fulv in *ESR1*-mutated mBC patients with progression on CDK4/6i and demonstrating activity of a novel SERM in this setting. All clinical outcomes numerically favored LAS vs Fulv in this signal-seeking study. LAS may be a new treatment option following endocrine/CDK4/6i therapies if efficacy is confirmed in a larger, adequately powered clinical study. A phase 3 combination study of LAS and abemaciclib is planned based on encouraging efficacy/safety in ELAINE 2.

Clinical trial information: NCT03781063
Editorial acknowledgement: Medical writing assistance was provided by Kathleen Ohleth, PhD of Precise Publications, LLC.