SAN ANTONIO BREAST CANCER SYMPOSIUM®

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Open-Label, Randomized, Multicenter, Phase 3, ELAINE 3 Study of the Efficacy and Safety of Lasofoxifene Plus Abemaciclib for Treating ER+/HER2-, Locally Advanced or Metastatic Breast Cancer with an *ESR1* Mutation

Matthew P Goetz,[1] Seth A Wander,[2] Thomas Bachelot,[3] Gerald Batist,[4] Javier Cortes,[5] Massimo A Cristofanilli,[6] Giuseppe Curigliano,[7] Alexandre de Nonneville,[8] Einav Nili Gal-Yam,[9] Komal Jhaveri,[10] Cynthia Ma,[11] Heather A Parsons,[12] Hope S Rugo,[13] Sarah L Sammons,[12] Daniel G Stover,[14] Chris Twelves,[15] Aditya Bardia,[2] Paul V Plourde,[16] David J Portman,[16] Senthil Damodaran[17]

[1]Mayo Clinic Rochester, Rochester, MN, USA; [2]Massachusetts General Hospital, Boston, MA, USA; [3]Centre Leon Berard, Lyon, France; [4]Segal Cancer Centre and McGill University Centre for Translational Research in Cancer, Jewish General Hospital, Montréal, Québec Canada; [5]International Breast Cancer Centre (IBCC), Barcelona, Spain; [6]Weill Cornell Medicine, New York, NY, USA; [7]Istituto Europeo di Oncologia, IRCCS and University of Milano, Milan, Italy; [8]Institut Paoli-Calmettes, Aix Marseille Université, Centre de Recherche en Cancérologie de Marseille (CRCM), Inserm U1068, CNRS U7258, France; [9]Breast Oncology Institute Sheba Medical Center, Tel-Hashomer Ramat Gan, Israel; [10]Department of Medicine, Memorial Sloan Kettering Cancer Center/Evelyn H. Lauder Breast And Imaging Center, New York, NY, USA; [11]Division of Oncology, Washington University School of Medicine, St. Louis, MO, USA; [12]Dana-Farber Cancer Institute, Boston, MA, USA; [13]University of California, San Francisco, CA, USA; [14]Ohio State University, Columbus, OH, USA; [15]University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, UK; [16]Sermonix Pharmaceuticals, Columbus, OH, USA; [17]MD Anderson Cancer Center, Houston, TX, USA

Background

- Mutations in the estrogen receptor (ER)-α–coding gene, *ESR1*, potentially drive resistance to endocrine therapy (ET) and tumor progression in women with ER+, metastatic breast cancer (mBC)[1-4]
  - Up to 40% of endocrine-resistant tumors are due to acquired *ESR1* mutations in the ligand binding domain,[5-7] which confer ligand-independent, constitutive ER activity[5,8]
- Treatment options are limited for endocrine-resistant mBC, particularly following treatment with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i)[9,10]
- Lasofoxifene, an oral, next-generation ET and breast ER antagonist, exhibited anti-tumor activities in two phase 2 studies of women with *ESR1*-mutated, ER+/HER2- mBC that progressed on previous ET and CDK4/6is
  - ELAINE 1: Numerically greater progression-free survival (PFS, median ~5.6 vs 3.7 months; *P*=0.138), objective response rate (ORR, 13.2% vs 2.9%; *P*=0.124), and clinical benefit rate (CBR, 36.5% vs 21.6%; *P*=0.117) with lasofoxifene monotherapy versus fulvestrant, and a favorable safety profile[11]
  - ELAINE 2: Lasofoxifene combined with abemaciclib was well tolerated with a median PFS of ~13 months, ORR of 55.6%, and CBR of 65.5% (**Figure 1**)[12]
- The median PFS with lasofoxifene plus abemaciclib in ELAINE 2[12] was greater when considering the same with various ET combinations in the post-CDK4/6i setting, as reported in separate studies[13-18] (**Figure 2**)
- *ESR1* mutant allele fraction (MAF) decreased or was undetectable from baseline to week 4 in
  - 83% of patients treated with lasofoxifene and 62% of those treated with fulvestrant (median percent change −87.1% vs −14.7%, respectively) in ELAINE 1[11]
  - 81% of patients treated with lasofoxifene plus abemaciclib in ELAINE 2[12]

Objective

To evaluate the efficacy and safety of lasofoxifene plus abemaciclib versus fulvestrant plus abemaciclib for the treatment of locally advanced or metastatic, ER+/HER2-, breast cancer with an *ESR1* mutation after ET-CDK4/6i progression

Figure 1. Patient responses in the ELAINE 2 study[12]

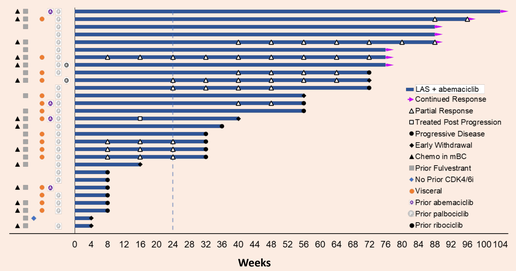
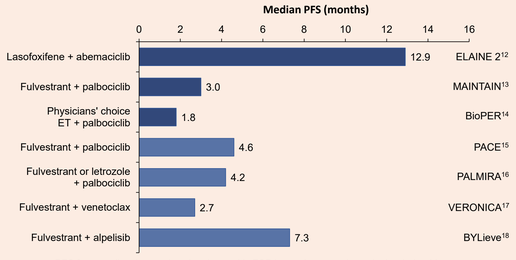


Figure 2. Median PFS in ELAINE 2 and separate studies with ET combinations after progression on a CDK4/6 inhibitor



PFS from studies that analyzed patients with *ESR1* mutations are shown in the darker blue.

The phase 3, registrational, ELAINE 3 trial was initiated based on the promising results from the ELAINE 1 and 2 trials

Study Design

ELAINE 3 (NCT05696626): Open-label, phase 3, multicenter, randomized-controlled study in 17 countries

Participants
- Women and men
- ER+/HER2-, locally advanced or metastatic breast cancer
- Progressed on AI plus palbociclib or ribociclib
- ≥1 *ESR1* mutation

Statistical Analysis
- Target sample size is 400 based on progression-free survival
- Outcomes between treatments will be compared using a stratified, Cox proportional hazards model and stratified logrank test

Lasofoxifene (oral; 5 mg/day) **plus** **abemaciclib** (oral; 150 mg BID)

Randomized 1:1

Fulvestrant (IM; 500 mg on days 1, 15, and 29, then monthly) **plus** **abemaciclib** (oral; 150 mg BID)

Taken until disease progression, death, unacceptable toxicity, or study withdrawal

Endpoints
- **Primary**
  - Progression-free survival
- **Secondary**
  - Objective response rate
  - Overall survival
  - Clinical benefit rate
- **Other**
  - *ESR1* MAF changes
  - Time to chemotherapy
  - Quality of life
  - Safety

Key Eligibility Criteria

Inclusion	Exclusion
Pre- and postmenopausal women and men aged ≥18 years with ER+/HER2-, local aBC and/or mBC (measurable [as per RECIST 1.1 criteria]) and/or non-measurable disease)	Visceral crisis needing immediate chemotherapy, brain metastasis, or lymphangitic carcinomatosis of the lung
≥1 acquired *ESR1* mutation as detected in ctDNA from blood or breast cancer biopsy	Prior progression of disease on fulvestrant or other SERD
Progression on an AI plus palbociclib or ribociclib as their first hormonal treatment for aBC/mBC	Known inactivating RB1 mutations or deletions (screening not required)
No disease progression for ≥6 months taking an AI/CDK1 combination for aBC	Radiotherapy within 30 days prior to randomization
≤1 line of cytotoxic chemotherapy in the advanced/metastatic and/or adjuvant setting	History of a PE, DVT, or any known thrombophilia
ECOG performance score of 0 or 1	History of long QTc syndrome or a QTc of >480 msec
Laboratory-confirmed, adequate organ function	Taking concomitant strong CYP3A4 inhibitors or strong and moderate CYP3A4 inducers

aBC, advanced breast cancer; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, cell-free circulating tumor DNA; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; mBC, metastatic breast cancer; PE, pulmonary embolism; RECIST 1.1, Response Evaluation Criteria in Solid Tumors (version 1.1); SERD, selective estrogen receptor degrader.

Study Sites

Key Takeaways

- Lasofoxifene alone[11] and when combined with abemaciclib[12] exhibited anti-tumor activity in ER+/HER-, *ESR1*-mutated, mBC that progressed on ET and CDK4/6is
- Reductions and clearance of *ESR1* MAF are consistent with target engagement of lasofoxifene[11,12]
- If the safety and efficacy of lasofoxifene plus abemaciclib are confirmed in the registrational, ELAINE 3 trial, this combination will be an option for women with ER+/HER2- mBC having *ESR1* mutations in the difficult-to-treat, post-CDK4/6i setting

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