ADELA: a double-blind, placebo-controlled, randomized phase 3 trial of elacestrant + everolimus versus elacestrant + placebo in ER+/HER2- advanced breast cancer patients with *ESR1*-mutated tumors progressing on endocrine therapy + CDK4/6 inhibitor

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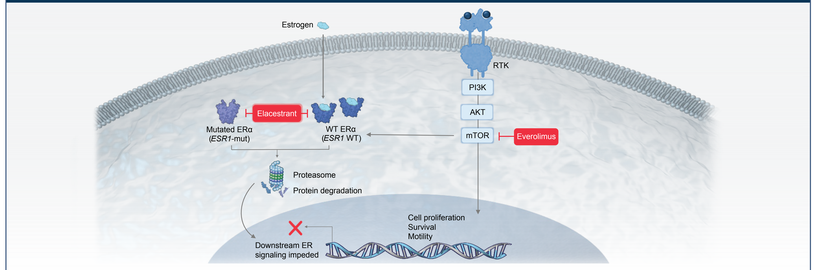
BACKGROUND

- Endocrine therapy plus a cyclin-dependent kinase 4/6 inhibitor (ET+CDK4/6i) is the standard-of-care (SOC) in first-line estrogen receptor-positive (ER+)/HER2-negative (HER2-) advanced breast cancer (aBC);[1-3] however, tumors eventually develop resistance.[4]
- Constitutive activation of the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway can contribute to endocrine resistance in breast cancer.[5-11]
- A common type of acquired resistance mechanism consists of alterations in the estrogen receptor 1 gene (*ESR1*). *ESR1*-mutated tumors occur in 40%-50% of patients with BC and predominantly emerge in the metastatic setting after prolonged exposure to aromatase inhibitor (AI) regimens.[5,12-18]
- There is an unmet need for novel therapeutic approaches to overcome different resistance mechanisms and improve clinical outcomes in patients with ER+/HER2- aBC with *ESR1*-mutated tumors who progress following ET+CDK4/6i.
- Elacestrant is a next-generation oral selective ER degrader (SERD) that binds to the ER alpha and induces its degradation.[19]
- In the pivotal phase 3 EMERALD study, single-agent elacestrant demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) versus SOC ET in patients with *ESR1*-mutated tumors (HR = 0.55; 95% CI, 0.39-0.77; P = 0.0005).[20]
  - Differences were particularly notable among patients who received prior ET+CDK4/6i ≥12 months; median PFS with elacestrant was 8.6 months vs 1.9 months with SOC ET (HR = 0.41; 95% CI, 0.26-0.63).[21]
- The crosstalk between the ER and PI3K/AKT/mTOR pathways are additional mechanisms of resistance to endocrine treatment and provides a rationale for evaluating the combination of elacestrant with specific PI3K/AKT/mTOR inhibitors.[22,23]
- Everolimus, an mTOR complex 1 (mTORC1) inhibitor, is indicated for the treatment of postmenopausal women with hormone receptor-positive (HR+)/HER2- aBC in combination with exemestane after progression on non-steroidal AIs.[24]
  - In preclinical models of ER+ breast cancer, the combination of elacestrant + everolimus showed significantly greater tumor growth inhibition.[25]
  - The recommended phase 2 dose (elacestrant 345 mg QD + everolimus 7.5 mg QD) was consistent with the known safety profile for everolimus + SOC ET.[26,27]
  - Preliminary efficacy data demonstrated antitumor activity with the combination (elacestrant + everolimus): objective response rate = 22%; clinical benefit rate at 24 weeks = 72%.[26]

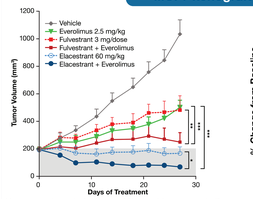
Rationale for Evaluating the Combination of Elacestrant With Specific PI3K/AKT/mTOR Inhibitors in ER+/HER2- aBC[22,23]



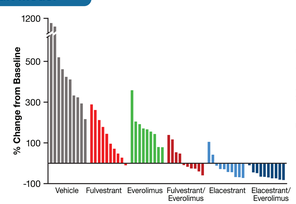
ERα, estrogen receptor alpha; *ESR1*, estrogen receptor 1; mTOR, mammalian target of rapamycin; aBC, advanced breast cancer; mut, mutated/mutation; PI3K, phosphoinositide 3-kinase; RTK, receptor tyrosine kinase; WT, wild type.

In Preclinical Models of ER+ Breast Cancer, the Combination of Elacestrant + Everolimus Showed Significantly Greater Tumor Growth Inhibition[24]

MCF7 xenograft model

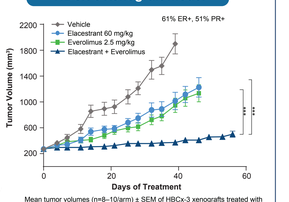


Mean tumor volumes (n=9–10/arm) ± SEM. Asterisks represent significant differences between the indicated treatment groups on Day 27. ****<0.0001, ** = 0.0025, * = 0.0138



Percent change in tumor volumes from individual animals from start to end of treatment.

HBCx-3 xenograft model



Mean tumor volumes (n=8–10/arm) ± SEM of HBCx-3 xenografts treated with elacestrant (60 mg/kg) and everolimus. Asterisks represent significant differences between the indicated treatment groups on Day 46. ***<0.0001

OBJECTIVE

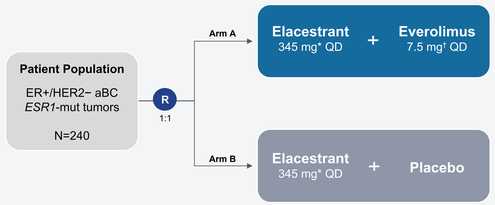
- The ADELA study (NCT06382948) will evaluate the efficacy and safety of elacestrant + everolimus compared with elacestrant + placebo in patients with ER+/HER2- advanced breast cancer and *ESR1*-mutated tumors progressing on ET + CDK4/6i.

METHODS

- ADELA is an international, multicenter, double-blind, placebo-controlled, randomized phase 3 trial.
- Patients will be randomized in a 1:1 ratio to receive elacestrant + everolimus or elacestrant + placebo until disease progression or unacceptable toxicity.
  - Elacestrant 345 mg once daily (QD) + everolimus 7.5 mg QD
  OR
  - Elacestrant 345 mg QD + placebo QD
- Patients will receive the study treatment in 28-day cycles until the earliest occurrence of documented disease progression, death, unacceptable toxicity, or discontinuation from the study treatment for any other reason.
- Patients will receive dexamethasone mouthwashes four times daily during the first 8 weeks and at the investigator's discretion for an additional 8 weeks.
- A total of 240 patients will be randomized.

ADELA Study Design

A phase 3 study of elacestrant ± everolimus in patients with ER+/HER2− aBC and *ESR1*-mut tumors who progressed on prior ET + CDK4/6i



PHASE 3 OBJECTIVES

Primary objective: Evaluate PFS based on BIRC‡

Secondary objectives: Evaluate investigator-assessed PFS, OS, ORR, CBR, DoR, TTR, best percentage of change in tumor burden,§ safety, and HRQoL

STRATIFICATION FACTORS
- Presence of visceral metastases (yes vs no)
- Duration of prior CDK4/6i therapy (≥12 mo vs <12 mo)

*Elacestrant 345 mg is equivalent to 400 mg elacestrant hydrochloride. †Recommended phase 2 dose (RP2D) for everolimus from ELEVATE (NCT05563220) trial. ‡Through the use of RECIST v.1.1. §Based on BIRC and local investigator assessment through use of RECIST v.1.1.

aBC, advanced breast cancer; BIRC, blinded independent review committee; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; mut, mutated; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; R, randomization; TTR, time to response.

Clinical trial collaboration with MEDSIR.

Statistical and Data Analysis

- Time-to-event endpoints will be reported using Kaplan-Meier estimates.
- Two interim analyses and a final efficacy analysis are planned.
- Stratified log-rank tests will be used to assess treatment-group differences.
- In general, statistical analyses will be performed for the overall population and subgroups of the population.
- Baseline demographics and other characteristics will be descriptively summarized.

Eligibility Criteria

Key Inclusion Criteria

- Women (pre-*, peri-*, or postmenopausal) and men age ≥18 years
- Histologically or cytologically confirmed ER+/HER2− unresectable locally recurrent or metastatic disease
- Confirmed *ESR1*-mutation
- PD on prior CDK4/6i + ET for aBC after ≥6 months
  - Patients receiving CDK4/6i-based therapy in the adjuvant setting are eligible if PD is confirmed after ≥12 months of treatment but no more than 12 months following CDK4/6i treatment completion
- Previously received 1-2 lines of ET for aBC
  - Progression during or within 12 months of adjuvant endocrine therapy is considered as a line of endocrine therapy for advanced disease
- No prior chemotherapy in the advanced setting
- No prior elacestrant or other investigational SERDs, PROTACs, CERANs, or novel SERMs, and/or PI3K/AKT/mTOR inhibitors, including everolimus†
- ECOG PS 0 or 1
- Adequate bone marrow and organ function

Key Exclusion Criteria

- Formal contraindication to ET defined as visceral crisis and/or rapidly or symptomatic progressive visceral disease
- Received treatment with approved or investigational cancer therapy ≤14 days prior to randomization (except for fulvestrant that must be completed ≥28 days before randomization)
- Known active uncontrolled or symptomatic CNS metastases and/or leptomeningeal disease
- Concurrent malignancy or malignancy ≤3 years before randomization
- Clinically relevant cardiovascular or cerebrovascular disease and/or cardiac dysfunction or conduction abnormalities**
- History of non-infectious ILD or pneumonitis that required steroids, current ILD or pneumonitis, or has suspected pneumonitis that cannot be ruled out by imaging at screening
- Current or prior coagulopathy ≤6 months, including history of DVT or pulmonary embolism

* Receiving a LHRH analogue for >28 days prior to study randomization and are planning to continue LHRH agonist treatment during the study. †Prior fulvestrant is permitted if treatment was administered at least 28 days before randomization.

aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CERANs, complete estrogen receptor antagonist; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, endocrine receptor; ET, endocrine therapy; *ESR1*, estrogen receptor 1 gene; DVT, deep vein thrombosis; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; LHRH, luteinizing hormone-releasing hormone; mTOR, mammalian target of rapamycin; mut, mutation; PD, progressive disease; PI3K, phosphatidylinositol 3-kinase; PROTACs, Proteolysis-targeting chimeras; SERDs, selective estrogen receptor degraders; SERMs, selective estrogen receptor modulators; SOC, standard of care.

SUMMARY

- ADELA, an international, multicenter, double-blind, placebo-controlled, randomized phase 3 trial, will evaluate the efficacy of elacestrant + everolimus relative to elacestrant + placebo in patients with ER+/HER2- advanced breast cancer and *ESR1*-mutated tumors progressing on ET + CDK4/6i.
- The primary objective is to evaluate the efficacy of elacestrant + everolimus relative to elacestrant + placebo in terms of PFS based on BIRC.
- The combination of elacestrant + everolimus may provide a novel and effective therapeutic option for patients with ER+/HER2- advanced breast cancer with *ESR1*-mutated tumors who progressed on ET+CDK4/6i that can potentially improve clinical outcomes and delay chemotherapy or antibody-drug conjugate-based regimens.
- Recruitment for ADELA is ongoing.

Austria
Brazil
Czech Republic
Spain
France
Greece
Italy
Germany
UK

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Plain Language Summary

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