

DISCLOSURES

- Elacestrant is not approved by FDA for use in combination with everolimus in patients with ER+/HER2- locally advanced or metastatic breast cancer, and the safety and effectiveness of this combination therapy for ER+/HER2- locally advanced or metastatic breast cancer has not been established.
- Elacestrant is indicated for the treatment of postmenopausal women or adult men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, *ESR1*-mutated advanced or metastatic breast cancer, as detected by an FDA-authorized test, with disease progression following at least one line of endocrine therapy.
- Elacestrant is indicated for use only as monotherapy and not in combination with any other products.
- Please see the Full Prescribing Information:
https://rxmenarinistemline.com/ORSERDU_elacestrant_Full_Prescribing_Information.pdf
- Please refer to the full Prescribing and Safety Information for everolimus.
- Limitations of this study are related to the single-arm, open-label, phase II trial design (N = 50), which limits the statistical power to detect differences in efficacy or safety across subgroups and precludes definitive conclusions.

Elacestrant Safety Information:¹

Warnings and Precautions

Dyslipidemia: Hypercholesterolemia and hypertriglyceridemia occurred in patients taking elacestrant at an incidence of 30% and 27%, respectively. The incidence of Grade 3 and 4 hypercholesterolemia and hypertriglyceridemia were 0.9% and 2.2%, respectively. Monitor lipid profile prior to starting and periodically while taking elacestrant.

Embryo-Fetal Toxicity: Based on findings in animals and its mechanism of action, elacestrant can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with elacestrant and for 1 week after the last dose.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with elacestrant and for 1 week after the last dose.

Adverse Reactions

Serious adverse reactions occurred in 12% of patients who received elacestrant.

Serious adverse reactions in >1% of patients who received elacestrant were musculoskeletal pain (1.7%) and nausea (1.3%). Fatal adverse reactions occurred in 1.7% of patients who received elacestrant, including cardiac arrest, septic shock, diverticulitis, and unknown cause (one patient each).

The following were employees of Stemline at the time of publication: Jennifer A. Crozier, and Tomer Wasserman

The following authors, editors or contributors to this publication, have or had consulting or other relationships with Stemline, for which they may have received compensation:

Hope S. Rugo, Sara M. Tolaney, Wassim McHayleh, Neelima Vidula, Erika Hamilton, Joyce O'Shaughnessy, Giuseppe Curigliano, Javier Cortés, Philippe Aftimos, Yuan Yuan, Vicente Valero, Paula Muñoz Romero, Faten Koraichi Auriol, Alessandro Paoli, and, Virginia Kaklamani

1. Elacestrant. Package Insert. Stemline Therapeutics; 2026.

Elacestrant in Combination with Everolimus for Estrogen Receptor-Positive, HER2-Negative Previously Treated Advanced Breast Cancer: Results from ELEVATE



Hope S. Rugo¹, Sara M. Tolaney², Nancy Chan³, Giuliano Borges⁴, Rinat Yerushalmi⁵, Marina N. Sharifi⁶, Wassim McHayleh⁷, Thaddeus Beck⁸, Neelima Vidula⁹, Erika Hamilton¹⁰, Kristine J. Rinn¹¹, Joyce O'Shaughnessy¹², Giuseppe Curigliano^{13,14}, Javier Cortés¹⁵, Isabel Garcia-Fructuoso¹⁶, Philippe Aftimos¹⁷, Begoña Bermejo de las Heras¹⁸, Pablo Tolosa¹⁹, Yuan Yuan²⁰, Vicente Valero²¹, Marla Lipsyc-Sharf²², Paula Muñoz Romero²³, Faten Koraichi Auriol²³, Alessandro Paoli²³, Jennifer A. Crozier²⁴, Tomer Wasserman²⁴, and Virginia Kaklamani²⁵

ABSTRACT

Purpose: Treatment options for progression on first-line endocrine therapy (ET) + cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) for estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) advanced breast cancer (ABC) include ET plus targeted agents [CDK4/6i or phosphatidylinositol 3-kinase/AKT/mechanistic target of rapamycin (PAM) pathway inhibitors]. Elacestrant is the first single-agent oral selective ER degrader that significantly improved progression-free survival (PFS) versus standard-of-care (SOC) ET in *ESR1*-mutated and overall ER+/HER2- ABC populations.

Patients and Methods: This phase Ib/II umbrella trial enrolled patients with ER+/HER2- ABC who received 1 to 2 lines of ET + CDK4/6i (including prior fulvestrant and primary endocrine resistance) and no prior chemotherapy for ABC. Patients received elacestrant with everolimus, alpelisib, capivasertib, abemaciclib, ribociclib, or palbociclib. We evaluated PFS of elacestrant plus everolimus.

Results: In phase Ib (*N* = 23), the optimal recommended phase II dose was determined as elacestrant 345 mg plus

everolimus 7.5 mg. The phase II patient population (*N* = 50) included 100% prior CDK4/6i, 50% prior fulvestrant, 72% visceral metastasis, 20% primary endocrine resistance, 42% *ESR1*-mutated, and 50% *PIK3CA*-mutated. Median PFS was 8.3 months [95% confidence interval (CI), 4–10.2] in all patients; 8.3 months (95% CI, 3.5–12.9) in *ESR1*-mutated, 9 months (95% CI, 4.2–12.7) in *ESR1* wild-type, 8.3 months (95% CI, 3.6–10.2) in *PIK3CA*-mutated, and 9.4 months (95% CI, 4–not reached) in *PIK3CA* wild-type. Adverse events (AEs) were consistent with the known safety of everolimus plus SOC ET. The most common AEs were grades 1 to 2. Any AE leading to drug withdrawal or dose reduction was 6% and 2%, respectively.

Conclusions: Elacestrant plus everolimus showed a clinically meaningful PFS benefit across clinical/genomic subgroups, irrespective of *ESR1* or *PIK3CA* mutation status. Elacestrant has the potential to become an ET backbone for combinations to inhibit the PAM pathway with everolimus as a promising all-oral treatment.

Introduction

Disease progression in patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) advanced breast cancer (ABC) on first-line standard-of-care (SOC) endocrine therapy (ET) + cyclin-dependent kinase 4/6 (CDK4/6) inhibitor (ET + CDK4/6i) is associated with mechanisms of resistance that affect the efficacy of subsequent therapy (1, 2). Resistance

mechanisms include intrinsic alterations in the phosphatidylinositol 3-kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR; together PAM) or cell-cycle pathways, or *ESR1* mutations representing acquired resistance emerging in up to 50% of patients receiving first-line ET in the advanced setting (3–17). Cross-talk between the ER and PAM pathways is an additional mechanism of ET resistance, providing a rationale for targeting both signaling pathways (18–21).

¹City of Hope Comprehensive Cancer Center, Duarte, California. ²Dana-Farber Cancer Institute, Boston, Massachusetts. ³NYU Langone Health, New York, New York. ⁴Catarina Pesquisa Clínica, Itajaí, Brazil. ⁵Rabin Medical Center, Petah Tikva, Israel. ⁶University of Wisconsin-Madison, Madison, Wisconsin. ⁷AdventHealth Cancer Institute, Orlando, Florida. ⁸Highlands Oncology, Springdale, Arkansas. ⁹Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. ¹⁰Sarah Cannon Research Institute, Nashville, Tennessee. ¹¹Cancer Care Northwest, Spokane, Washington. ¹²Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, Texas. ¹³Istituto Europeo di Oncologia, IRCCS, Milano, Italy. ¹⁴Department of Oncology and Hemato-Oncology, University of Milano, Milano, Italy. ¹⁵International Breast Cancer Center (IBCC), Quironsalud Group, Barcelona, Spain. ¹⁶Hospital Clinic of Barcelona, Barcelona, Spain. ¹⁷Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium. ¹⁸Hospital Clínico Universitario de Valencia, Valencia, Spain. ¹⁹Hospital 12 de Octubre, Madrid, Spain. ²⁰Cedars-Sinai Cancer, Cedars-Sinai Medical Center, Los Angeles,

California. ²¹The University of Texas MD Anderson Cancer Center, Houston, Texas. ²²University of California, Los Angeles, Los Angeles, California. ²³Menarini Group, Florence, Italy. ²⁴Menarini Group, New York, New York. ²⁵University of Texas Health Sciences Center San Antonio, San Antonio, Texas.

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Corresponding Author: Hope S. Rugo, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA 91010. E-mail: Hrugo@coh.org

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Translational Relevance

Disease progression in patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) advanced breast cancer (ABC) receiving first-line endocrine therapy (ET) + cyclin-dependent kinase 4/6 inhibitor is associated with mechanisms of resistance that affect the efficacy of subsequent therapy. Elacestrant is the first single-agent oral selective ER degrader to significantly improve progression-free survival (PFS) versus standard-of-care ET in the *ESR1*-mutated subgroup and overall ER+/HER2- ABC population. This analysis shows that elacestrant plus everolimus provides clinically meaningful PFS irrespective of *ESR1* or *PIK3CA* mutation status, with consistent benefit across clinical subgroups. The pharmacokinetic analysis shows that the everolimus 7.5 mg dose level maintains efficacy while improving tolerability compared with the 10 mg dose level. The safety profile was consistent with everolimus plus standard ET. No bradycardia or photopsia was reported, with low rates of adverse events leading to drug withdrawal or dose reduction. Findings underscore the potential of elacestrant to serve as an ET backbone for combination strategies to inhibit the phosphatidylinositol 3-kinase/AKT/mechanistic target of rapamycin pathway with everolimus.

Following first-line ET + CDK4/6i, treatment options include ET with or without targeted agents, including PAM pathway inhibitors or CDK4/6i (22–26). Everolimus, an mTOR complex 1 (mTORC1) inhibitor, is indicated for the treatment of postmenopausal women with hormone receptor-positive/HER2- ABC in combination with exemestane after progression on a nonsteroidal aromatase inhibitor (27). Fulvestrant may be combined with everolimus in clinical practice (28, 29). Elacestrant is a next-generation, oral selective ER degrader (SERD) that binds to ER α and induces its degradation (30–32).

Results of the phase III EMERALD trial led to multiple regulatory approvals of elacestrant as the first oral SERD for the treatment of postmenopausal women or adult men with ER+/HER2- *ESR1*-mutated ABC or metastatic breast cancer (mBC) with disease progression following at least one line of ET (33, 34). Elacestrant is the first and only single-agent oral SERD to significantly improve progression-free survival (PFS) versus SOC ET in patients with tumors harboring *ESR1* mutations [HR, 0.55; 95% confidence interval (CI), 0.39–0.77; $P = 0.0005$] and in all patients (HR, 0.70; 95% CI, 0.55–0.88; $P = 0.0018$; ref. 35). In patients with *ESR1*-mutated tumors, elacestrant demonstrated a 45% reduction in the risk of progression or death versus SOC ET. An early decline in the Kaplan–Meier PFS curves in both arms indicated ET resistance in some patients, followed by a clear separation of the survival curves, suggesting a treatment benefit favoring elacestrant in patients with more endocrine-sensitive tumors and ER-driven disease.

An exploratory subgroup analysis from EMERALD was performed by prior duration of ET + CDK4/6i (36). In patients with *ESR1*-mutated tumors who received prior ET + CDK4/6i for ≥ 12 months, the median PFS for elacestrant versus SOC ET was 8.6 versus 1.9 months (HR, 0.41; 95% CI, 0.26–0.63), and a clinically meaningful improvement in PFS for elacestrant compared with SOC ET was also consistent across relevant subgroups, suggesting

retained endocrine sensitivity to elacestrant (36). In EMERALD, the safety profile of elacestrant was consistent with SOC ET, showing manageable tolerability, with most adverse events (AEs) of grade 1 and 2 severity and no reported grade 4 treatment-related AEs (35, 36).

In multiple ER+ breast cancer patient-derived xenograft models, including resistance to CDK4/6i, elacestrant in combination with everolimus showed significantly greater tumor growth inhibition than either agent alone (30, 37). The safety and efficacy of elacestrant combined with everolimus from the phase Ib/II ELEVATE trial (clinicaltrials.gov identifier: NCT05563220) in patients with ER+/HER2- ABC who had progressed on prior ET + CDK4/6i are reported herein.

Patients and Methods

Study design

ELEVATE, a global, multicenter, open-label, phase Ib/II umbrella trial enrolling at 99 centers in 14 countries, is evaluating elacestrant in combination with everolimus, alpelisib, capivasertib, abemaciclib, ribociclib, or palbociclib to address different resistance mechanisms. In the phase Ib portion, patients received each combination in stepwise dosing to determine the recommended phase II dose (RP2D) by evaluating the number of patients who experienced dose-limiting toxicities (DLTs) during the first cycle. The phase II portion evaluated the efficacy of elacestrant with various combinations for PFS (see study schema in Supplementary Fig. S1).

The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. The Institutional Review Board of each participating center approved the protocol. All patients provided written informed consent before study entry.

Patients

Eligible patients were at least 18 years of age with histopathologic or cytologic confirmation of ER+/HER2- breast cancer as defined by the American Society of Clinical Oncology/College of American Pathologists (38, 39) and at least 1 not previously irradiated measurable lesion as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and/or at least 1 lytic or mixed (lytic + sclerotic) bone lesion with identifiable soft-tissue components meeting the definition of measurability by RECIST v1.1 evaluable by CT or MRI. Patients must have received 1 or 2 prior lines of ET for ABC or mBC, one of which was in combination with a CDK4/6i. Treatment with prior fulvestrant was allowed. Other inclusion criteria were an Eastern Cooperative Oncology Group performance status of 0 to 1 and adequate bone marrow and organ function. Exclusion criteria included active or newly diagnosed untreated central nervous system metastases, advanced symptomatic visceral spread with a risk of life-threatening complications in the short term, and prior chemotherapy in the advanced setting.

Treatment

In phase Ib, the elacestrant–everolimus combination was evaluated in four different cohorts: elacestrant 258 mg + everolimus 5 mg, elacestrant 345 mg + everolimus 5 mg, elacestrant 345 mg + everolimus 10 mg, and elacestrant 345 mg + everolimus 7.5 mg (Supplementary Fig. S1). Selection of the phase II treatment arm was made by investigators based on eligibility. Patients received the RP2D of elacestrant 345 mg plus everolimus 7.5 mg, both given orally daily. Each treatment cycle was 28 consecutive days. Luteinizing hormone-releasing hormone agonists were required for men

and pre- and perimenopausal women. Treatment was administered until disease progression, death, development of unacceptable toxicity, withdrawal of consent, or other reasons.

Endpoints and assessments

The primary endpoint of phase II was PFS, defined as the time from the date of the first dose of any study treatment to the date of the first documentation of progressive disease (per RECIST v1.1) or death due to any cause, whichever occurred first, regardless of whether the patient withdrew from study treatment. Secondary endpoints included objective response rate (ORR), duration of response (DoR), clinical benefit rate (CBR), PFS, overall survival (OS), and safety (AEs and serious AEs). Investigator-determined tumor assessments were performed during the screening/baseline period [day –28 to cycle 1 day 1 (C1D1)], every 8 weeks after C1D1 during the first year, every 3 months thereafter until disease progression, and as clinically indicated if disease progression was suspected. Tumor imaging assessments included chest (CT with contrast); abdomen, pelvis, and other known or suspected sites of disease (CT with contrast or MRI with contrast); and brain MRI (with or without contrast). A whole-body bone scan using Technetium-99m was performed during screening to establish a baseline (a bone scan performed per local SOC within 6 weeks before C1D1 was acceptable), approximately every 24 weeks (in conjunction with a scheduled tumor assessment visit), and as clinically indicated until disease progression. Responses were confirmed no less than 28 days after the initial response assessment, and stable disease as the best overall response had to occur ≥ 6 weeks from the first dose. *ESR1* and *PIK3CA* mutational status at baseline was evaluated in cell-free nucleic acid at a central laboratory; blood samples were analyzed using the Guardant360 CDx (Guardant Health). Safety assessments included monitoring and recording of all AEs as coded using the Medical Dictionary for Regulatory Activities version 24.1 and severity graded by the NCI Common Terminology Criteria for Adverse Events version 5.0 until 28 days after the last study treatment or until study discontinuation or initiation of subsequent anticancer therapy.

Statistical analysis

The safety analysis dataset, as well as the intention-to-treat (ITT) dataset, included all patients who received at least 1 dose of any of the study drugs. For this trial, the ITT population was the analysis set for PFS and OS. The response-evaluable analysis set included patients in the ITT who had a baseline radiologic tumor assessment and at least one postbaseline radiologic tumor assessment (patients without a target lesion reported at baseline were excluded). This was the primary analysis set for efficacy assessments, except for PFS and OS. The data cutoff was September 15, 2025, with a subsequent data download performed on February 23, 2026.

Baseline demographics and characteristics were descriptively summarized. Descriptive statistics were used for all continuous measures, and percentages and frequencies were used for all categorical measures. ORR and CBR were calculated with the two-sided 95% CI using the Clopper–Pearson method (exact CI for a binomial proportion; ref. 40). Time-to-event endpoints for PFS were reported using Kaplan–Meier estimates along with the two-sided 95% CIs calculated according to Brookmeyer and Crowley using a linear transformation. The phase Ib portion of the study was designed to select the RP2D for the elacestrant–everolimus combination, defined as ≤ 1 patient experiencing a DLT among 6 DLT-evaluable patients per cohort. If additional cohorts or

intermediate dose levels were needed to determine the RP2D, more patients could be enrolled at the recommendation of the study steering committee. For the phase II portion of the study, a sample size of 50 patients receiving the elacestrant–everolimus combination, followed for at least 6 months, was estimated to provide greater than 85% power to detect a HR of 0.55 relative to the literature-based estimate, at an alpha level of 0.05 (41–44). Data analysis was performed using SAS Enterprise Guide 8.3 (SAS Institute, Inc.; RRID:SCR_008567).

Results

Patients and treatment exposure

Overall, a total of 73 patients were enrolled in both phase I and II portions of the elacestrant plus everolimus combination; 52% ($n = 38$) were recruited in the United States, 42% ($n = 31$) were recruited in Europe (EU), and 6% ($n = 4$) were recruited from the rest of the world (RoW). Out of 23 patients in the phase I cohort that led to the characterization of safety and identification of the RP2D for the combination, 87% were enrolled in the United States, 9% in the EU, and 4% in RoW.

In the phase Ib cohort that received elacestrant 345 mg + everolimus 10 mg ($n = 4$), two patients experienced grade 3 toxicity (one with pharyngeal mucositis and diarrhea and one with mucositis). No DLTs were observed at the elacestrant 345 mg + everolimus 7.5 mg dose level ($n = 7$), and pharmacokinetic (PK) analyses of these doses when coadministered showed no impact on exposure (AUC, maximum concentration, trough concentration) compared with single-agent administration (Supplementary Fig. S2). Everolimus exposure was similar for both 7.5 and 10 mg doses (Supplementary Fig. S3). Based on the totality of safety, tolerability, and PK data of elacestrant combined with everolimus 7.5 or 10 mg, the optimal dose of elacestrant 345 mg + everolimus 7.5 mg was determined to be the RP2D. Across all phase Ib dose cohorts, preliminary efficacy data showed a median PFS of 8.3 months with the elacestrant–everolimus combination and a safety profile consistent with everolimus + SOC ET.

The phase II portion of the elacestrant–everolimus combination has been completed, enrolling 50 patients across 33 centers in 10 countries between April and August 2024; of these participants, 58% were located in the EU, 36% were located in the United States, and 6% were located in the RoW. Baseline characteristics are summarized in **Table 1**. Among all patients, the median age was 58 years; 100% had prior CDK4/6i; 70% had one line of prior ET for ABC; 72% had visceral metastasis; 20% had primary endocrine resistance; 42% had *ESR1* mutations; and 50% had *PIK3CA* mutations. Of all patients, 50% received prior fulvestrant. Prior CDK4/6i exposure in the metastatic setting included ribociclib (50%), palbociclib (44%), and abemaciclib (22%). The representativeness of study participants is shown in Supplementary Table S1.

Steady-state trough concentrations of elacestrant 345 mg and everolimus 7.5 mg were comparable between US and ex-US patients, regardless of *ESR1* mutational status (Supplementary Fig. S4). Moreover, exposures in both subgroups exceeded the efficacy thresholds established for elacestrant monotherapy (based on the ER target engagement threshold from study RAD1901-106; ref. 44) and for everolimus (based on prior exposure–response analyses; Supplementary Fig. S2), suggesting that geographic region or *ESR1* mutation status did not meaningfully influence the PK profile of either agent when administered in combination.

Table 1. Baseline demographic and patient characteristics.

Characteristic	Elaacestrant–everolimus	
	Phase Ib (N = 23)	Phase II (N = 50)
Median age, years (range)	64 (38–76)	58 (30–83)
Female sex, n (%)	23 (100)	50 (100)
Race, n (%)		
White	19 (83)	42 (84)
Asian	3 (13)	2 (4)
Black	1 (4)	2 (4)
Other or not reported	0	4 (8)
ECOG performance status, n (%)		
0	15 (65)	26 (52)
1	8 (35)	24 (48)
Postmenopausal status, n (%)	20 (87)	40 (80)
Pre- or perimenopausal status, n (%)	3 (13)	10 (20)
Median number of prior therapies for ABC, n (range)	2 (1–3)	1 (1–4)
Number of prior lines of ET for ABC, n (%)		
0	1 (4)	0
1	14 (61)	35 (70)
2	8 (35)	14 (28)
≥3	0	1 (2)
Prior treatments, n (%)		
CDK4/6i	23 (100)	50 (100)
Ribociclib	6 (26)	25 (50)
Palbociclib	16 (70)	22 (44)
Abemaciclib	6 (26)	11 (22)
Chemotherapy in ABC	0	0
Fulvestrant in ABC	11 (48)	25 (50)
Visceral metastasis, n (%)	18 (78)	36 (72)
Liver	12 (52)	26 (52)
Lung	5 (22)	14 (28)
Brain	1 (4)	1 (2)
Bone	18 (78)	39 (78)
Nonvisceral disease, n (%)	5 (22)	14 (28)
Primary endocrine resistance, n (%)	5 (22)	10 (20)
<i>ESR1</i> mutation, n (%)	10 (43)	21 (42)
<i>PIK3CA</i> mutation, n (%)	6 (26)	25 (50)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Efficacy

The median follow-up was 4.1 months (95% CI, 3.6–8.3), with 9 (18%) patients still on treatment. The overall median PFS was 8.3 months (95% CI, 4–10.2; **Fig. 1**).

The elacestrant–everolimus combination demonstrated a consistent PFS benefit across relevant subgroups (**Table 2**). In genomic subgroups, the median PFS was 8.3 months in *ESR1*-mutated tumors ($n = 21$; 95% CI, 3.5–12.9), 9 months in *ESR1* wild-type ($n = 27$; 95% CI, 4.2–12.7), 8.3 months in *PIK3CA*-mutated tumors ($n = 25$; 95% CI, 3.6–10.2), and 9.4 months in *PIK3CA* wild-type [$n = 23$; 95% CI, 4–not reached (NR)]. In clinical subgroups, the median PFS in patients with visceral disease was 7.7 months ($n = 36$; 95% CI, 3.6–9.4), 12 months in those with no visceral disease ($n = 14$; 95% CI, 4–NR), 8.3 months in those with no prior fulvestrant ($n = 25$; 95% CI, 4.2–12.9), 5.6 months in those with prior fulvestrant ($n = 25$; 95% CI, 3.6–10.1), 8.3 months in those without primary endocrine resistance ($n = 40$; 95% CI, 4–12.9), 9 months in postmenopausal patients ($n = 40$; 95% CI, 4–12), and 7.7 months in pre-/perimenopausal patients ($n = 10$; 95% CI, 3.6–NR).

In patients with measurable disease ($n = 41$), an 82.9% disease control rate (proportion of patients who achieve a confirmed complete response, partial response, or stable disease) was observed, with a CBR at 24 weeks of 43.9% (95% CI, 28.5–60.3). A 19.5% ORR (95% CI, 8.8–34.9) was also observed with an 8.5-month median DoR (95% CI, 5.65–NR; **Table 3**).

Safety

The most common treatment-emergent AEs with elacestrant–everolimus were mostly grades 1 to 2 (**Table 4**) and were consistent with the known safety profiles of everolimus + SOC ET. The most common AEs included nausea ($n = 29$, 58%), diarrhea ($n = 23$, 46%), fatigue ($n = 22$, 44%), vomiting ($n = 21$, 42%), and stomatitis ($n = 20$, 40%). The most common grade ≥3 AEs included anemia ($n = 4$, 8%), fatigue ($n = 3$, 6%), diarrhea ($n = 3$, 6%), and neutropenia ($n = 3$, 6%). No bradycardia or photopsia were reported, and no new safety signals were observed. Any treatment-emergent AEs leading to drug withdrawal or dose reduction of either drug were 6% and 2%, respectively.

Discussion

Results from the phase Ib portion of the ELEVATE trial identified elacestrant 345 mg + everolimus 7.5 mg as the optimal dose, and phase II findings showed a clinically meaningful PFS of 8.3 months with this combination in patients with ER+/HER2– ABC following disease progression on prior ET + CDK4/6i.

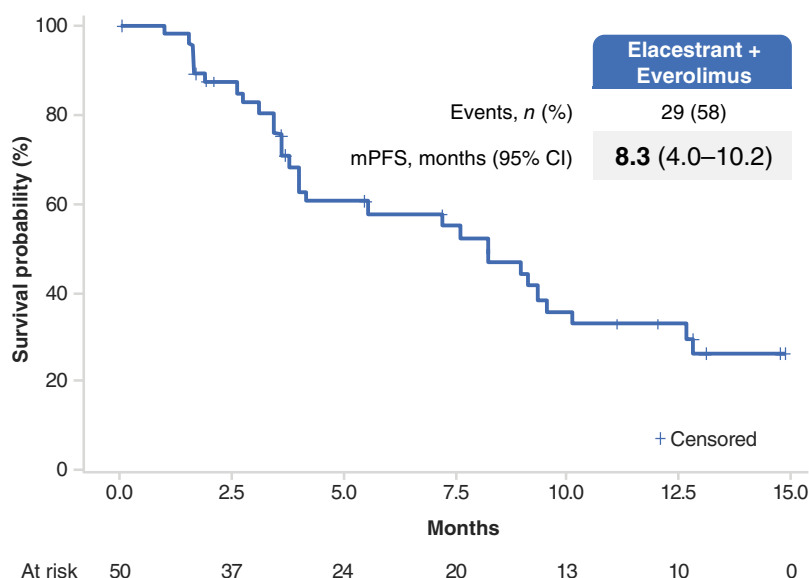
In this pretreated population with prior ET + CDK4/6i exposure (50% prior ribociclib, 44% prior palbociclib, 22% prior abemaciclib, and prior fulvestrant 50%) and visceral metastases (72%), efficacy with elacestrant–everolimus did not seem to be affected regardless of *ESR1* or *PIK3CA* mutation status and showed a consistent PFS benefit across clinical/genomic subgroups.

Unlike other recent studies showing improved outcomes with ET-targeted combination regimens, ELEVATE tested a combination aimed at simultaneously blocking the ER and the PAM pathway in a broader, less-selected patient population. The EMBER-3 trial reported a median PFS of 9.4 months for imlunestrant + abemaciclib; however, the study population was heterogeneous, including 30% of patients who received the combination as first-line treatment, 65% with prior exposure to CDK4/6i, and 32% with *ESR1*-mutated tumors, while excluding patients who had received prior chemotherapy or fulvestrant (45). The phase III evERA trial of giredestrant + everolimus in patients with ER+/HER2– ABC after ET + CDK4/6i reported a median PFS of 8.77 months in the ITT population, which was enriched for patients with a detectable *ESR1* mutation at baseline (55%) and included only patients who received ≥6 months of ET + CDK4/6i in the advanced setting (11). In the context of these data, the median PFS of 8.3 months observed with elacestrant–everolimus is clinically relevant, particularly given the enrollment of patients with primary endocrine resistance, 50% of patients with prior exposure to fulvestrant, and 58% of patients with tumors without detectable *ESR1* mutations.

When evaluating patients by *ESR1* mutation status, the evERA trial showed that giredestrant + everolimus was associated with a median PFS of 9.99 months in the *ESR1*-mutated population relative to 5.72 months observed in those without detectable *ESR1* mutations (11). In a French prospective, real-world evidence study of fulvestrant + everolimus after prior CDK4/6i, median PFS was 6.8 months in the overall population, with no significant difference observed in patients harboring *ESR1* mutations ($P = 0.15$; ref. 29).

Figure 1.

PFS. Kaplan-Meier estimates of PFS are shown for patients treated with elaprestrant + everolimus in the phase II portion of the study. Bold text indicates mPFS. mPFS, median PFS.



Data from our analysis (elaprestrant-everolimus) in subgroups based on *ESR1* mutation status showed a consistent median PFS of 8.3 months in patients with *ESR1*-mutated tumors and 9 months in those with *ESR1* wild-type tumors, including those with primary endocrine resistance. Additional investigations of elaprestrant in combination with everolimus in patients with ER+/HER2- ABC with *ESR1*-mutated tumors are ongoing in the registrational phase III ADELA trial (clinicaltrials.gov identifier: NCT06382948).

Other trials and subgroup analyses have evaluated PAM pathway inhibitors in patients with or without PI3K pathway alterations after prior CDK4/6i exposure. A subgroup analysis of the ITT population in eVERA showed a median PFS of 7.98 months (PI3K pathway alteration detected) and 9.26 months (PI3K pathway alteration not detected; ref. 46). In the *ESR1*-mutated population, the median PFS was 10.15 months (PI3K pathway alteration detected) and 9.99 months (PI3K pathway alteration not detected; ref. 46). A subgroup analysis from the CAPItello-291 trial in patients with prior CDK4/6i exposure and AKT pathway-altered tumors

(determined by next-generation sequencing from tumor tissue) showed a median PFS of 5.5 months with capivasertib + fulvestrant (47, 48). In an exploratory ctDNA analysis restricted to only patients who received first-line ET + CDK4/6i and no prior chemotherapy for advanced disease, the combination of capivasertib + fulvestrant showed a median PFS of 5.6 months in all patients, 7 months in AKT pathway-altered tumors, 7 months in coexisting *ESR1*-mutated and AKT pathway-altered tumors, 7.4 months in AKT pathway-altered tumors (no *ESR1* mutation detected), and 5.5 months in tumors in which AKT pathway alteration was not detected (49). In the FINER trial, ipatasertib + fulvestrant achieved a median PFS of 5.5 months in patients with PI3K/AKT/PTEN alterations and 3.7 months in those with *ESR1*-mutated tumors (50). Our analysis (elaprestrant-everolimus) showed a consistent PFS benefit of 8.3 months in patients with *PIK3CA*-mutated tumors.

In the VIKTORIA-01 trial, patients with *PIK3CA* wild-type tumors who received prior CDK4/6i had a median PFS of 9.3 months with the gedatolisib + palbociclib + fulvestrant triplet and 7.4 months with the gedatolisib + fulvestrant doublet (51). Reported data with fulvestrant + everolimus after prior CDK4/6i treatment

Table 2. Phase II median PFS in all patients and subgroups after prior ET + CDK4/6i.

Subgroup	n (%)	Elaprestrant + everolimus
		mPFS, months (95% CI)
All patients	50 (100)	8.3 (4-10.2)
<i>ESR1</i> mut	21 (42)	8.3 (3.5-12.9)
<i>ESR1</i> wt	27 (54)	9 (4.2-12.7)
<i>PIK3CA</i> mut	25 (50)	8.3 (3.6-10.2)
<i>PIK3CA</i> wt	23 (46)	9.4 (4-NR)
No prior fulvestrant	25 (50)	8.3 (4.2-12.9)
No primary endocrine resistance	40 (80)	8.3 (4-12.9)
Visceral disease	36 (72)	7.7 (3.6-9.4)
Nonvisceral disease ^a	14 (28)	12 (4-NR)
Postmenopausal status ^a	40 (80)	9 (4-12)
Pre/perimenopausal status ^a	10 (20)	7.7 (3.6-NR)

Abbreviations: mPFS, median PFS; mut, mutation; wt, wild-type.

^aData were downloaded on February 23, 2026.

Table 3. Phase II tumor response in patients with measurable disease.

Response	Elaprestrant-everolimus (N = 41)
Best overall response, n (%) ^a	
Complete response	1 (2.4)
Partial response	7 (17.1)
Stable disease	26 (63.4)
Progressive disease	6 (14.6)
ORR, n (%; 95% CI)	8 (19.5; 8.8-34.9)
Disease control rate, n (%)	34 (82.9)
CBR at 16 weeks, n (%; 95% CI)	19 (46.3; 30.7-62.6)
CBR at 24 weeks, n (%; 95% CI)	18 (43.9; 28.5-60.3)
Median DoR, months (95% CI)	8.54 (5.7-NR)

^aInvestigator-assessed in patients with ER+/HER2- ABC who had measurable disease (i.e., at least 1 target lesion) at baseline and at least 1 postbaseline assessment using RECIST. One patient was not evaluable for response.

Table 4. Phase II most common ($\geq 10\%$) treatment-emergent AEs.

Preferred term, <i>n</i> (%)	Any grade (<i>N</i> = 50)	Grade ≥ 3 (<i>N</i> = 50)
Nausea	29 (58)	2 (4)
Diarrhea	23 (46)	3 (6)
Fatigue	22 (44)	3 (6)
Vomiting	21 (42)	1 (2)
Stomatitis	20 (40)	1 (2)
Hypercholesterolemia	16 (32)	2 (4)
Abdominal pain	15 (30)	1 (2)
Rash	14 (28)	2 (4)
Anemia	13 (26)	4 (8)
Dysgeusia	12 (24)	0
Mucosal inflammation	12 (24)	1 (2)
AST increase	10 (20)	2 (4)
Headache	10 (20)	1 (2)
Hyperglycemia	10 (20)	2 (4)
Thrombocytopenia	10 (20)	1 (2)
Arthralgia	9 (18)	0
Constipation	9 (18)	0
Decreased appetite	9 (18)	0
Pneumonitis	9 (18)	1 (2)
ALT increase	8 (16)	1 (2)
Cough	8 (16)	0
Dyspnea	8 (16)	1 (2)
Hypertriglyceridemia	8 (16)	2 (4)
Neutropenia	8 (16)	3 (6)
Back pain	7 (14)	0
Dyspepsia	6 (12)	0
Insomnia	6 (12)	0
Leukopenia	6 (12)	2 (4)
Myalgia	6 (12)	0
Pain in extremity	6 (12)	0
Pyrexia	6 (12)	0
Dizziness	5 (10)	0
Dry skin	5 (10)	0
Edema peripheral	5 (10)	0
Gastroesophageal reflux disease	5 (10)	0
Hypokalemia	5 (10)	0
Hypophosphatemia	5 (10)	0
Oropharyngeal pain	5 (10)	0
Urinary tract infection	5 (10)	1 (2)
Weight decreased	5 (10)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

showed a median PFS of 3.4 months in patients with *PIK3CA*-mutated tumors (29). Our analysis (elacestrant–everolimus) showed a consistent PFS benefit regardless of *PIK3CA* mutation status; the median PFS was 9.4 months in patients with *PIK3CA* wild-type tumors, irrespective of the length of prior exposure to ET + CDK4/6i. In a subgroup analysis of the EMERALD study, in an endocrine-sensitive patient population (prior ET + CDK4/6i >12 months) with *ESR1*-mutated and *PIK3CA* wild-type tumors, the median PFS was 9 months with elacestrant monotherapy.

The findings reported in the ELEVATE trial further support the mechanistic rationale to combine elacestrant with everolimus, representing a dual-pathway blockade strategy that targets ER signaling at the receptor level while inhibiting downstream resistance pathways. Elacestrant functions as a broad-spectrum ER inhibitor, degrading the

ER regardless of *ESR1* mutation status, overcoming a key limitation of fulvestrant, which has reduced activity in *ESR1*-mutated tumors. Everolimus inhibits mTORC1 downstream of PI3K/AKT/PTEN, suppressing proliferative escape mechanisms independently of PI3K pathway mutations (*PIK3CA* mutations, *AKT* alterations, or *PTEN* loss of function; refs. 52, 53). The mutation-agnostic PFS benefit in this trial observed with elacestrant–everolimus across genomic subgroups supports the scientific rationale for evaluating the combination in a broader, unselected patient population following CDK4/6i-based therapy, rather than in genomically restricted subgroups.

Whether the combination of an oral SERD with capivasertib will offer superior PAM pathway blockade in specific genomic subgroups remains an important unanswered question warranting further investigation. Preliminary phase Ib data from ELEVATE evaluating elacestrant + capivasertib showed a clinically meaningful PFS of 11.3 months in patients with *PIK3CA/AKT1/PTEN*-altered tumors and 10.9 months in those with coexisting *ESR1* and *PIK3CA* mutations (54).

The safety profile of the elacestrant–everolimus phase II combination was manageable, mostly grade 1 or 2 in severity, and consistent with the known safety profiles of everolimus + SOC ET. The use of prophylactic dexamethasone mouthwash was encouraged for the prevention of mucositis; the rates of stomatitis were 40% any grade and 2% grades 3 to 4. In the evERA trial, the reported rates of stomatitis were 47% any grade and 3% grades 3 to 4, including dexamethasone mouthwash prophylaxis (11, 46). Notably, the low rate of stomatitis was likely related to the 7.5 mg dose of everolimus employed in this trial. In addition, the evERA trial reported grade 1 to 2 bradycardia ($n = 7$; 3.8%) in patients who received giredestrant–everolimus (11, 46); no bradycardia was reported with the elacestrant–everolimus combination (11, 46).

Any treatment-emergent AE leading to elacestrant–everolimus drug withdrawal or dose reduction was 6% and 2%, respectively. In the evERA trial, the giredestrant–everolimus group reported a 31% everolimus dose reduction due to AEs, and AEs leading to treatment discontinuation were 8.2% with giredestrant, 17% with everolimus, and 17% with any (11). Considering that a 7.5 mg dose of everolimus was used in this trial, the higher dose reduction and discontinuation rates observed in evERA may be attributable to the 10 mg dose of everolimus used in that trial.

Limitations of this study are related to the single-arm, open-label, phase II trial design ($N = 50$), which limits the statistical power to detect differences in efficacy or safety across subgroups and precludes definitive conclusions. Without a randomized comparator arm, all cross-trial comparisons with other ET–everolimus combinations remain indirect and should be interpreted with caution, as differences in patient populations, eligibility criteria, genomic enrichment strategies, prior treatment exposure, and definitions of endocrine resistance can meaningfully influence outcomes. A strength of this trial is the meaningful data ELEVATE provides on the clinically relevant treatment combination of elacestrant–everolimus for both *ESR1*-mutant and *ESR1* wild-type ABC, irrespective of the *PIK3CA* mutation status.

In conclusion, elacestrant in combination with everolimus showed a clinically meaningful PFS irrespective of *ESR1* or *PIK3CA* mutation status in patients with ER+/HER2– ABC after progressive disease on prior ET + CDK4/6i. The elacestrant–everolimus combination showed a consistent PFS benefit across clinical/genomic subgroups. The safety profile is consistent with the everolimus + SOC ET; no bradycardia or photopsia was reported. Any AE leading to drug withdrawal or dose reduction was low. Elacestrant has the

potential to become an ET backbone for combination strategies to inhibit the PAM pathway with everolimus as a promising all-oral treatment approach for patients after ET + CDK4/6i.

Data Availability

Data that underlie the results reported in a published article may be requested for products and the relevant indications that have been authorized by the regulatory authorities in the EU/the United States (or, if not, data can be requested for up to 6 years after publication). The Menarini Group will review requests individually to determine whether (i) the requests are legitimate and relevant and meet sound scientific research principles, (ii) they are within the scope of the participants' informed consent, and (iii) they are compliant with any applicable laws and regulations and with any contractual relationships that the Menarini Group, its affiliates, and partners have in place with respect to the study and/or the relevant product. Before data are made available, requestors must sign a data use agreement covering obligations such as compliance with privacy laws, secure handling of data within an approved analysis environment, nonattempted reidentification, and appropriate acknowledgment of the data source. Requests will generally be acknowledged within a reasonable time frame, and if approved, data access will be provided through a secure platform rather than direct download. Proposals should be directed to medicalinformation@menarinistemline.com.

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Authors' Contributions

H.S. Rugo: Conceptualization, formal analysis, investigation, writing–review and editing. **S.M. Tolaney:** Investigation, writing–review and editing. **N. Chan:** Investigation, writing–review and editing. **G. Borges:** Investigation, writing–review and editing. **R. Yerushalmi:** Investigation, writing–review and editing. **M.N. Sharifi:** Investigation, writing–review and editing. **W. McHayleh:** Investigation, writing–review and editing. **T. Beck:** Investigation, writing–review and editing. **N. Vidula:** Investigation, writing–review and editing. **E. Hamilton:** Investigation, writing–review and editing. **K.J. Rinn:** Investigation, writing–review and editing. **J. O'Shaughnessy:** Investigation, writing–review and editing. **G. Curigliano:** Investigation, writing–review and editing. **J. Cortés:** Investigation, writing–review and editing. **I. Garcia-Fructuoso:** Investigation, writing–review and editing. **P. Aftimos:** Investigation, writing–review and editing. **B. Bermejo de las Heras:** Investigation, writing–review and editing. **P. Tolosa:** Investigation, writing–review and editing. **Y. Yuan:** Investigation, writing–review and editing. **V. Valero:** Investigation, writing–review and editing. **M. Lipsyc-Sharf:** Investigation, writing–review and editing. **P. Muñoz Romero:** Resources, data curation, formal analysis, validation, writing–original draft, writing–review and editing. **F. Koraichi Auriol:** Resources, data curation, formal analysis, validation, methodology, writing–original draft. **A. Paoli:** Investigation, writing–review and

editing. **J.A. Crozier:** Writing-review and editing. **T. Wasserman:** Conceptualization, data curation, formal analysis, methodology, writing-original draft, writing-review and editing. **V. Kaklamani:** Conceptualization, investigation, writing-review and editing.

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