

EMERALD: Phase III trial of elacestrant (RAD1901) vs endocrine therapy for previously treated ER+ advanced breast cancer

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Elaeestrant is a novel, nonsteroidal, orally bioavailable selective estrogen receptor degrader (SERD) that has demonstrated activity in patients with estrogen receptor (ER)-positive/HER2-negative breast cancer previously treated with endocrine therapies including fulvestrant and/or CDK 4/6 inhibitor therapy, and in those with *ESR1* mutations (*ESR1-mut*) known to confer endocrine resistance. Herein, we describe the design and methodology of EMERALD, an international, multicenter, randomized, open-label, active-controlled, Phase III clinical study comparing the efficacy and safety of elaeestrant to standard-of-care endocrine monotherapy treatment (fulvestrant or an aromatase inhibitor, per investigator's choice) in patients with ER-positive/HER2-negative advanced breast cancer. Primary end points are progression-free survival in *ESR1-mut* patients and in all patients (NCT03778931; EudraCT 2018-002990-24).

Lay abstract: EMERALD is an international, randomized, open-label, active-controlled, Phase III clinical study comparing the efficacy and safety of an investigational oral hormone therapy, elaeestrant (RAD1901), to the standard-of-care hormone therapy options of fulvestrant or an aromatase inhibitor in patients with advanced or metastatic breast cancer that expresses the estrogen receptor (ER-positive) and does not express HER2. The objective of the study is to determine if elaeestrant prolongs time until disease progresses in all patients and in patients who have developed a tumor-specific ER mutation that might reduce response to standard hormonal treatments (NCT03778931).

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Keywords: aromatase inhibitor • breast cancer • elaeestrant • endocrine therapy • *ESR1* mutation • estrogen receptor (ER)-positive • fulvestrant • RAD1901 • selective estrogen receptor degrader (SERD)

Breast cancer continues to be the leading malignancy among women with over 260,000 cases diagnosed annually in the USA and 2.1 million cases globally [1,2]. Approximately 75% of all breast cancers are estrogen receptor (ER)-positive and HER2-negative (ER+/HER2-) [3]. Among postmenopausal women with locally advanced or metastatic ER+/HER2- breast cancer, endocrine therapy remains the cornerstone of treatment [4–6].

Endocrine therapy regimens most commonly consist of an agent targeting peripheral estrogen production or the ER itself [4,5]. Aromatase inhibitors (AI; e.g., letrozole, anastrozole and exemestane) decrease peripheral estrogen synthesis through inhibition of aromatase, the enzyme that catalyzes the conversion of androgens to estrogens [7,8]. Agents that target the ER directly include selective ER modulators (SERMs; e.g., tamoxifen and toremifene) and selective ER degraders (SERDs; e.g., fulvestrant). SERMs reduce ER activity through competitive ER blockade and effects on ER transcriptional machinery [8,9]. SERDs inhibit the ER by creating an unstable SERD-ER protein

complex that can be targeted for degradation via proteasome degradation pathways [10]. Currently, fulvestrant is the only marketed SERD.

Endocrine resistance in advanced ER+ breast cancers remains a clinical challenge. Recent advancements have demonstrated emergence of acquired mutations following AI therapy in the ligand-binding domain of estrogen receptor gene α (*ESR1*), which encodes the ER [11]. These mutations can lead to ligand (estrogen)-independent ER activation. The activity of fulvestrant or AIs in the context of *ESR1* mutation (*ESR1*-mut) has not been fully characterized due to limited and retrospective-only data sets. In a prespecified retrospective analysis of the Phase III SoFEA and PALOMA-3 trials, following AI therapy fulvestrant demonstrated a similar level of activity regardless of patients' tumor *ESR1* mutational status [11]. However, in patients having received multiple lines of prior endocrine therapy for ER+ advanced breast cancer, the objective response rate (ORR) observed with fulvestrant is generally $\leq 10\%$ [12–14], and recent data examining the *ESR1* status of fulvestrant-treated patients in the PALOMA-3 trial demonstrated the selection of the Y537S *ESR1*-mut after treatment [15]. These data, along with fulvestrant's low oral bioavailability requiring intramuscular administration, suggest the need for an oral SERD with improved properties.

In addition to endocrine therapies, newer targeted agents, such as CDK 4/6 inhibitors (e.g., palbociclib, abemaciclib and ribociclib), can inhibit pathways related to cellular proliferation in ER+ breast cancer. Combinations of CDK4/6 inhibitors and endocrine therapies (AI or fulvestrant) have been recently shown to delay breast cancer progression beyond that achieved with endocrine monotherapy, forming the basis of these combinations as standard-of-care (SoC) first-line regimens [16–18]. While these combination regimens significantly increase progression-free survival (PFS), patients eventually relapse and will require additional therapies in the second-line and beyond setting. As such, development of novel SERDs with oral administration, improved bioavailability and the potential ability to overcome acquired resistance are of interest for patients with breast cancer.

Elacestrant

Elacestrant is a novel, nonsteroidal, orally bioavailable SERD (Figure 1) that has demonstrated dose-dependent ER degradation and inhibition of estradiol-dependent induction of ER target gene transcription and cell proliferation in multiple ER+ breast cancer cell lines [19–21]. In the *in vivo* setting, elacestrant inhibited estradiol-stimulated tumor growth in the ER+ MCF-7 cell line xenograft model, as well as multiple patient-derived xenograft models derived from heavily-pretreated patients [19–21]. Finally, elacestrant demonstrated antitumor activity in models resistant to CDK4/6 inhibitors and fulvestrant, including those harboring the commonly detected *ESR1* mutations Y537S and D538G [19,22,23].

The EMERALD trial

Herein, we describe the design and methodology of the EMERALD trial, an international, multicenter, randomized, open-label, active-controlled, Phase III clinical study comparing the efficacy and safety of elacestrant to the SoC endocrine treatment options of either fulvestrant or an AI in men and postmenopausal women with ER+/HER2- advanced or metastatic breast cancer with or without *ESR1* mutations (NCT03778931; EudraCT 2018-002990-24).

Background & rationale

The development of resistance to fulvestrant, AIs and CDK4/6 inhibitors demonstrates a significant unmet medical need for a potent oral agent to treat ER+/HER2- advanced breast cancer. In early clinical trials, elacestrant demonstrated antitumor activity in patients with ER+ breast cancer that was heavily pretreated, including those whose tumors harbored *ESR1*-mut. Preliminary analysis of a Phase I trial (RAD1901-005) demonstrated antitumor activity of elacestrant 400 mg once daily in 40 heavily pretreated patients with ER+/HER2- advanced/metastatic breast cancer who had received a median of three prior therapies, including prior treatment with a CDK4/6 inhibitor (n = 16; 40%), and *ESR1*-mut detected by circulating tumor DNA (ctDNA; n = 20; 50%) [25]. The overall response rate was 27.3% in 22 patients evaluable for response, and median PFS was 5.4 months, which compares favorably to response rates of $\leq 10\%$ and median PFS of approximately 5 months with standard endocrine monotherapies given in earlier lines of therapy (i.e., second or third line) in patients with ER+/HER2- advanced or metastatic breast cancer [12–14,26]. Furthermore, responses or clinical benefit with elacestrant was observed in patients with prior CDK4/6 inhibitor therapy, and in patients with *ESR1*-mut tumors as well as those with *ESR1* mutation not detected (*ESR1*-mut-nd; includes *ESR1* wild-type as well as mutations below limit of detection of the

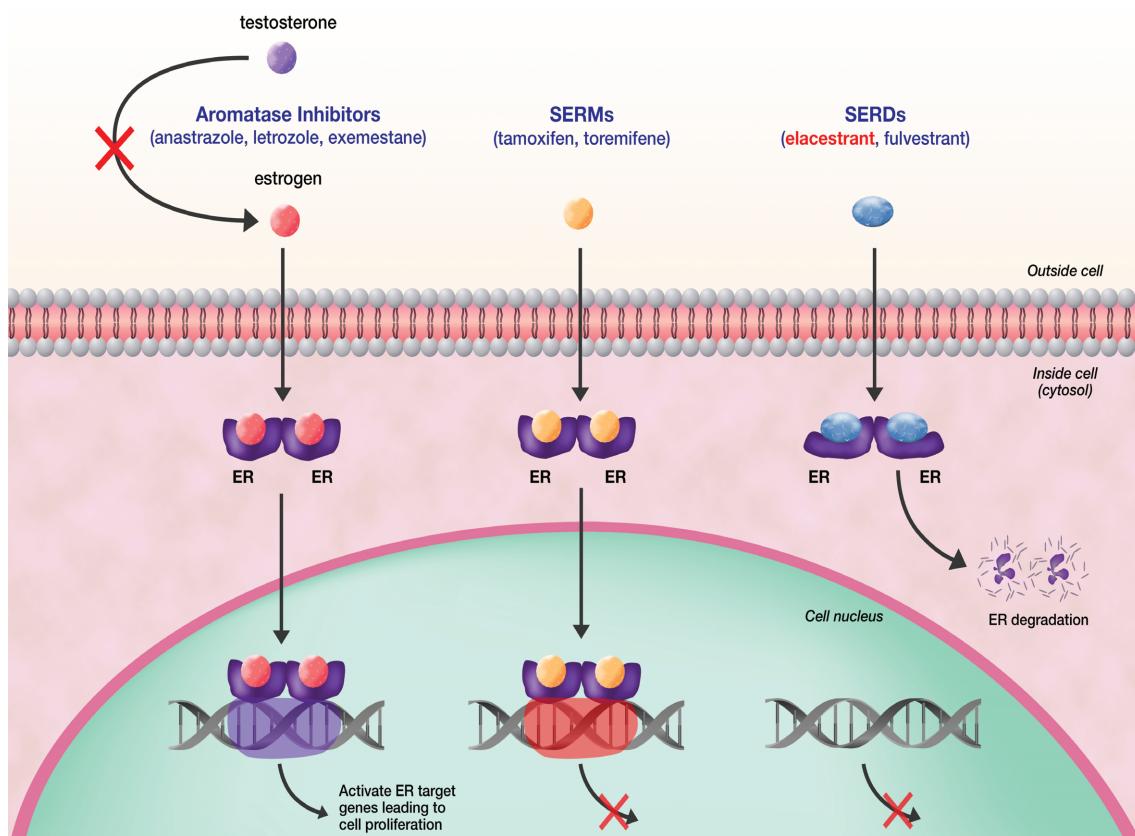


Figure 1. Elacestrant mechanism of action.

ER: Estrogen receptor; SERD: Selective estrogen receptor degrader; SERM: Selective estrogen receptor modulator. Adapted with permission from [24].

assay) [25]. Grade 1–2 nausea (43%) was the only adverse event reported in ≥20% patients treated with elacestrant 400 mg tablet daily.

Based on these promising Phase I data, the EMERALD study was designed to evaluate safety and efficacy of elacestrant in patients who have progressed following first- or second-line treatment with a CDK4/6 inhibitor/endocrine therapy combination regimen, and to further assess efficacy in patients who have developed *ESR1* mutations, as well as the overall population.

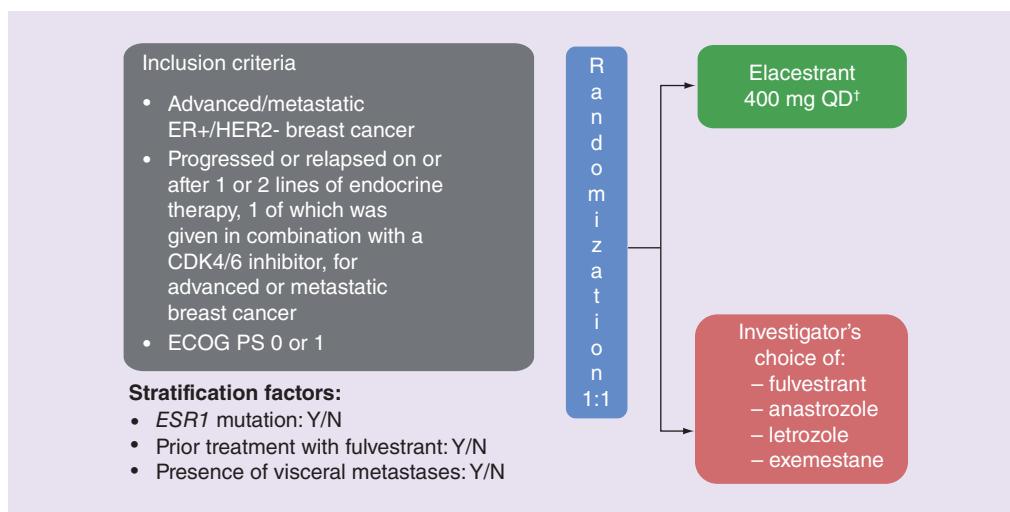
Design

Study design

This trial consists of a screening phase, active treatment phase (Figure 2) and a follow-up phase including safety and survival follow-up periods. The EMERALD study protocol and relevant supplementary information will be approved by the institutional review board at each participating site. The trial is performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council of Harmonisation/Good Clinical Practice and applicable regulatory requirements. Written informed consent will be obtained from each trial participant.

Eligibility criteria

Eligible patients will meet the following key inclusion criteria: men and postmenopausal women ≥18 years old with a histologically or cytologically proven diagnosis of ER+/HER2- adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease. Postmenopausal is defined as: documented bilateral surgical oophorectomy; age ≥60 years with amenorrhea ≥1 year since last menses; age <60 years with amenorrhea ≥1 year since last menses with no alternative pathological or physiological cause (including ongoing or recent chemotherapy, treatment with tamoxifen or toremifene, or a gonadotropin-releasing hormone agonist), and serum estradiol and

**Figure 2. EMERALD study design.**

†Protocol-defined dose reductions will be permitted.

ECOG PS: Eastern Cooperative Oncology Group performance status; ER: Estrogen receptor; ESR1: Estrogen receptor gene α ; QD: Daily.

follicle stimulating hormone (FSH) level within the laboratory reference range for postmenopausal women; or age <60 years with tamoxifen or toremifene therapy within the last 12 months, with documentation of 12 months of amenorrhea prior to tamoxifen or toremifene therapy and serum estradiol and FSH levels within the laboratory reference range for postmenopausal women.

The breast cancer must have progressed during or within 28 days after treatment with at least one and no more than two prior lines of endocrine therapy for advanced or metastatic disease. Prior therapy must have included a CDK4/6 inhibitor in combination with an AI or fulvestrant. No more than one chemotherapeutic regimen in the advanced/metastatic setting is allowed. Patients must have measurable disease per response evaluation criteria in solid tumors (RECIST) v1.1 [27] or evaluable bone-only disease, Eastern Cooperative Oncology Group performance status 0–1 and adequate organ function. Hormonal monotherapy with one of the SoC drugs (fulvestrant, anastrozole, letrozole and exemestane) must be an appropriate treatment option.

ER+ and HER2- status are to be confirmed per local laboratory testing. ER-positivity is defined as $\geq 1\%$ staining by immunohistochemistry (IHC) [28], with or without progesterone receptor positivity. HER2-negativity is defined as an immunohistochemistry result of 0 or 1+ for cellular membrane protein expression or an *in situ* hybridization negative result, as per American Society of Clinical Oncology/College of American Pathologists guidelines [29].

Key exclusion criteria include presence of symptomatic metastatic visceral disease; history of endometrial intraepithelial neoplasia (in patients with an intact uterus); other malignancy within 5 years before enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma *in situ* of the cervix; and any of the following within 6 months prior to enrollment: myocardial infarction, severe/unstable angina, ongoing grade ≥ 2 cardiac dysrhythmias, prolonged QT corrected by Fridericia's formula (QTcF) grade ≥ 2 , uncontrolled atrial fibrillation of any grade, coronary/peripheral artery bypass graft, heart failure of New York Heart Association Class II or greater, cerebrovascular accident including transient ischemic attack and coagulopathy (thrombosis).

Planned sample size

Among all patients (ESR1-mut and ESR1-mut-nd), a total of approximately 340 PFS events will provide 92% power to detect a hazard ratio (HR) of 0.667 at the two-sided α level of 2.5%. Among ESR1-mut patients, approximately 160 PFS events are required for 80% power to detect a HR of 0.610 at the two-sided α level of 2.5%. The two-sided α level of 2.5% is selected to ensure that at least one of the two primary efficacy end points will pass the Hochberg procedure to control the overall α level at 5.0%. This study will need to randomize approximately 220 ESR1-mut patients ($n = 110$ /treatment group) and approximately 466 patients total (ESR1-mut and ESR1-mut-nd; $n = 233$ /treatment group) in a 1:1 ratio to the two treatment groups.

Planned study period

This study is event-driven. Final analysis of the primary end points will be performed after approximately 160 PFS events have occurred among the *ESR1*-mut patients and 340 PFS events have occurred among the total population, estimated to occur at 30–33 months after the first patient is randomized. The study will be completed when approximately 50% of patients have died. However, patients will be provided with study treatment, if still on active treatment, until all patients discontinue study participation or elacestrant is approved for marketing in a patient's country, at which time the study may be closed for patient participation.

Study procedures

Patients will be randomized 1:1 to elacestrant or SoC. Randomization will be stratified by *ESR1* mutational status detected in ctDNA (*ESR1*-mut vs *ESR1*-mut-nd), prior treatment with fulvestrant (yes vs no), and presence of visceral metastases (yes vs no). Study sites are requested to collect ctDNA samples immediately after obtaining informed consent to ensure that samples are analyzed as soon as possible while other eligibility criteria are confirmed. The projected turnaround time is 7–14 days, allowing ample time for analysis within the 35-day screening period. Patients randomized to elacestrant will receive 400 mg orally once daily. Elacestrant may be dose-reduced to 300 mg daily or 200 mg daily for toxicity. Patients randomized to SoC will receive monotherapy with fulvestrant, anastrozole, letrozole or exemestane per the investigator's choice and dosed according to the product labeling.

At screening, patients will provide medical history and undergo physical exam, including vital signs and 12-lead ECG, and will provide blood samples for hematology, chemistry, coagulation parameters and ctDNA. Blood samples will be analyzed at a central laboratory for ctDNA to determine *ESR1* mutational status. Tumor assessments will be performed via computed tomography/MRI (CT/MRI) unless performed within 28 days of randomization and radionuclide bone scan or whole-body MRI unless performed within the prior 12 weeks.

During treatment, vital signs, ECG, hematology, chemistry and coagulation parameters will be obtained predose on day 1 and 15 of cycle 1, day 1 of each remaining cycle, and at end of treatment. For patients receiving elacestrant, additional postdose blood pressure and ECG measurements will be taken on days 1 and 15 of cycle 1 when pharmacokinetic samples are obtained.

Following randomization, tumor assessments via CT/MRI will be performed every 8 weeks (± 7 days) during treatment (and in the follow-up period for patients who have discontinued study drug for reasons other than progressive disease and have not yet started new anticancer therapy). Complete responses (CR) or partial responses are to be confirmed at least 4 weeks after the first documented response. For patients with bone metastases at baseline, radionuclide bone scan or whole-body MRI is to be performed every 24 weeks from randomization, at end of treatment, and every 24 weeks during follow-up. Abnormalities will be confirmed with CT scan with bone windows or MRI of bone lesions. Bone scan or whole-body MRI will also be performed to confirm CR.

For patients receiving elacestrant, pharmacokinetic samples will be taken predose and 4 hours postdose on days 1 and 15 of cycle 1; an additional predose sample will be taken on day 1 of cycle 2.

For patients who consent, optional tumor biopsies will be performed pretreatment, on-treatment and at end of treatment. Biopsies will be used for retrospective pharmacodynamic analysis of ER and other oncogenic pathway markers and proliferation markers.

The patient-reported outcomes questionnaires, Euro-QoL-5 Dimension-5 Level (EQ-5D-5L), European Organisation for the Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), are to be completed by the patient at the study site on day 1 of each cycle, day 15 of cycle 1, at the end of treatment and at the safety follow-up visit (if visit occurs in person).

Adverse events will be collected throughout the study until 30 days after the last study drug dose. Adverse event severity will be assessed using the National Cancer Institute CTCAE Version 5.0.

Outcome measures

The primary end points of the EMERALD study are blinded imaging review committee (IRC)-assessed PFS in patients with tumors harboring *ESR1*-mut and in all patients (*ESR1*-mut and *ESR1*-mut-nd). Key secondary end points are overall survival (OS) in *ESR1*-mut patients and in all patients. Other secondary end points analyzed in *ESR1*-mut and all patients are IRC-assessed ORR, duration of response and clinical benefit rate (defined as the percentage of patients who have achieved either a confirmed CR or partial response, or stable disease [SD] at

≥24 weeks from randomization); investigator-assessed PFS, ORR, duration of response and clinical benefit rate; safety and tolerability; elacestrant pharmacokinetics; and PRO measures.

Statistics

PFS and OS analyses will be performed based on the intention-to-treat population using standard Kaplan–Meier methods. The Cox regression model, including treatment and the stratification factors, will be used to estimate the HR and 95% CI for the difference between treatment groups in PFS and OS. The two primary end points will be evaluated using the Hochberg procedure to maintain the overall two-sided α level at 5.0% as follows: the p-value for each of the two primary end points will be derived without any adjustment; these two p-values will be sorted based on size of p-value; if the larger p-value is <0.05, statistical significance will be claimed for both end points; if the larger p-value is ≥0.05 and the smaller p-value is <0.025, statistical significance will be claimed only for the end point associated with smaller p-value; if the larger p-value is ≥0.05 and the smaller p-value is ≥0.025, no statistical significance will be claimed. Unless otherwise specified, analyses of all other efficacy end points will be performed at the two-sided α level of 5% without adjustment for p-values. To differentiate the benefit of elacestrant for second-line and third-line therapy, subgroup analyses of the primary and key secondary end points for *ESR1*-mut and all patients (*ESR1*-mut and *ESR1*-mut-nd) by the number of lines of the prior therapy will be performed.

Conclusion

The EMERALD study is a pivotal Phase III registration trial evaluating the safety and efficacy of elacestrant, an investigational oral SERD, for treatment of men or postmenopausal women with ER+/HER2-advanced or metastatic breast cancer who have progressed following one or two prior lines of endocrine therapy and CDK4/6 inhibitor therapy in combination with an AI or fulvestrant for advanced or metastatic disease. This trial is the first prospective study to evaluate the efficacy of any agent versus SoC in patients with *ESR1* mutations. Results from this study may provide a new treatment option for management of endocrine-resistant ER+ advanced or metastatic breast cancer.

Future perspective

If the EMERALD trial demonstrates safety and efficacy of elacestrant in the setting of previously treated endocrine-resistant advanced or metastatic breast cancer, future studies are warranted to evaluate elacestrant in earlier lines of therapy and early breast cancer. The potential role of a novel SERD such as elacestrant in earlier advanced or metastatic disease, or in the (neo)adjuvant curative setting would be of great interest. Additionally, the potential benefit of combining elacestrant with other active agents in ER-positive breast cancer, such as CDK4/6 inhibitors, mammalian target of rapamycin inhibitors or phosphoinositide 3-kinase inhibitors should be evaluated.

Supplementary data

An infographic accompanies this paper at the end of the references section. To download the infographic that accompanies this paper, please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fon-2019-0370

Author contributions

Radius Health (T Bihani, AT Anderson-Villaluz, J Jung, MG Conlan) designed the trial in collaboration with clinical and academic investigators (A Bardia, P Aftimos and VG Kaklamani). A Bardia, P Aftimos and VG Kaklamani are Study Steering Committee members and clinical site investigators for this trial. J Jung developed the statistical plan for the trial. This manuscript was principally written by A Bardia with assistance from MG Conlan and J Jung, and was critically reviewed, edited and approved by all authors.

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Ethical conduct of research

Investigators are obtaining the appropriate institutional review board approval and will follow the principles outlined in the Declaration of Helsinki. In addition, informed consent will be obtained from the participants involved.

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Executive summary

Background

- Approximately 75% of breast cancers are estrogen receptor ER+/HER2-. Among postmenopausal women with advanced or metastatic ER+/HER2- breast cancer, endocrine therapy remains the cornerstone of treatment.
- Despite recent development of targeted agents that augment endocrine therapy efficacy and mitigate endocrine resistance, eventual treatment failure remains a challenge and new agents to overcome endocrine resistance are needed. Endocrine resistance may be due to estrogen receptor gene α (*ESR1*) mutations.
- Among current endocrine therapies, selective estrogen receptor degraders (SERDs) promote proteasome-induced degradation of the ER. Fulvestrant is the only available SERD. Fulvestrant requires intramuscular administration and resistance has been demonstrated.

Elacestrant

- Elacestrant is an investigational, nonsteroidal, orally bioavailable SERD that inhibits estradiol-dependent induction of target gene transcription and cell proliferation in breast cancer cell lines and induces proteasome-dependent ER degradation.
- In preclinical models, elacestrant has demonstrated antitumor activity in models resistant to cyclin-dependent kinase (CDK)4/6 inhibitors and fulvestrant, and in models harboring *ESR1* mutations (*ESR1-mut*) associated with endocrine resistance.
- In a Phase I trial, elacestrant demonstrated responses in patients with ER+ advanced or metastatic breast cancer previously treated with fulvestrant and/or a CDK4/6 inhibitor, and in patients whose tumors harbored *ESR1-mut*. Elacestrant had an acceptable safety profile, with most adverse reactions consisting of grade 1 or 2 gastrointestinal events.

EMERALD study

- EMERALD is an international, multicenter, randomized, open-label, active-controlled, Phase III clinical study comparing the safety and efficacy of elacestrant to the standard-of-care endocrine treatment options of either fulvestrant or an aromatase inhibitor (investigator's choice) in patients with ER+/HER2- advanced or metastatic breast cancer.
- Eligible patients are adult men and postmenopausal women whose breast cancer progressed while on, or within 28 days after the end of treatment with at least one and no more than two prior lines of endocrine therapy for advanced or metastatic disease. Prior therapy must have included a CDK4/6 inhibitor in combination with an aromatase inhibitor or fulvestrant. No more than one chemotherapeutic regimen in the metastatic setting is allowed.
- Primary end points are blinded imaging review committee-assessed progression-free survival in patients with *ESR1-mut* tumors and in all patients. Key secondary end points are overall survival in patients with *ESR1-mut* tumors and in all patients.

Conclusion

- Results from this study will help establish the potential role of this investigational oral SERD in the management of endocrine-resistant ER+ advanced breast cancer and assess its activity in patients with tumors harboring *ESR1* mutations.

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