Review

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Elacestrant in the treatment landscape of ER-positive, HER2-negative, ESR1-mutated advanced breast cancer: a contemporary narrative review

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Introduction: Estrogen receptor-positive (ER +), human epidermal growth factor receptor 2-negative (HER2 –) breast cancer with ESR1 mutations presents a significant therapeutic challenge due to its adaptive resistance mechanisms to chemotherapy, especially endocrine treatment. Elacestrant, a novel oral selective estrogen receptor degrader (SERD), has emerged as a promising agent in this treatment-resistant era.

Method: A comprehensive search was conducted on pivotal clinical trials, including the RAD1901-005 Trial, EMERALD TRIAL, ELIPSE, and ELEVATE, focusing on their methodologies, patient populations, treatment regimens, and outcomes.

Discussion: This narrative review describes the available preclinical and clinical evidence on elacestrant, focusing on its pharmacodynamics, pharmacokinetics, efficacy, and safety within the existing literature. Elacestrant has demonstrated excellent activity against ESR1 mutations associated with resistance to first-line endocrine therapies. Clinical trials have shown improved progression-free survival in patients with advanced ER + /HER2 – , ESR1-mutated breast cancer. Safety profiles indicate a tolerable side effect spectrum consistent with other agents. Its oral bioavailability offers a convenient alternative to injectable SERDs, with potential implications for patient adherence and quality of life. The review also discusses the comparative efficacy of elacestrant relative to existing endocrine therapies and its possible use in combination regimens.

Conclusion: Ongoing clinical trials assessing elacestrant and other SERDs will yield data that might aid clinicians in determining the optimal selection and order of endocrine treatment drugs for ER + breast cancer. The integration of targeted and immunotherapeutic agents with traditional chemotherapy represents a pivotal shift in Breast Cancer treatment, moving towards more personalized and effective regimens.

Keywords: advanced breast cancer, elacestrant, ESR1 mutation, estrogen receptor-positive, HER2-negative, selective estrogen receptor degrader

Introduction

Carcinogenesis, characterized by six primary hallmarks, has the potential to develop in all cells, tissues, and organs, giving rise to pathological changes that contribute to a broad spectrum of cancer types[1]. The primary processes facilitating the advancement of this condition encompass the evasion of programmed cell death, unrestricted proliferation, heightened formation of new blood vessels, insensitivity to signals that inhibit growth, self-stimulation of growth signals, and the ability to spread to distant sites in the body[2,3]. The process of carcinogenesis is complex and influenced by several factors, with genetic predispositions and environmental factors being the primary stimuli[3]. The incidence of cancer-related mortality has exhibited a concerning upward trend, positioning it among the prominent contributors to global mortality rates. While it is true that a considerable proportion of cancer cases may not always lead to mortality, they do have a substantial negative impact on the overall quality of life and impose enormous financial burdens[4]. Quality of life (QoL) is a prominent health concern for cancer patients. This refers to a distinct and multifaceted category of patient-reported outcomes

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(PROs) that patients view as encompassing several aspects of their lives, including social, economic, psychological, and physical activities[4,5]. According to the GLOBOCAN 2020 data, breast cancer is presently among the most often diagnosed forms of cancer and ranks as the fifth leading cause of cancer-related mortality. It is predicted that there will be around 2.3 million new cases of breast cancer globally[6]. As the primary purpose of this paper is to provide up-to-date information and current data about the role of Elacestrant in the therapy of advanced breast cancer, we will give just a brief overview of the risk factors and types of breast cancer.

Methods

A systematic literature search was conducted on the following databases: PubMed, Scopus, and Google Scholar from inception till March 2024. The following keywords were used: 'Elacestrant', 'ER-positive', 'HER2-negative', and 'Advanced breast cancer'. Titles and abstracts were screened for relevant articles, followed by the full-text screening of the eligible studies. The reference lists of all included citations were hand-searched to identify other additional studies. After removing duplicates, only original English language articles of any study design were considered.

HIGHLIGHTS

- According to the GLOBOCAN 2020 data, breast cancer is presently among the most often diagnosed forms of cancer and ranks as the fifth leading cause of cancer-related mortality. It is predicted that there will be around 2.3 million new cases of breast cancer globally.
- Endocrine therapy is the primary therapeutic approach for individuals diagnosed with metastatic breast cancer (mBC) characterized by estrogen receptor-positive status. Nevertheless, a significant proportion of patients diagnosed with estrogen receptor-positive metastatic breast cancer encounter disease progression, which is primarily attributed to the emergence of resistance to endocrine therapy.
- On 27 January 2023, the Food and Drug Administration approved Elacestrant, a newly developed oral selective estrogen receptor degrader. It effectively suppresses estrogen receptor signaling and exhibits anti-tumor effects in cell lines of hormone receptor-positive breast cancer.
- Several trials, such as ELECTRA, ELEVATE, ELIPSE, and EORTC-2129-BCG, etc. study the efficacy of elacestrant in advanced breast cancer.

Review

Epidemiology of breast cancer

Based on the WHO's data, malignant neoplasms pose a significant global burden for women, with an estimated 107.8 million disability-adjusted life years (DALYs)[7]. Among these DALYs, breast cancer accounts for around 19.6 million[7]. Breast cancer is the most often detected form of cancer among women globally, with a reported 2.26 million cases being diagnosed in the year 2020[8]. In addition to its prevalence, breast cancer holds the distinction of being the primary contributor to cancer-related mortality among women on a global scale. Breast cancer accounted for a total of 684 996 fatalities worldwide. The age-adjusted mortality rate for breast cancer was estimated to be 13.6 per 100 000 individuals[8]. While industrialized nations exhibited the highest incidence rates, it is noteworthy that Asia and Africa collectively accounted for 63% of the total fatalities in the year 2020[7,8]. The survival rates for women diagnosed with breast cancer differ significantly between high-income nations and low- to middle-income countries. In high-income countries, the 5-year survival rates for breast cancer exceed 90%, whereas in countries like India, the rate is about 66%, and in South Africa, it's around 40%. These differences reflect inequities due to factors such as late diagnosis, inadequate services, and low coverage of breast cancer care within essential health benefit packages and universal health coverage agendas. While high-income countries have seen a 40% reduction in breast cancer mortality since the 1980s, such decreases have not yet been achieved in the majority of low- and middle-income countries[9]. Research indicates that racial and ethnic minorities, particularly Black women, experience poorer breast cancer outcomes compared to White women. Differences in tumor stage or biology alone do not fully explain this. In a study, the 5-year overall survival rate for Black women was significantly lower than that for White women, and race and ethnicity remained independent prognostic factors even after adjusting for factors like tumor grade, stage, estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2) status[8,9]. This suggests that intrinsic differences in tumor biology between ethnic groups, healthcare access disparities, and other social determinants of health play significant roles in these outcomes[9,10].

Risk factors for breast cancer

The female sex is the most significant risk factor for the increased propensity of breast cancer development due to augmented hormonal stimulation compared to males[10]. In contrast to males, who typically exhibit low estrogen levels, females possess breast cells highly susceptible to hormonal influences, particularly estrogen and progesterone, as well as any perturbations in their equilibrium[10,11]. There is a positive correlation between the presence of circulating estrogens and androgens and the heightened susceptibility to breast cancer[12]. The fluctuations in endogenous sex hormone levels at the physiological level contribute to an increased susceptibility to breast cancer in both premenopausal and post-menopausal women[13,14].

Eighty percent of the patients with breast cancer are over 50 years old, with a significant proportion, ~40% of the patients being over 65 years or older[15–17]. The likelihood of developing breast cancer steadily increased with age, with an incidence of 1.5% for patients forty to fifty years of age, 3% for patients aged fifty to sixty, and over 4% risk for patients older than 75[18]. It is noteworthy that a correlation has been identified between a specific molecular subtype of cancer and the age of the patient. Specifically, the aggressive resistant triple-negative breast cancer subtype is predominantly detected in individuals under the age of 40. In contrast, the luminal A subtype is usually diagnosed in people over 70[16]. Young adults are more likely to have a genetic predisposition and key biomarkers, including endocrine receptors, the HER2 receptor, and proliferation biomarkers, which appear different from older adults[19]. The presence of a familial

history of breast cancer is a prominent factor that is strongly correlated with an elevated susceptibility to developing breast cancer. An analysis of over 50 epidemiological studies, which included over 52 000 women with breast cancer, found that 13–19% of patients diagnosed with breast cancer had a first-degree relative also affected by breast cancer[20]. Moreover, the incidence of breast cancer exhibits a notable elevation in correlation with an escalating count of first-degree relatives afflicted. Furthermore, the risk may be further amplified when the affected relatives are below 50[21,22].

Several genetic mutations have been identified as being correlated with an elevated susceptibility to breast cancer[23]. Two prominent genes, BRCA1 and BRCA2, are distinguished by their strong penetrance and situated on chromosomes 17 and 13, respectively[24,25]. However, these are also associated with increased incidence of ovarian as well as prostate cancer[23]. The mutations observed in the abovementioned genes are mostly transmitted by autosomal dominant inheritance. However, spontaneous mutations are also often documented. Additional breast cancer genes with strong penetrance include TP53, CDH1, PTEN, and STK11[23,26–28].

The role of hormones in breast cancer

The established literature recognizes the significant influence of hormones, particularly the steroid hormone estrogen, in driving the development and progression of breast cancer[29]. The actions of estrogen are mediated by nuclear estrogen receptors, with a particular emphasis on ERα[29]. The therapy of HR-positive malignancies has focused on regulating estrogen production and/or ER activity due to their dependence on ER signaling for tumor growth and progression[30]. Hormone-based treatments continue to be the primary therapy modalities for breast cancer that are positive for hormone receptors[31]. These therapeutic approaches encompass the utilization of certain compounds that diminish the concentration of naturally occurring estrogens within the body. Examples of such compounds include aromatase inhibitors like anastrozole, letrozole, and exemestane[32–34].

Additionally, a selective estrogen receptor modulator (SERM) called tamoxifen is employed to mitigate the impact of estradiol by competitively binding to the ER[35]. Another strategy involves using a selective estrogen receptor degrader (SERD) known as fulvestrant, which completely antagonizes and degrades the ER[30]. These therapeutic interventions may also demonstrate efficacy in individuals with truncating mutations in the CHEK2 gene, such as the 100delC variant, which has been linked to a positive ER status[36].

Despite the significant progress achieved in the management of hormone receptor-positive breast cancer through the utilization of hormonal therapy, there are still unresolved gaps and deficiencies that persist. Disease relapse is a common phenomenon, with a substantial proportion of patients (about 30–50%) experiencing relapse in the adjuvant context[37,38]. The limited efficacy of endocrine therapy is a challenge in the therapeutic care of patients whose tumor development is still driven by signaling through the ER[39]. Resistance to these medicines remains a crucial concern in achieving optimal outcomes. Recent studies have shown that a significant proportion of patients, ranging from around 15–30%, do not experience any therapeutic benefits from conventional standard-of-care therapies. This lack of response is mainly attributed to the emergence of de novo resistance mechanisms[40,41]. The development of resistance to endocrine therapy is a significant contributing factor to unfavorable outcomes in medical treatment[41].

Endocrine therapy for breast cancer

Endocrine therapy (ET) is the primary therapeutic approach for individuals diagnosed with metastatic breast cancer (mBC) characterized by estrogen receptor-positive (ER +) status. Nevertheless, a significant proportion of patients diagnosed with estrogen receptor-positive metastatic breast cancer (ER + mBC) encounter disease progression, which is primarily attributed to the emergence of resistance to ET[42,43]. It is worth mentioning that mutations in the estrogen receptor gene alpha (ESR1) are linked to the development of resistance to ET and a decrease in the length of progression-free survival (PFS) in patients who are being treated with aromatase inhibitors (AIs)[42,43]. On the other hand, the PFS of patients receiving the SERD fulvestrant appears to be unaffected by the presence of ESR1 mutations[44,45]. Nonetheless, the occurrence of acquired ESR1 mutations is also observed after fulvestrant therapy, may be due to suboptimal absorption and inadequate estrogen receptor blocking resulting from the intramuscular injection method[44]. Fulvestrant was until recently the sole SERD that has received approval for the therapeutic management of hormone receptor-positive mBC in post-menopausal women[46,47]. Hence, there was a prevailing requirement for a SERD that exhibits efficacy in cancers carrying ESR1 mutations. It also demonstrates enhanced bioavailability to enable oral delivery, potentially improving its therapeutic effectiveness.

Elacestrant

Elacestrant is an anti-estrogen antagonist of the estrogen receptors, and it targets endogenous estrogen like estradiol[48]. It is specifically an antagonist of the estrogen receptor alpha (Erα). It is also a SERD[48]. On 27 January 2023, the Food and Drug Administration (FDA) approved Elacestrant, a newly developed oral ER SERD that possesses an amino basic side chain. It has been shown to effectively suppress estrogen receptor (ER) signaling and exhibit anti-tumor effects in cell lines of hormone receptor-positive breast cancer (HR + BC) as well as patient-derived xenografts (PDX). These effects have been observed when elacestrant is administered as a standalone treatment and when used with palbociclib or everolimus[48,49]. Elacestrant was assessed in both in vitro and in vivo models of CDK4/6 inhibitor-resistant breast cancer, demonstrating its ability to effectively suppress tumor development, even in the presence of ESR1 mutations[50].

This approval is specifically for the treatment of patients diagnosed with metastatic breast cancer that is positive for ER and/or progesterone receptor (PR) and negative for HER2. Furthermore, this treatment is indicated for patients whose tumors contain a missense mutation in the ESR1 gene, namely ESR1-mut, and who have previously undergone at least one line of endocrine therapy (ET). The FDA's decision was informed by the randomized phase 3 EMERALD trial, which successfully achieved its primary objective of demonstrating enhanced median progression-free survival (mPFS) through the use of elacestrant monotherapy compared to standard-of-care endocrine monotherapy in the entire intention-to-treat population[51]. However,

it is essential to note that this improvement was primarily observed in the subset of patients with ESR1 mutations.

Elacestrant is a compound with dose-dependent characteristics as a mixed agonist/antagonist of the ER. At higher dosages, it functions as a direct antagonist of the ER and selectively downregulates the activity of the ER[52]. The bioavailability of the substance is 11%, with its primary metabolism occurring in the liver through the action of CYP3A4 enzymes and subsequent excretion in the feces. This results in potential drug-drug interactions when combined with potent CYP3A4 inhibitors, such as itraconazole, or inducers, such as rifampin[52]. Based on the prescribed clearance pathway, it is advisable to reduce dosage in those exhibiting mild hepatic dysfunction, whereas no such adjustment is warranted for those with renal dysfunction. The mechanism of action of Elacestrant is shown in Figure 1.

Ongoing investigations are being conducted to assess the efficacy of elacestrant in individuals with severe hepatic dysfunction, as well as in patients belonging to racial and ethnic minority groups. In general, elacestrant represents a significant milestone as the initial orally accessible SERD sanctioned by the FDA for administration to individuals diagnosed with metastatic breast cancer. Ongoing clinical trials are now assessing the use of this treatment in the adjuvant context for individuals diagnosed with early-stage estrogen receptor-positive breast tumors. Integration of Elacestrant into current clinical guidelines for ER-positive, HER2-negative, and ESR1-mutated advanced breast cancer is shown in Table 1.

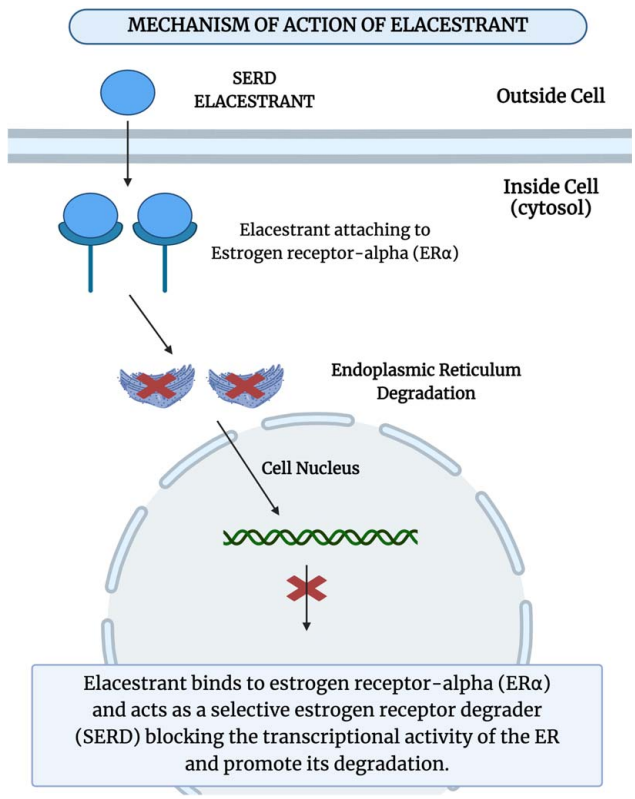

Figure 1. Mechanism of action of elacestrant.

Table 1

The integration of elacestrant into current clinical guidelines for ER-positive, HER2-negative, and ESR1-mutated advanced breast cancer

Guidelines/organization	First-line therapy	Second-line therapy	Third Line and subsequent therapies	Specific mention of elacestrant	Notes
NCCN Guidelines	AI ± CDK4/6i or SERD	Fulvestrant ± CDK4/6i	Chemotherapy or further endocrine therapy	Recommended for patients with ESR1 mutations after progression on initial endocrine therapy	AI: aromatase inhibitor, CDK4/6i: cyclin-dependent kinase 4/6 inhibitor
ASCO Recommendations	Endocrine therapy of choice	Endocrine therapy ± targeted agent	Clinical trial or further endocrine therapy	Mentioned as an option post-progression on prior endocrine therapy	—
ESMO Guidelines	SERD or AI ± targeted therapy	Fulvestrant ± CDK4/6i	Endocrine therapy or clinical trial	Included as a treatment alternative for ESR1 mutant-positive patients	SERD: selective estrogen receptor degrader;
St. Gallen International Expert Consensus	AI ± CDK4/6i or SERD	SERD or AI switch	Investigational agents or approved therapies based on mutation status	Elacestrant as a potential therapy in ESR1-mutated cases, pending further evidence	AI: aromatase inhibitor

ASCO, American Society of Clinical Oncology; ER, estrogen recepto; ESMO, European Society for Medical Oncology; ESR1, estrogen receptor gene alpha; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network.

Comparative efficacy

Elacestrant vs. standard endocrine therapy

The luminal subtype of breast cancer, which accounts for roughly 75% of cases, is characterized by the presence of hormone receptors (HR-positive) and the absence of HER2-negative status[53]. The conventional first intervention for individuals diagnosed with metastatic breast tumors that are hormone receptor-positive and HER2-negative is endocrine therapy[54]. Endocrine treatment includes pharmaceutical interventions that suppress estrogen synthesis and substances that directly affect the ER within malignant cells. The synthesis of estrogen can be hindered by gonadotropin-releasing hormone agonists as well as aromatase inhibitors, such as letrozole, anastrozole, and exemestane. Tamoxifen and toremifene are examples of SERMs[54].

Fulvestrant, an ER antagonist, exerts its action mechanism by specifically inducing estrogen receptor degradation within cancer cells. Furthermore, it is worth noting that targeted treatments, such as cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), everolimus, and alpelisib, can be employed in conjunction with endocrine therapy medications. Despite the existence of several therapeutic drugs, inevitably, patients diagnosed with advanced hormone receptor-positive breast cancer will ultimately encounter disease progression because of developing resistance to endocrine therapy[55].

Fulvestrant received approval from the US FDA in 2002 and has maintained its status as the sole licensed SERD for almost two decades, specifically for treating advanced hormone receptor-positive breast cancer. The efficacy of Fulvestrant as a monotherapy in improving overall survival has been demonstrated in previous studies. Specifically, a monthly intramuscular dosage of 500 mg was more beneficial than a dose of 250 mg[56]. It has been demonstrated that fulvestrant has efficacy when used with CDK4/6 inhibitors (CDK4/6i). In a recent Phase 3 clinical trial, adding alpelisib to fulvestrant resulted in a prolonged PFS for patients with advanced disease and a PIK3CA mutation who had previously undergone endocrine therapy[57]. The presence of mutations in the ESR1, responsible for encoding the ER, has been linked to the development of resistance against aromatase inhibitors in individuals diagnosed with advanced hormone receptor-positive breast cancer. Additionally, these alterations can induce partial resistance to tamoxifen and fulvestrant[58]. Moreover, data indicates that specific individuals exhibit inadequate decreases in endoplasmic reticulum (ER) availability. This phenomenon could be associated with the advancement of the disease[59].

The emergence of resistance to presently authorized endocrine treatment drugs, along with the necessity for intramuscular injections in the case of fulvestrant, has generated a desire for agents that possess enhanced bioavailability and offer more comfortable modes of administration. Elacestrant, or RAD1901, is an orally administered nonsteroidal small-molecule SERD that specifically targets and triggers ER degradation[49]. The metastatic breast cancer management guidelines are shown in Figure 2.

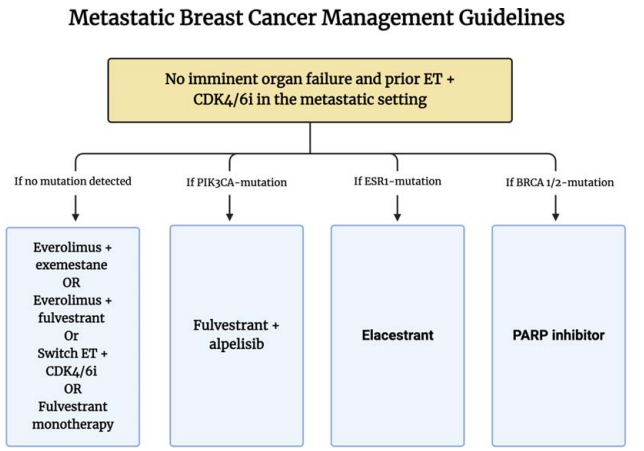

Figure 2. Metastatic breast cancer management guidelines.

Preclinical and clinical evidence

The RAD1901-005 trial

The RAD1901-005 study was a multicenter study that followed an open-label design. This Phase I study evaluated elacestrant, an oral selective estrogen receptor degrader (SERD), in treating ER + , HER2 – metastatic breast cancer (mBC), focusing on doses from 200 to 600 mg once daily[60]. The recommended phase 2 dose (RP2D) was set at 400 mg daily, showing a tolerable safety profile and reduced gastrointestinal (GI) toxicity with the tablet formulation. Elacestrant demonstrated notable anti-tumor activity, especially at the 400 mg daily dose, in heavily pretreated post-menopausal women, including those with prior treatments like fulvestrant and CDK4/6 inhibitors and ESR1 mutations linked to endocrine resistance. The study reported an overall response rate (ORR) of 19.4%, a clinical benefit rate (CBR) of 42.6%, and a median PFS of 4.5 months. Additionally, elacestrant reduced ER availability and showed activity across various ESR1 mutations. These results suggest that elacestrant could be more effective than existing treatments like fulvestrant in patients with ESR1 mutations, who often resist other therapies. GI side effects were notably less with the tablet form of elacestrant compared to the capsule, leading to the adoption of the tablet formulation. The safety profile was characterized mainly by grade 1–2 GI events[48,60].

EMERALD Trial

The EMERALD phase III clinical trial findings indicate that elacestrant exhibited a statistically significant extension in progression-free survival (PFS) compared to standard of care (SOC) endocrine therapy[51]. This was observed in patients with advanced/metastatic ER-positive/HER2-negative breast cancer who had experienced progression after receiving prior endocrine and CDK4/6 inhibitor therapy. The observed effect was seen in the entire population and patients exhibiting identifiable ESR1 mutations. The drug elacestrant demonstrated tolerable toxicity, with most adverse events being of grade 1 or 2 intensity. Nausea was the most often reported adverse event (AE), with a severity score of 3 observed in 2.5% of the patient population[51]. No instances of cardiac or ocular damage were documented with other selective estrogen receptor degraders (SERDs)[61,62].

The EMERALD study was an international phase III open-label research that evaluated the safety and effectiveness of elacestrant compared to standard-of-care endocrine treatment. The research encompassed a cohort of 477 individuals, consisting of

both males and post-menopausal females, who were diagnosed with locoregional recurrent or metastatic breast cancer that was estrogen receptor-positive and HER2-negative. These individuals had previously had 1 or 2 rounds of endocrine therapy as a treatment for advanced-stage cancer. Prior administration of a CDK4/6 inhibitor was a prerequisite, and only a single round of chemotherapy for advanced illness was permissible[62].

The participants were subjected to randomization to receive either a daily dosage of 400 mg of elacestrant or an endocrine medication of the investigator's choosing, which might consist of fulvestrant or one of the aromatase inhibitors, namely anastrozole, letrozole, or exemestane. According to the study protocol, researchers were advised to choose fulvestrant in cases where the patient had not previously had treatment with fulvestrant. Conversely, for patients who had seen progression while on fulvestrant, an aromatase inhibitor was indicated. Selecting an aromatase inhibitor drug should evaluate the patient's past therapy with an aromatase inhibitor. The patients were categorized based on identifying ESR1 mutation in ctDNA using the Guardant360 CDx test, their previous administration of fulvestrant, and the presence or absence of visceral metastases[63].

The study's primary goals encompassed PFS in patients with ESR1 mutation and the entire patient population. The patients assigned to the elacestrant group were administered a daily oral dose of 400 mg. In case of any observed toxicity, dose reductions to 300 or 200 mg per day were permitted. The study findings indicate that 43% of the patients included in the analysis had undergone two previous rounds of endocrine therapy for advanced illness. Additionally, 48% of the patients had a detectable mutation in the ESR1 gene. Furthermore, it was observed that 29% of the patients who were randomly assigned to receive elacestrant had previously received fulvestrant treatment[64].

The elacestrant arm demonstrated a significant extension in PFS compared to the standard of care across all patients. This was seen by a relative decrease of 30% in the occurrence of progression or death. However, the absolute difference in PFS between the two arms was only a few weeks. The hazard ratio (HR) for PFS was 0.70 (95% CI, 0.55–0.88; $P = 0.002$), with a median PFS of 2.8 months in the elacestrant arm compared to 1.9 months in the standard of care arm.

The study observed a significant extension in PFS among patients with ESR1 mutation who received elacestrant. The relative reduction in the risk of progression or death was 45% (HR 0.55; 95% CI, 0.39–0.77; $P = 0.0005$), resulting in a median PFS of 3.8 months compared to 1.9 months for the standard of treatment group. In the patient cohort receiving elacestrant, the 12-month PFS rate was 22.3%, whereas the standard of care group exhibited a PFS rate of 9.4%. Furthermore, among patients with an ESR1 mutation, the 12-month PFS rate was 26.8% for those treated with elacestrant, compared to 8.2% for those receiving standard care. The authors also noted the advantages of elacestrant in comparison to fulvestrant[51].

Except for patients who had been administered fulvestrant before the study, the 12-month PFS rate was 22.3% for elacestrant, compared to 9.5% for the fulvestrant group. In the cohort of patients exhibiting ESR1 mutation, the 12-month PFS rates were 26.8% and 8.3% in the elacestrant and fulvestrant treatment groups, respectively. It is worth mentioning that subgroup analysis revealed the efficacy of elacestrant in patients who had previously had fulvestrant treatment. The overall survival results exhibited immaturity. The prevailing adverse reactions seen in the study population were nausea, lethargy, vomiting, reduced appetite, and arthralgia. The study observed 27% of elacestrant patients experienced grade 3/4 adverse effects.

The most frequently reported adverse effects in these patients were nausea, back pain, and elevated ALT levels. In comparison, 20% of patients who received standard-of-care medication also experienced grade 3/4 adverse effects. Additional results from the EMERALD study revealed a correlation between the length of previous CDK4/6 inhibitor (CDK4/6i) treatment and PFS. Specifically, it was seen that a more significant duration of prior CDK4/6i medication in the context of metastatic cancer led to an extended PFS when comparing elacestrant to the standard of care therapy. In the cohort of patients administered at least 12 months of CDK4/6 inhibitors, the median PFS was found to be 3.8 months in the elacestrant group, compared to 1.9 months in the standard-of-care group. The HR for PFS between the two groups was 0.61, with a 95% CI of 0.45–0.83. It is worth mentioning that a significant disparity was observed in patients with ESR1 mutations. The median PFS in patients who had received at least 12 months of prior CDK4/6 inhibitor treatment was 8.6 months when treated with elacestrant, compared to just 1.9 months when treated with the standard of care. This difference corresponds to a hazard ratio 0.41 (95% CI: 0.26–0.63).

The FDA approved elacestrant on 27 January 2023, for the treatment of advanced or metastatic breast cancer in post-menopausal women and men with ER-positive, HER2-negative, ESR1-mutated tumors who had disease progression after receiving a minimum of one line of endocrine therapy, as per the findings of the EMERALD study.

Ongoing trials

The landscape of breast cancer treatment is being reshaped by several promising clinical trials focusing on elacestrant, a novel drug targeting ER-positive, HER2-negative breast cancer. These trials, spanning various stages and patient groups, aim to explore the efficacy and safety of elacestrant in different therapeutic scenarios.

ELIPSE trial

Firstly, the ELIPSE study (NCT04797728), an early Phase I trial, is investigating the effects of elacestrant in post-menopausal women diagnosed with early-stage (stage cT1-3N0) ER-positive, HER2-negative breast cancer. In this trial, participants received 400 mg of elacestrant orally daily for four weeks. The primary outcome measure is the achievement of complete cell cycle arrest, indicated by a Ki-67 level of 2.7% or lower, in a cohort of 23 patients. This study is significant as it evaluates the potential of elacestrant as a preoperative treatment, providing insights into its effectiveness in halting cancer cell growth[65].

EORTC-2129-BCG trial

Next, the EORTC-2129-BCG trial (NCT05512364), a more extensive Phase III study, is designed for a diverse group of patients, including pre-and post-menopausal women and men with high-risk early-stage ER-positive, HER2-negative breast cancer. This trial compares the effectiveness of elacestrant against traditional treatments like tamoxifen or aromatase inhibitors (AI). The key endpoint is distant metastasis-free survival, a

critical measure of the drug's ability to prevent cancer spread. Approximately 220 patients are expected to participate, making it a significant study for understanding elacestrant's role in early-stage breast cancer management[66].

ELECTRA trial

Another critical trial is ELECTRA (NCT05386108), a combined Phase Ib/II study. It enrolls both pre-and post-menopausal women and men with advanced ER-positive, HER2-negative breast cancer, including those with brain metastases. ELECTRA explores elacestrant as a monotherapy and in combination with abemaciclib, a CDK4/6 inhibitor. This trial focuses on evaluating adverse events and the efficacy of the combination therapy, aiming to enroll around 106 patients. Its unique aspect is the investigation of elacestrant's effectiveness in treating brain metastases, a challenging and often under-researched area in breast cancer treatment[67].

ELEVATE trial

Lastly, the ELEVATE study (NCT05563220), also a Phase Ib/II trial, targets a similar patient group as ELECTRA but explores elacestrant in combination with a broader range of drugs: alpelisib, everolimus, abemaciclib, ribociclib, or palbociclib. This umbrella study aims to determine the recommended Phase 2 dose in its initial phase and evaluate PFS in its subsequent phase. With an expected enrollment of 322 patients, ELEVATE is significant for its comprehensive approach, testing multiple combination therapies to identify the most effective regimen for treating advanced metastatic breast cancer[68].

Together, these trials represent a concerted effort to understand and establish elacestrant's role in breast cancer treatment across various stages and patient populations. They highlight the ongoing commitment to advancing breast cancer therapies, offering hope for improved outcomes for those battling this disease. Ongoing trial data is shown in Table 2.

Safety and tolerability

In clinical studies, the administration of Elacestrant at a daily dosage of 400 mg was generally well tolerated, with the primary adverse effects seen being upper gastrointestinal discomfort and exhaustion. The RAD1901-106 study showed that individuals administered a daily dose of 200 mg of elacestrant saw a significant decrease in FES absorption. This finding implies that utilizing 200 mg dosages might be a viable alternative for patients who cannot handle the higher dosage of 400 mg[67,68].

In clinical studies, the administration of Elacestrant at a daily dosage of 400 mg was generally well tolerated. The primary adverse effects seen were upper gastrointestinal discomfort and exhaustion[66]. According to the findings of the RAD1901-106 study, patients who were administered a daily dose of 200 mg of elacestrant saw a notable decrease in FES absorption. This indicates that using 200 mg dosages is an alternative for patients who cannot handle the higher dosage of 400 mg.

Musculoskeletal discomfort and nausea were observed as severe adverse events in more than 1% of individuals who were administered Elacestrant. The predominant adverse effects, with a prevalence of over 10%, encompassing both physical symptoms and laboratory abnormalities, associated with the administration of Elacestrant were musculoskeletal pain, nausea,

Table 2
Ongoing trials data for elacestrant

Study	Phase	Study population	Intervention	Primary outcome(s)	Estimated enrollment
ELIPSE: Elacestrant in Preoperative Setting, a Window of Opportunity Study (NCT04797728)	Early phase I	Post-menopausal women with ER-positive, HER2-negative breast cancer, stage Ct I-3N0	Elacestrant 400 mg PO daily for 4 weeks	Complete cell cycle arrest (Ki-67 <2.7%)	23 patients
EORTC-2 129-BCG: Elacestrant for Treating ER+/HER2− Breast Cancer Patients With ctDNA Relapse. (NCT05512364)	Phase III	Pre- and post-menopausal women and men with high-risk early-stage ER-positive, HER2-negative breast cancer	Elacestrant versus tamoxifen or AI	Distant metastasis-free survival	220 patients
ELECTRA: An Open-label Multicenter Phase I b-2 Study of Elacestrant as Monotherapy and in Combination With Abemaciclib in Women and Men With Brain Metastasis From Estrogen Receptor-Positive, HER-2 Negative Breast Cancer (NCT05386108)	Phase Ib/II	Pre- and post-menopausal women and men with ER-positive and HER2-negative advanced breast cancer	Elacestrant as a single agent and in combination with abemaciclib	Adverse events Efficacy of the combination of elacestrant with abemaciclib	106 patients
ELEVATE: A Phase 1b/2, Open-Label Umbrella Study To Evaluate Safety And Efficacy Of Elacestrant In Various Combinations in Patients With Metastatic Breast Cancer (NCT05563220)	Phase Ib/II	Pre- and post-menopausal women and men with ER-positive and HER2-negative advanced breast cancer	Combination with alpelisib, everolimus, abemaciclib, ribociclib or palbociclib	Phase Ib: recommended phase 2 dose Phase II: PFS	322 patients
Multicenter Open-Label Phase Ib/II Trial of Abemaciclib and Elacestrant in Patients With Brain Metastasis Due to HR+/Her2− Breast Cancer (NCT04791 384)	Phase Ib/II	Post-menopausal women with HR-positive and HER2-negative metastatic breast cancer with brain metastasis. Prior treatment with up to 2 lines of chemotherapy for advanced disease	Elacestrant in combination with abemaciclib	Adverse effects Overall intracranial response rate and clinical benefit rate	44 patients

AI, aromatase inhibitor; ER-positive, estrogen receptor-positive; HER2-negative, human epidermal growth factor receptor 2 negative; HR-positive, hormone receptor-positive.

Table 3

Adverse effects of elacestrant and their management

Adverse event	Management strategies
Gastrointestinal disorders	Supportive care
1. Nausea	Dose reduction
2. Diarrhea	
3. Vomiting	
4. Constipation	
5. Abdominal pain	
6. Dyspepsia	
7. Decreased appetite	
Musculoskeletal pain	Analgesics
	Physiotherapy
Hematologic disorders	Growth factors
1. Anemia	Transfusion
Central nervous system effects	Symptomatic treatment
1. Headache	Dose reduction
Vascular disorders	Antihypertensives
1. Hot flush	Dose modifications
Endocrine disorders	Hormone replacement
	Dose adjustments
Biliary disorders	Supportive care
1. Cholesterol increased	Dose reduction
2. Triglyceride increased	
3. Aspartate aminotransferase increased	
4. Alanine aminotransferase increased	

elevated cholesterol levels, increased AST levels, heightened triglyceride levels, fatigue, reduced hemoglobin levels, vomiting, increased ALT levels, decreased sodium levels, increased creatinine levels, diminished appetite, diarrhea, headache, constipation, abdominal pain, hot flushes, and dyspepsia[69]. All adverse effects and their management are shown in Table 3.

Conclusion

Elacestrant has shown efficacy as the initial oral SERD in enhancing PFS among individuals with HR-positive, HER2-negative metastatic breast cancer who had received prior treatment, in comparison to the conventional endocrine therapy considered as standard of care. Significantly, the treatment demonstrated more efficacy in individuals exhibiting the ESR1 mutation, a well-established cause of resistance to aromatase inhibitors. This resulted in the FDA's approval of this therapeutics specifically for this subgroup of patients. Ongoing clinical trials assessing elacestrant and other SERDs will yield data that might aid clinicians in determining the optimal selection and order of endocrine treatment drugs for hormone receptor-positive breast cancer.

Ethical approval

Our study was a narrative review and therefore, did not involve patients. Thus, ethical approval from the ethics committee was not applicable.

Consent

Our study was a narrative review and therefore, did not involve patients. Thus, taking consent was not applicable.

Source of funding

Not applicable.

Author contribution

Z.Q.: data curation, conceptualization, methodology, supervision; A.J.: writing—original draft; writing—reviewing and editing; F.A.: writing—reviewing and editing, supervision; R.S.: writing—original draft; E.A.: writing—reviewing and editing; E.F.: writing—original draft; S.S.: writing—original draft.

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The authors declare no conflicts of interest.

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