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REVIEW

Evaluating Elacestrant in the Management of ER-Positive, HER2-Negative Advanced Breast Cancer: Evidence to Date

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Abstract: Breast cancer remains the second leading cause of cancer mortality in women. Endocrine therapy is the backbone treatment for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer, the most common subtype. Although several endocrine therapy agents are available, essentially all HR-positive metastatic breast cancers will become resistant to these drugs. *ESR1* mutations represent an important mechanism of resistance to aromatase inhibitors. Elacestrant is a novel oral selective estrogen receptor degrader (SERD) that selectively binds to the estrogen receptor in breast cancer cells, inhibiting tumor growth. Preclinical data suggested greater efficacy of elacestrant in combination with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) or everolimus. In a Phase III clinical trial, elacestrant demonstrated a significant although modest improvement in median progression-free survival (PFS) compared to standard of care endocrine therapy in patients with HR-positive, HER2-negative advanced breast cancer. Importantly, there was also a significant benefit in patients with *ESR1* mutations, which led to the FDA approval of elacestrant in this patient group. Elacestrant was generally well tolerated, with main side effects being upper gastrointestinal symptoms. There are several ongoing clinical trials evaluating the efficacy of elacestrant in the early setting as well as in combination with other targeted agents in the treatment of metastatic breast cancer. Other novel oral SERDs are also currently being evaluated in the treatment of HR-positive breast cancer. Results of ongoing clinical trials with these drugs will help clinicians decide the best sequence and combination of endocrine therapy agents.

Keywords: RAD1901, elacestrant, oral SERD, breast cancer

Introduction

Approximately 288,000 new cases of invasive breast cancer are expected in the United States in 2022, and more than 43,000 women will die from breast cancer this year.[1] Although breast cancer mortality has declined by 42% in the past 3 decades, breast cancer remains the second leading cause of cancer mortality in women.[2] The most common subtype of breast cancer (approximately 75%) is the luminal subtype, defined by hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative status.[3] Despite being the subtype with the best prognosis, distant recurrences in this biological group can occur more than 20 years after diagnosis.[4]

Endocrine therapy is the standard initial treatment for patients with metastatic breast cancers that are HR-positive, HER2-negative.[5,6] Endocrine therapy includes drugs that act by inhibiting estrogen production, and agents that modulate estrogen receptor (ER) directly in cancer cells. Estrogen production can be inhibited by gonadotropin-releasing hormone agonists and by aromatase inhibitors (letrozole, anastrozole, and exemestane). Selective ER modulators (SERMs) include tamoxifen and toremifene. The ER antagonist fulvestrant acts by selectively degrading the ER in the cancer cells. Moreover, targeted agents, which include cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), everolimus, and alpelisib, can be used in addition to endocrine therapy drugs. Despite all these available agents, eventually all patients with advanced HR-positive breast cancer will experience disease progression due to endocrine therapy resistance.

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Fulvestrant was approved by the US Food and Drug Administration (FDA) in 2002 and remained the only selective estrogen receptor degrader (SERD) approved for the treatment of advanced HR-positive breast cancer for more than 2 decades. Fulvestrant has been shown to improve overall survival as a single agent,[7] and a 500 mg intramuscular monthly dose was found to be more effective than 250 mg (HR for overall survival of 0.81; 95% CI = 0.69 to 0.96; P = 0.02).[8] In the past decade fulvestrant was also shown to be effective in combination with CDK4/6i.[9–11] More recently, a Phase 3 clinical trial showed prolonged PFS with the addition of alpelisib to fulvestrant for patients with advanced disease and a *PIK3CA* mutation who had received previous endocrine therapy, with PFS of 11.0 months in the alpelisib-fulvestrant group, as compared with 5.7 months in the placebo-fulvestrant group (HR for progression or death, 0.65; 95% CI, 0.50 to 0.85; P<0.001).[12]

Mutations in the estrogen receptor gene α (*ESR1*) which encodes the ER have been associated with resistance to aromatase inhibitors in patients with advanced HR-positive breast cancer. These mutations can also cause partial resistance to tamoxifen and fulvestrant.[13] There is also evidence that some patients have incomplete reduction in ER availability, which may correlate with progression of disease.[14]

The occurrence of resistance to currently approved endocrine therapy agents and the fact that fulvestrant requires intramuscular injections have led to an interest in agents with better bioavailability and more convenient administration. Elacestrant (RAD1901) is an oral nonsteroidal small-molecule SERD that selectively binds to the ER and activates its degradation.[15] In this review, we will analyze the rationale for the use of elacestrant, the currently available data regarding efficacy and toxicity, and future directions.

Evidence to Date

Preclinical Data

Wardell et al evaluated the pharmacological activities of elacestrant. The authors found that elacestrant inhibited *ESR1* activation both in vitro and in vivo, inhibited breast cancer cell proliferation, and inhibited xenograft tumor growth.[16]

Garner et al demonstrated that elacestrant inhibits expression of ERα in cultured breast tumor cell lines, causing complete degradation of the ER. Elacestrant also inhibited proliferation of ER-positive MCF-7 cells in vitro and inhibited tumor growth in MCF-7 xenograft models. When compared to tamoxifen and fulvestrant, elacestrant led to greater tumor growth inhibition. Importantly, in a mouse xenograft model of brain metastasis, elacestrant prolonged survival in comparison to fulvestrant, as 41% (5/12) of these animals treated with elacestrant survived until the end of the study at day 54, whereas no animal in the fulvestrant group survived beyond day 34. In this study, elacestrant was well tolerated in mice, and protected against bone loss in ovariectomized rats. Elacestrant did not affect endometrial thickness and actually antagonized the effect of estradiol in the uterus. These data suggested that elacestrant has a possible agonist action in the bone and antagonist action in the uterus.[15]

In a preclinical study, Bihani et al evaluated the efficacy of elacestrant alone and in combination with palbociclib or everolimus in ER-positive breast cancer models. Elacestrant caused a similar degradation of ER than fulvestrant in cell lines in vitro, a decrease in progesterone receptor (PR) expression, and complete tumor growth inhibition at 4 weeks in an MCF7 xenograft model. When compared to elacestrant alone, the combination of elacestrant with palbociclib or everolimus resulted in greater tumor growth inhibition. In two patient-derived xenograft models harboring *ESR1* mutations, elacestrant also inhibited tumor growth, and the inhibition was greater with the combination of elacestrant with palbociclib.[17]

Elacestrant was also evaluated in preclinical models of CDK4/6i resistance. Patel et al found that elacestrant inhibited growth in cells resistant to CDK4/6i, including in cells with *ESR1* mutation. Elacestrant also inhibited tumor growth of xenografts derived from patients previously treated with a CDK4/6i or who had de novo resistance to CDK4/6i.[18]

These preclinical data provided rationale for testing elacestrant in clinical trials, either alone or in combination with other agents, in the treatment of advanced HR-positive breast cancer.

Clinical Trials

Several clinical studies have evaluated the use of elacestrant in advanced breast cancer (Table 1). A Phase 1b clinical trial (RAD1901-106) assessed the impact of elacestrant on the availability of ER in ER-positive breast cancer lesions using 16α-^{18}F-fluoro-17β-estradiol positron emission tomography with low-dose computed tomography (FES-PET/CT). The trial included 16 post-menopausal women with advanced ER-positive, HER2-negative breast cancer who had disease progression after at least 6 months of 1–3 lines (median 2.5) of endocrine therapy for advanced disease. No patients had received prior CDK4/6i. Elacestrant was given continuously in two different doses, 400 mg daily or 200 mg daily, with escalation to 400 mg after 2 weeks. The median reduction in FES uptake in tumor lesions from baseline to day 14, which was the primary endpoint of the study, was 89.1%, and was similar in both dose cohorts. The overall objective response rate (ORR) was 11.1%, the time to response was 8 weeks, and the clinical benefit rate (CBR) was 30.8%. Median progression-free survival (PFS) was 5.3 months. Patients in the 400 mg cohort remained on elacestrant longer than patients who started at 200 mg and later escalated to 400 mg. The percentage change in FES uptake did not correlate with response, although it was a small number of patients. The trial also explored a potential correlation of response rates and *ESR1* mutations in circulating tumor DNA (ctDNA); 56% of patients (N=9) had *ESR1* mutations at baseline and the reduction of FES uptake was independent of the mutational status at baseline. The most common side effects were nausea (69%), fatigue (50%), dyspepsia (44%), and vomiting (37%).[19]

The Phase I study RAD1901-005 evaluated the safety and antitumor activity of elacestrant in heavily pre-treated post-menopausal women with advanced ER-positive, HER2-negative breast cancer. A total of 57 patients with a median of 3 prior lines of therapy for advanced disease were enrolled to receive elacestrant as a single agent, with dose increments from 200 mg to 1000 mg. Of note, 52% of patients had received a prior SERD, 52% had received a prior CDK4/6i, and 50% of women had at least one *ESR1* mutation at baseline ctDNA. The elacestrant dose selected for Phase II was 400 mg orally once a day, and a total of 50 patients were treated with this dose. The ORR was 19.4%, and the CBR was 42.6%;

Table 1 Clinical Trials That Evaluated the Use of Elacestrant in Advanced Breast Cancer

Study	Study Setting	Study Population	Number of Patients	Intervention	Primary Endpoint(s)	Results
RAD1901-106[19]	Phase Ib	Post-menopausal women with ER-positive HER2-negative advanced breast cancer who had disease progression after ≥ 6 months of 1–3 lines of endocrine therapy for advanced disease No prior CDK4/6i	16	Elacestrant 400 mg daily Elacestrant 200 mg daily with escalation to 400 mg after 2 weeks	Percentage difference in FES uptake in tumor lesions after 14 days of treatment, compared to baseline	Median reduction in FES uptake in tumor lesions from baseline to day 14: 89% (similar in both dose cohorts) ORR: 11.1% CBR: 30.8% Median PFS: 5.3 months
RAD1901-005[20]	Phase I	Post-menopausal women with ER-positive HER2-negative advanced breast cancer, heavily pre-treated (median of 3 prior lines of therapy for advanced disease) Allowed prior CDK4/6i and prior SERD	57	Elacestrant 200–1000 mg daily	Frequency of dose-limiting toxicities (DLT) during the first 28 days	No DLT up to 600 mg daily Most common side effects: nausea, increase triglycerides, decreased serum phosphorus ORR: 19.4% CBR: 42.6% Median PFS: 4.5 months
EMERALD[21]	Phase III	Men and post-menopausal women with ER-positive HER2-negative advanced breast cancer who had progressed on 1 or 2 lines of endocrine therapy for advanced disease Prior CDK4/6i was required	477	Elacestrant 400 mg daily versus standard of care endocrine therapy (fulvestrant or AI)	PFS in all patients and PFS in patients with *ESR1* mutation	PFS in all patients: relative reduction in progression or death of 30% (HR 0.70; P = 0.002) vs SoC PFS in patients with *ESR1* mutation: relative reduction in progression or death of 45% (HR 0.55; 95%; P = 0.0005) vs SoC 12-month PFS in all patients: 22.3% with elacestrant vs 9.4% with SoC 12-month PFS in patients with *ESR1* mutation: 26.8% with elacestrant vs 8.2% with SoC

Abbreviations: ER-positive, estrogen receptor positive; HER2-negative, human epidermal growth factor receptor 2 negative; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; FES, 16α-^{18}F-fluoro-17β-estradiol; ORR, objective response rate; CBR, clinical benefit rate; PFS, progression free survival; SERD, selective estrogen receptor degrader; DLT, dose-limiting toxicities; AI, aromatase inhibitor; SoC, standard of care; *ESR1*, estrogen receptor gene α.

the median PFS was 4.5 months. The median time to response was 2 months, and the median duration of response was 5.8 months. The CBR in patients with an *ESR1* mutation was 56.5%, and 30.4% in patients who had received prior CDK4/6i. Among patients with baseline *ESR1* mutation and an available post-baseline blood sample, 82% had a reduction of mutant allele fraction at the end of cycle 1. The most frequent side effects were nausea, increase in triglycerides, and decrease in serum phosphorus levels. Gastrointestinal toxicity was less common with tablet than capsule formulation. There were no dose-limiting toxicities.[20] This study provided preliminary evidence of clinical activity and rationale for phase III trials.

The EMERALD clinical trial was an international phase III open-label study comparing the safety and efficacy of elacestrant with standard of care endocrine therapy. The study included 477 men and post-menopausal women with locoregional recurrent or metastatic ER-positive, HER2-negative breast cancer who had received 1 or 2 lines of endocrine therapy for advanced disease. Previous treatment with a CDK4/6i was required, and no more than one prior line of chemotherapy for advanced disease was allowed. Patients were randomized to receive either elacestrant 400 mg daily or investigator's choice endocrine treatment with fulvestrant or an aromatase inhibitor (anastrozole, letrozole or exemestane). The study protocol recommended that investigators choose fulvestrant if the patient had not yet received fulvestrant, and an aromatase inhibitor for the patients who had progressed on fulvestrant. Selection of aromatase inhibitor agent should take in consideration the prior therapy with aromatase inhibitor. Patients were stratified by *ESR1* mutation detected in ctDNA using the Guardant360 CDx assay, prior treatment with fulvestrant, and presence or not of visceral metastasis. Primary endpoints were PFS in patients with *ESR1* mutation and in all patients. Patients randomized to elacestrant received 400 mg orally once a day, and dose reductions to 300 mg or 200 mg daily were allowed if toxicity. A total of 43% of patients had received 2 prior lines of endocrine therapy for advanced disease, 48% had a detectable *ESR1* mutation, and 29% of patients randomized to elacestrant had received prior fulvestrant. PFS was prolonged in the elacestrant arm versus standard of care in all patients, with a relative reduction in progression or death of 30% but an absolute difference in PFS of few weeks (HR 0.70; 95% CI, 0.55 to 0.88; P = 0.002; median PFS 2.8 months vs 1.9 months). PFS was also prolonged in patients with *ESR1* mutation treated with elacestrant, with a relative reduction in progression or death of 45% (HR 0.55; 95% CI, 0.39 to 0.77; P = 0.0005; median PFS 3.8 months vs 1.9 months) comparing to standard of care. The 12-month PFS was 22.3% in patients treated with elacestrant versus 9.4% with standard of care, and in patients with *ESR1* mutation it was 26.8% versus 8.2%, respectively. The authors also reported the benefit of elacestrant comparing to fulvestrant. Excluding patients who had received fulvestrant prior to the trial, the 12-month PFS was 22.3% with elacestrant versus 9.5% in the fulvestrant group. Among patients with *ESR1* mutation, the 12-month PFS was 26.8% and 8.3% in the elacestrant versus fulvestrant group, respectively. Of note, subgroup analysis showed that elacestrant was also beneficial among patients who had received prior fulvestrant. Overall survival data was immature. The most common side effects were nausea, fatigue, vomiting, decreased appetite and arthralgia. Grade 3/4 adverse effects happened in 27% of patients receiving elacestrant, most commonly nausea, back pain and increased ALT, and in 20% of patients receiving standard of care therapy.[21] Further data from the EMERALD trial demonstrated that the duration of prior CDK4/6i therapy was associated with PFS, and the longer the duration of prior CDK4/6i in the metastatic setting, the longer the PFS on elacestrant versus standard of care therapy. For patients that received at least 12 months of CDK4/6i, the median PFS was 3.8 months in the elacestrant group versus 1.9 months in the standard of care group (HR 0.61, 0.45–0.83). Of note, the difference was higher in patients with ESR1 mutations (median PFS in patients with $\geq$ 12 months prior CDK4/6i therapy of 8.6 months versus 1.9 months in patients treated with elacestrant versus standard of care, respectively; HR 0.41, 0.26–0.63).[22] Based on the results of the EMERALD trial, on January 27, 2023, the FDA approved elacestrant for post-menopausal women and men with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer who had disease progression following at least one line of endocrine therapy. The Guardant360 CDx assay was also approved by the FDA as a companion diagnostic device to identify patients for treatment with elacestrant.

Discussion

Preclinical evidence revealed that elacestrant was effective in decreasing ER-positive cell proliferation and tumor growth in xenograft models and in cells with *ESR1* mutation or resistance to CDK4/6i.[15–18] Both RAD1901-005 and RAD1901-106 studies confirmed elacestrant efficacy in the clinical setting, with impact in both ORR and CBR.[19,20]

Elacestrant was the first oral SERD to be shown to increase progression-free survival in patients with advanced HR-positive, HER2-negative breast cancer in a phase III trial, comparing to standard of care single-agent endocrine therapy. The EMERALD trial design was innovative due to the inclusion of *ESR1* mutation as a stratification factor. The trial demonstrated that elacestrant was more beneficial for patients whose tumors harbored an *ESR1* mutation compared to fulvestrant, leading to the approval by the FDA in this patient population. However, it should be noted that the study showed a short PFS in the overall population and in patients with *ESR1* mutations, irrespective of treatment arm, recognizing that these were patients previously treated with CDK4/6i. Taking into account that some patients in this trial could already have resistance to endocrine therapy, the authors also reported the 6-month and 12-month PFS rates, which highlighted the benefit of elacestrant.[21] Although elacestrant was beneficial regardless of the duration of prior exposure to CDK4/6i in the EMERALD trial, patients who received prior CDK4/6i for a longer period of time seemed to benefit more from elacestrant.[22]

Elacestrant was generally well tolerated at a dose of 400 mg daily in clinical trials, with the main side effects being upper gastrointestinal symptoms and fatigue.[19–21] In the RAD1901-106 trial, patients treated with 200 mg daily dose of elacestrant also had a significant reduction in FES uptake, suggesting that 200 mg doses may be an option for patients who do not tolerate 400 mg.[19]

The currently available data on elacestrant use in the treatment of patients with advanced breast cancer provided rationale for the development of multiple other clinical trials investigating the use of elacestrant in early-stage breast cancer, and in combination with other drugs for metastatic disease, including alpelisib, everolimus, and CDK4/6i (Table 2).[23–27] Although pre-menopausal women were not eligible for the RAD1901-106, RAD1901-005, and EMERALD trials, some of the new clinical protocols are enrolling pre-menopausal women and combining elacestrant with ovarian suppression.[24–26] Trials comparing elacestrant versus fulvestrant as the backbone endocrine therapy in combination with CDK4/6i, alpelisib, and everolimus will help guide clinical decision-making regarding the SERD of

Table 2 Ongoing Clinical Trials Examining the Use of Elacestrant in Breast Cancer

Study	Study Setting	Study Population	Intervention	Primary Outcome(s)	Estimated Enrollment
ELIPSE: Elacestrant in Preoperative Setting, a Window of Opportunity Study (NCT04797728)[23]	Early phase I	Post-menopausal women with ER-positive, HER2-negative breast cancer, stage cT1-3N0	Elacestrant 400 mg PO daily for 4 weeks	Complete cell cycle arrest (Ki-67 ≤ 2.7%)	23 patients
EORTC-2129-BCG: Elacestrant for Treating ER+/HER2- Breast Cancer Patients With ctDNA Relapse (NCT05512364)[24]	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 1b-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)[25]	Phase Ib/II	Pre- and post-menopausal women and men with ER-positive and HER2-negative advanced breast cancer	Elacestrant as 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 Combination In Patients With Metastatic Breast Cancer (NCT05563220)[26]	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 (NCT04791384)[27]	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

Abbreviations: ER-positive, estrogen receptor positive; HER2-negative, human epidermal growth factor receptor 2 negative; ctDNA, circulating tumor DNA; AI, aromatase inhibitor; HR-positive, hormone receptor positive.

choice in second-line therapy. When choosing second- or third-line therapy for advanced HR-positive, HER2-negative patients, the cost will also have to be taken into consideration as elacestrant reached the market at a much higher price than aromatase inhibitors and fulvestrant.

Several other oral SERDs have been shown to have preclinical efficacy in HR-positive breast cancer, including amcenestrant, giredestrant, imlunestrant, camizestrant, and rintodestrant, among others. These drugs are currently undergoing investigation into the treatment of HR-positive breast cancer patients, both in early-stage and metastatic settings.[28]

Amcenestrant (SAR439859) was tested in a single-arm phase I/II trial (AMEERA-1) as monotherapy in post-menopausal women with pre-treated ER-positive, HER2-negative advanced breast cancer. ORR was 11%, and CBR was 28%, and amcenestrant also demonstrated efficacy among patients with *ESR1* mutations. There were no dose-limiting toxicities, and the most common treatment-related adverse effect was gastrointestinal symptoms, hot flashes, and arthralgia.[29] In the phase II randomized clinical trial AMEERA-3 of amcenestrant compared with standard endocrine therapy of physician's choice in pre-treated patients, however, amcenestrant failed to improve PFS, the primary endpoint of the study.[30] Giredestrant (GDC-9545), another oral SERD, failed to improve PFS when compared to aromatase inhibitor or fulvestrant in pre-treated men and women with advanced breast cancer in the phase II acelERA BC study.[31]

Imlunestrant (LY3484356) has also been shown to have activity in pre-treated pre- and post-menopausal patients with advanced breast cancer in the phase Ia EMBER trial, without dose limiting toxicities.[32] Rintodestrant (G1T48) was tested in a phase I trial in pre-treated ER-positive, HER2-negative advanced breast cancer patients that had not received a CDK4/6i, and was found to be effective, including in patients with *ESR1* mutations.[33]

In the phase I clinical trial SERENA-1 evaluating camizestrant (AZD9833) in pre-treated patients with advanced ER-positive, HER2-negative breast cancer, the main adverse effects were visual disturbances, bradycardia, and nausea. In that trial, camizestrant had an ORR of 16% and CBR of 42%.[34] The SERENA-2 trial evaluated the efficacy and safety of different camizestrant doses as monotherapy in comparison with fulvestrant in 240 patients with ER-positive and HER2-negative advanced breast cancer. Patients should have received no more than one line of endocrine therapy and no more than one line of chemotherapy in an advanced setting. Approximately 50% of patients had received a prior CDK4/6i, and ESR1 mutation was present in 36.7% of patients. Camizestrant increased PFS comparing to fulvestrant, with median PFS of 7.2 months with camizestrant 75 mg, 7.7 months with camizestrant 150 mg, and 3.7 months with fulvestrant (HR 0.58, CI 0.41–0.81, p = 0.0124, and HR 0.67, CI 0.48–0.92, p = 0.0161, respectively). Camizestrant also increased PFS in patients with prior exposure to CDK4/6i. In patients with an ESR1 mutation, the median PFS was 6.3 months with camizestrant 75 mg, 9.2 months with camizestrant 150 mg, and 2.2 months with fulvestrant (HR 0.33, CI 0.18–0.58, and HR 0.55, CI 0.33–0.89, respectively). Both camizestrant doses were well tolerated.[35]

Several of these oral SERDs are being tested in combination with CDK4/6i, alpelisib, and everolimus in ongoing phase III clinical trials for advanced breast cancer. These drugs are also undergoing investigation in early-stage disease in neoadjuvant and adjuvant settings.[28] At the moment, there are no head-to-head comparison studies of elacestrant with other oral SERDs.

Conclusion

Elacestrant was the first oral SERD to improve PFS in previously treated patients with HR-positive, HER2-negative advanced breast cancer when compared to standard of care endocrine therapy. Importantly, it was more beneficial in patients with *ESR1* mutation, a known mechanism of resistance to therapy to aromatase inhibitors, leading to FDA approval in this patient population. Ongoing clinical trials evaluating elacestrant and other SERDs will provide data that may assist clinicians decide the best choice and sequence of endocrine therapy agents for HR-positive breast cancer.

Disclosure

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