Oral SERDs in Breast Cancer: Imulnestrant and Elacestrant

Key Takeaways

- Imulnestrant, an oral SERD, shows promise in overcoming resistance in ER+/HER2– breast cancer, especially when combined with abemaciclib, as seen in the EMBER-3 trial.
- Elacestrant, the first FDA-approved SERD for ESR1-mutant HR+ metastatic breast cancer, demonstrated significant PFS improvements in the EMERALD trial.
- Both imulnestrant and elacestrant highlight the evolving landscape of ER+ breast cancer treatment, emphasizing the importance of ongoing research and collaboration among health care professionals.

Oral selective estrogen receptor degraders (SERDs) are a promising line of treatments for patients with breast cancer.

Breast cancer is a common type of cancer among women, according to the National Library of Medicine. Estrogen-receptor–positive (ER+) disease is treated with endocrine therapies; however, patients commonly develop resistance to these therapies, making treatment a challenge. A second-generation drug, selective estrogen receptor degraders (SERDs), can overcome these existing treatment limitations. Additionally, they can be administered orally, which is often more convenient and less invasive for patients with ER+ breast cancer.1 Notable oral SERDs that have demonstrated positive benefits in patients with breast cancer are imulnestrant (Eli Lilly & Co) and elacestrant (Orserdu; Stemline Therapeutics).

Imulnestrant

Imulnestarnt is a brain-penetrant, oral SERD that delivers continuous ER inhibition, including in ESR1-mutant cancers. Because the ER is the key therapeutic target for patients with ER+, human epidermal growth factor receptor 2 negative (HER2–) breast cancer, novel degraders of ER may overcome resistance to endocrine therapy in addition to providing consistent oral pharmacology and convenience of administration. Imlunestrant is undergoing investigation for advanced breast cancer and as an adjuvant treatment in early breast cancer in the phase 3 trials EMBER-3 (NCT04975308) and EMBER-4 (NCT05514054), as well as the phase 1a/1b EMBER (NCT04188548) and PIKASSO-01 (NCT05307705) trials.[2]

EMBER-3 Clinical Trial

Although imlunestrant is not yet approved by the FDA, clinical data—such as those demonstrated in the open-label, randomized phase 3 EMBER-3 clinical trial—show support for an indication in ER+/HER2– breast cancer. The trial assessed the efficacy of imlunestrant compared with the investigator's choice of endocrine therapy, as well as the efficacy of imlunestrant with abemaciclib (Verzenio; Eli Lilly and Company) compared with imlunestrant alone.[2,3]

A total of 874 patients who recurred or progressed during or after therapy with an aromatase inhibitor, administered either alone or with a CDK4/6 inhibitor, were enrolled and randomly assigned to receive imlunestrant (n = 331), standard therapy (n = 330), or imlunestrant with abemaciclib (n = 256). The trial's

primary end point was investigator-assessed progression-free survival (PFS) with imlunestrant compared with standard therapy among those with ESR1 mutations (n = 256) and among all patients, as well as with imlunestrant with abemaciclib compared with imlunestrant among all patients who had undergone concurrent randomization. Findings were published in the New England Journal of Medicine.[2-4]

EMBER-3 Results

Among the patients with ESR1 mutations, those treated with imlunestrant achieved a PFS of about 5.5 months compared with 3.8 months for those treated with standard therapy. In the overall population, the median PFS was 5.6 months with imlunestrant and 5.5 months with standard therapy (HR for progression or death, 0.87; 95% CI, 0.72-1.04; P = .12). When specifically evaluating PFS of imlunestrant plus abemaciclib compared with imlunestrant alone, the median PFS was 9.4 months and 5.5 months, respectively (HR, 0.57; 95% CI, 0.44-0.73; P < .001). Further, investigators also reported mean survival times of 19.4 months, 7.9 months (95% CI, 6.8–9.1) with imlunestrant, and 5.4 months (95% CI, 4.6-6.2) with standard therapy (difference: 2.6 months [95% CI, 1.2-3.9]; P < .001).[2,4]

Elacestrant

Elacestrant is the first FDA-approved SERD for patients with ESR1-mutant HR+ metastatic breast cancer who are refractory to endocrine therapy, according to speakers from a 2025 American Society of Clinical Oncology Annual Meeting presentation. Its approval, which was granted in 2023, is specifically for postmenopausal women or adult men. It is a novel SERD degrader that has previously demonstrated its positive activity in early studies, but its approval is based on findings from the phase 3 EMERALD clinical trial (NCT03778931).[5,6]

EMERALD Clinical Trial

EMERALD is a randomized, open-label phase 3 trial that enrolled patients with ER+/HER2– advanced breast cancer who had 1 to 2 lines of endocrine therapy, required pretreatment with a CDK4/6 inhibitor, and had up to 1 prior line of chemotherapy. Patients were randomly assigned to receive either elacestrant (400 mg; n = 239) or standard of care endocrine monotherapy (n = 238) once per day.[6,7]

The primary end points were PFS by blinded independent central review in all patients and in those with detectable ESR1 mutations. Secondary end points included overall survival in all patients and those with detectable ESR1 mutations.[6,7]

EMERALD Results

The investigators detected ESR1 mutation in approximately 47.8% of patients. Additionally, 43.4% of the patient population had received 2 prior endocrine therapies.[7]

PFS was shown to be prolonged in all patients (HR, 0.70; 95% CI, 0.55-0.88; P = .002) and patients with an ESR1 mutation (HR, 0.55; 95% CI, 0.39-0.77; P = .0005). Treatment-related grades 3 and 4 adverse events (AEs) occurred in about 7.2% and 3.1% of patients receiving elacestrant and standard of care, respectively. Treatment-related AEs that led to treatment discontinuations were more common in the elacestrant treatment group (3.4%) compared with the standard of care group (0.9%). Nausea of any grade occurred in 35.0% of those treated with elacestrant and 18.8% treated with standard of care (grade 3 or 4: 2.5% and 0.9%, respectively).[7]

Imlunestrant and Elacestrant in Clinical Practice

The EMBER-3 findings support the potential of imlunestrant—particularly in combination with abemaciclib—as a promising treatment strategy for patients with ER+/HER2– advanced breast cancer who have experienced disease progression on prior endocrine therapy. However, continued investigation and regulatory review will pave the way for this new therapeutic option for this high-need population.

Additionally, elacestrant is a SERD that demonstrates a significant PFS improvement compared with the standard of care both in the overall population of patients and in those with ESR1 mutations. It has also demonstrated manageable safety in a phase 3 trial for patients with ER+/HER2– advanced breast cancer.[4,7]

Pharmacists can remain vigilant as data on imlunestant and elacestrant continues to update by staying up to date on ongoing clinical trials and their findings. Additionally, pharmacists can collaborate with other health care professionals in the implementation of these SERDs in clinical practice. Most importantly, pharmacists are a valuable source of information for patients on these treatments, educating them on the differences, AEs, and proper dosing.

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