

Targeting ESR1 mutations: Imlunestrant and the next chapter in ER-positive breast cancer care

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Abstract

Around 80% of breast cancers in women aged 45 years and older are estrogen receptor-positive (ER+). Despite advances in endocrine therapy, resistance driven by ESR1 mutations remains a major clinical challenge. These mutations cause constitutive receptor activation even in estrogen-deprived environments, limiting the efficacy of aromatase inhibitors and fulvestrant. Imlunestrant (Inluriyo™) is the first FDA-approved oral selective estrogen receptor degrader (SERD) designed to overcome ESR1-mediated resistance. As a potent, brain-penetrant agent, it blocks coactivator binding and promotes proteasomal degradation of both wild-type and mutant receptors, including the resistant Y537S variant. The phase 3 EMBER-3 trial demonstrated improved progression-free survival and favorable tolerability compared with standard endocrine therapy. Imlunestrant's oral formulation, safety profile, and ability to target ESR1 mutations mark a pivotal step toward personalized care for ER-positive, HER2-negative breast cancer. Its approval highlights the evolving landscape of precision oncology, emphasizing mutation-guided treatment selection and the potential of next-generation SERDs to reshape hormone-driven cancer management.

Dear Editor,

Estrogen receptor-positive (ER+) breast cancer is the most prevalent subtype, representing nearly 80% of breast cancer cases in women aged 45 years and above. Despite major improvements in screening and hormone therapy, approximately 44% of women eventually develop advanced or metastatic disease, which remains treatable but rarely curable [1]. Among HER2-negative tumors, treatment resistance continues to pose a major clinical challenge. Recent findings by Kulkarni *et al.* demonstrated that many patients with high-risk early-stage disease do not respond adequately to chemotherapy or immunotherapy, underscoring the urgent need for novel, more selective endocrine strategies [2]. Resistance to endocrine therapy in ER-positive breast cancer is often driven by acquired ESR1 mutations, which enable the estrogen receptor to remain active even in the absence of estrogen. These mutations typically emerge following aromatase inhibitor therapy, promoting continuous tumor growth despite hormonal suppression. In addition, ESR1 fusion genes have been identified as contributors to advanced disease and therapeutic resistance, complicating disease control in metastatic settings [3]. To address this challenge, the U.S. FDA recently approved imlunestrant (Inluriyo), a next-generation oral selective estrogen receptor degrader (SERD). Unlike traditional therapies such as fulvestrant or exemestane, imlunestrant binds to and degrades both wild-type and mutant forms of the receptor, effectively blocking estrogen-driven signaling. Clinical findings demonstrated a significant improvement in progression-free survival among patients harboring ESR1 mutations, marking a major advancement in the treatment of endocrine-resistant, ER-positive, HER2-negative breast cancer [3]. Imlunestrant is a next-generation, oral, brain-penetrant SERD with pure antagonistic

properties. It selectively binds to and degrades the estrogen receptor (ER), including mutant forms arising from *ESR1* gene alterations. These mutations, often emerging after aromatase inhibitor therapy, cause constitutive ER activation and confer resistance to standard endocrine therapies. By competitively binding to the ER ligand-binding domain, imlunestrant prevents coactivator recruitment and promotes proteasomal degradation, effectively overcoming resistance associated with mutations such as Y537S. Additionally, it induces cell cycle arrest and modulates immune response pathways, contributing to its anti-tumor activity [4]. The EMBER-3 trial, a prospective, randomized, phase 3 study in patients with recurrent or advanced breast cancer previously treated with CDK4/6 inhibitors, evaluated the safety and efficacy of oral imlunestrant, with or without abemaciclib. Patients harboring ESR1 mutations demonstrated significantly longer progression-free survival when treated with imlunestrant versus standard therapy (5.5 vs. 3.8 months). Doses ranging from 200 to 1,200 mg daily were well tolerated, with no dose-limiting toxicities or treatment discontinuations due to adverse events [5]. Safety data confirmed that imlunestrant was generally well tolerated. The most common adverse events were fatigue, diarrhea, and nausea, with fewer grade 3 or higher events compared to standard therapy (17.1% vs. 20.7%). No bradycardia or ocular toxicities were observed, and rates of dyslipidemia were comparable between treatments [5].

As the first oral SERD approved for ESR1-mutated ER-positive breast cancer, imlunestrant offers the convenience of oral administration, improving patient compliance and quality of life relative to monthly intramuscular fulvestrant injections. Its ability to penetrate the blood-brain barrier also addresses a critical limitation of fulvestrant, potentially providing intracranial anti-tumor activity in patients with brain metastases [6]. Imlunestrant exemplifies how comprehensive genomic profiling can guide personalized treatment strategies, improving outcomes for patients with limited options following endocrine therapy failure. By targeting both wild-type and mutant ESR1 receptors, it offers a clinically meaningful advancement in ER-positive breast cancer management, particularly for those with endocrine-resistant disease [6]. Its approval represents a significant milestone in the care of ER-positive, HER2-negative patients, combining oral convenience, favorable tolerability, and demonstrated intracranial activity—advantages over fulvestrant.

Future research should focus on expanding access, conducting long-term follow-up studies, and incorporating routine ESR1 mutation testing to guide individualized therapy. Overall, imlunestrant marks a key step toward precision endocrine therapy, offering renewed hope for patients facing hormone-resistant breast cancer.

Ethical Approval

Ethics approval was not required for this article as it does not involve primary research, human participants or animals. This is a correspondence/review article.

Consent

Informed consent was not required for this article as it does not involve human participants or personal data. This is a correspondence/review article.

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Author's Contribution

S.M.S. conceived and supervised the study, providing overall mentorship and guidance throughout the project. I.H. prepared the main body of the manuscript, performed literature referencing, and drafted the abstract. S.M. developed the introduction and conclusion, compiled the complete manuscript, and served as the corresponding author. Finally, S.M.S. conducted the critical review, provided revisions, and approved the final version of the manuscript for submission.

Conflicts of Interest Disclosure

None declared.

Guarantor

All the authors of this paper accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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