REVIEW ARTICLE

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Imlunestrant: A Novel Weapon Against Endocrine-Resistant Breast Cancer

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Abstract

Background: Breast cancer, particularly Estrogen Receptor-positive (ER+) and Human Epidermal Growth Factor Receptor 2-negative (HER2-) disease, frequently develops resistance to endocrine therapy due to ESR1 gene mutations, highlighting the need for more effective estrogen receptor-targeted therapies.

Methods: This review summarizes available preclinical and clinical evidence on IMLUNESTRANT, a next-generation oral Selective Estrogen Receptor Downregulator (SERD), including findings from Phase Ia/Ib EMBER trials, EMBER-2, and Phase 3 EMBER-3 trial.

Results: Imlunestrant demonstrated meaningful monotherapy activity in early-phase trials with an Objective Response Rate (ORR) of 11.8%, Clinical Benefit Rate (CBR) of 54.9%, and Progression-Free Survival (PFS) of 7.2 months. Combination therapy, particularly with ABEMACICLIB, showed improved outcomes (ORR up to 61.8%, PFS ~19 months). EMBER-2 confirmed strong biological activity, with reductions in ER and PR expression (~80%) and Ki-67 (~70%), establishing 400 mg once daily as the optimal dose. In the Phase 3 EMBER-3 trial, IMLUNESTRANT significantly improved PFS in ESR1-mutated patients (5.5 vs 3.8 months; RMST difference 2.6 months; $P < 0.001$), while showing comparable outcomes to standard therapy in the overall population (5.6 vs 5.5 months; HR 0.87). The combination with ABEMACICLIB demonstrated the greatest benefit (PFS 9.4 vs 5.5 months; HR 0.57; $P < 0.001$).

Conclusion: Imlunestrant is a potent and well-tolerated oral SERD with strong biological activity and clinically meaningful efficacy, particularly in ESR1-mutated breast cancer and when combined with CDK4/6 inhibitors, offering a promising strategy to overcome endocrine resistance

Keywords: Imlunestrant • ER-positive breast cancer • ESR1 mutation • Selective Estrogen Receptor Degrader (SERD) • CDK4/6 inhibitors

Introduction

Breast cancer is the most common malignancy affecting women worldwide. (1) It accounts for 2.3 million new cases and 6,70,000 deaths globally. (1) In India, approximately 1.8 lakh new cases are reported annually. It contributes for 14% of all female cancers. (2) Risk Factors include genetic factors like Breast Cancer Gene 1 (BRCA1), Breast Cancer Gene 2 (BRCA2), Tumor Protein 53 (TP53) and Phosphatase and Tensin Homolog (PTEN) gene mutations and positive family history in first degree relatives, hormonal factors like prolonged estrogen exposure (Post-menopausal Hormone Replacement Therapy), age related risk like after menopause peak around 70-80 years, geographic variations like higher incidence in North America, Northern & Western Europe and life style factors like obesity, radiation exposure, smoking and alcohol consumption. (3) Based on American Joint Committee on Cancer (AJCC) Breast Carcinoma classified as: a) Early Breast Cancer (Stage I-II and Operable stage IIIA) b) Locally Advanced Breast Cancer (Stage IIIB-IIIC) c) Advanced/Metastatic Breast Cancer. (3) Based on molecular subtypes (gene expression profiling) classified as a) Luminal A: Estrogen Receptor (ER)+, Human Epidermal Growth Factor Receptor 2 (HER2) - (best prognosis) b) Luminal B: ER +, HER2 ± (intermediate prognosis) c) HER2-enriched: HER2 +, ER - (aggressive) d) Basal-like/Triple negative : ER -, Progesterone Receptor (PR) - , HER2 - (poor prognosis). (3)

Breast cancer treatment depends on stage: Early stage (I–II): Surgery is main treatment ± radiotherapy, chemotherapy, hormonal therapy and HER2 targeted therapy. (2) Locally advanced stage (III): neoadjuvant chemotherapy→surgery→ radiotherapy ± endocrine/HER2 therapy. (2) Metastatic Breast Cancer stage (IV): mainly systemic therapy (endocrine, chemotherapy, HER2 drugs, immunotherapy) with radiotherapy for symptoms. (2) ER+, HER2- breast cancer is the most common subtype and is primarily treated with endocrine therapy including selective estrogen receptor modulators (SERMs) e.g. tamoxifen, selective estrogen receptor down regulators (SERDs) e.g. FULVESTRANT and aromatase inhibitors (AI) e.g. letrozole, anastrozole. (4) The ESR1 gene makes the estrogen receptor (ER) — the main target of endocrine therapy. (5) Normally, ER needs estrogen hormone to get activated. (5) When we give treatments like aromatase inhibitors, SERMs, or SERDs, we reduce estrogen or block the receptor, so the cancer slows down. (6) But when ESR1 mutations develop, the receptor changes its shape. Because of this change the estrogen receptor becomes active even without estrogen. (7)

SERMs block the estrogen receptor but do not destroy it. AIs lower estrogen levels in the body but do not act directly on the receptor. (8) SERDs bind to the receptor and destroy it, giving the strongest ER shutdown. (8) Therefore, SERDs work best in endocrine-resistant or ESR1-mutated cancers. (9) Fulvestrant is the only approved SERD, but due to poor bioavailability, is given by intramuscular injections which is painful and limited efficacy in ESR1 mutations patients. (10–12).

Imlunestrant

Imlunestrant is a next-generation oral SERD, brain penetrant and pure ER antagonist that continuously blocks the estrogen receptor and shows activity even in ESR1-mutated tumors. (13–15)

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Chemical structure

The chemical name for Imlunestrant tosylate is (5R)-5-(4-(2-(3-(flouromethyl) azetidin-1-yl) ethoxy) phenyl)-8-(trifluoromethyl)-5H-(1) benzopyrano (4,3-c)quinolin-2-ol, tosylate salt. (16)

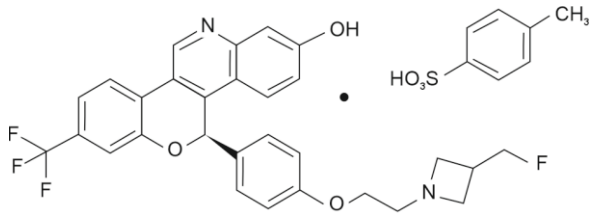

Figure 1: Chemical structure for Imlunestrant tosylate

Mechanism of action

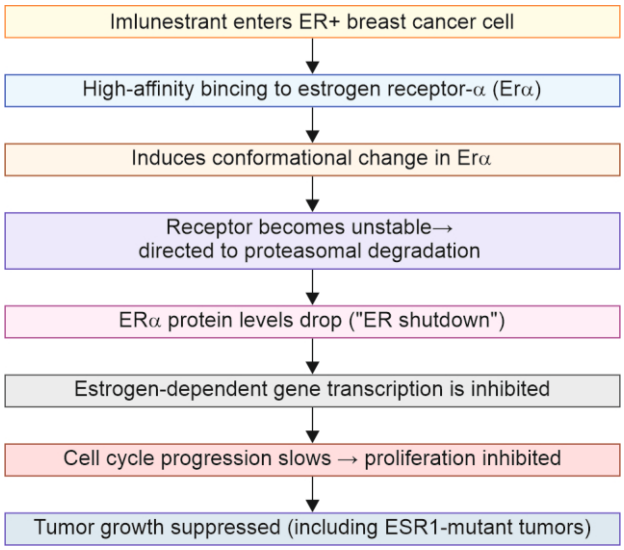

Figure 2: Mechanism of action of Imlunestrant

Pharmacokinetic characteristics

Table 1 depicts pharmacokinetic characteristics of IMLUNESTRANT. (16)

Table 1: Pharmacokinetics characteristics of imlunestrant

Parameter	Imlunestrant
Dosage	Oral tablets 400 mg once daily
Time to steady state	~6 days
Absolute oral bioavailability	10%
Tmax	4 hours
Plasma protein binding	>99%
Half-life (t½)	30 hours
Metabolism	Sulfation, CYP3A4 and glucuronidation
Excretion	97% in faeces (unchanged), 0.3% in urine

Adverse drug reactions

The adverse drug reactions (≥10%) including hematological abnormalties (↓hemoglobin, ↓neutrophils, ↓platelets) and biochemical abnormalities such as ↑AST/ALT, ↑triglycerides/cholesterol and ↓calcium (17). GI effects are frequent mainly diarrhea, nausea, constipation and abdominal pain along with fatigue and musculoskeletal pain (17). Less common reactions include vomiting, headache, cough, decreased appetite, hot flushes, pruritus, dyspepsia and stomatitis (16).

Precautions & contraindications

Imlunestrant has no absolute contraindications, but it can cause embryo-fetal toxicity so avoided in pregnancy and breastfeeding (16).

Table 2: Summary of EMBER 1 trial

Study ID / Phase	*Intervention Arm (N) & Regimen*	*Efficacy Outcomes*	*Safety Outcomes*
EMBER Phase Ia/Ib18	Imlunestrant Monotherapy (RP2D 400 mg once daily) (N = 51)	ORR: 11.8%, CBR: 54.9%, Median PFS: 7.2 months (95% CI: 3.7–8.3), ESR1-mutated: 7.1 months, ESR1-non mutated: 5.6 months	Mostly Grade 1–2: nausea (39%), fatigue (39%), diarrhea (29%), Grade ≥3 TEAEs: 19.6%, Discontinuations: None, Dose reductions: 3.9%
	Imlunestrant + Abemaciclib (CDK4/6 inhibitor) (N = 42)	ORR: 32.1%, CBR: 71.4%, Median PFS: 19.2 months (95% CI: 13.8–Not reached), 18-month PFS: 60.7%	Common TEAEs: diarrhea (95%), nausea (60%), fatigue (43%), neutropenia (43%), Grade ≥3 TEAEs: 59.5%, Discontinuation: 2.4%
	Imlunestrant + Abemaciclib + Aromatase Inhibitor (N = 43)	ORR: 61.8%, CBR: 79.1%, Median PFS: Not Reached, Estimated 18-months PFS: 73.4%	Common TEAEs: diarrhea (81%), fatigue (58%), nausea (63%), neutropenia (44%), Grade ≥3 TEAEs: 48.8%, Discontinuation: 7%
	Imlunestrant + Everolimus (N = 42)	ORR: 21.4%, CBR: 61.9%, Median PFS: 15.9 months (95% CI: 11.3–19.1)	TEAEs: diarrhea (57%), fatigue (48%), ↑AST (38%), Grade ≥3 TEAEs: consistent with EVEROLIMUS profile, Discontinuation: 9.5%
	Imlunestrant + Alpelisib (N = 21)	ORR: 58.3%, CBR: 61.9%, Median PFS: 9.2 months (95% CI: 3.7–11.1)	Grade ≥3 TEAEs: 81%, Common severe AEs: rash (48%), hyperglycemia (10%), diarrhea (10%), Discontinuation: 38.1%

**RP2D- Recommended Phase 2 Dose, ORR – Objective Response Rate, CBR – Clinical Benefit Rate, PFS – Progression-Free Survival, TEAEs – Treatment-Emergent Adverse Events, AEs – Adverse Events, CI- Confidence Interval*

Table 3: Summary of EMBER 2 trial

Study ID / Phase	*Intervention Arm (N) & Regimen*	*Efficacy Outcomes*	*Safety Outcomes*
EMBER-2/Phase I, Preoperative Window-of-Opportunity Study[19]	Imlunestrant 200 mg OD (N=28) 2 weeks before surgery	ER ↓ 89%, PR ↓ 85%, Ki-67 ↓ 69%, CCCA: 15%	TEAE ≥1: 75% (mostly Grade 1) Common AE: Diarrhea 11%, Hot flush 14%, Nausea 11%, Headache 7% Grade ≥3 TEAE: 1 patient (pt) (4%), none related to drug No discontinuations
EMBER-2/ Phase I[19]	Imlunestrant 400 mg OD (N=30) Optimal biological dose	ER ↓ 82%, PR ↓ 76%, Ki-67 ↓ 71%, CCCA: 23%	TEAE ≥1: 57% Common AE : Fatigue 20%, Diarrhea 10%, Hot flush 7%, Nausea 3% Grade ≥3 TEAE: 1 pt (3%), No treatment-related diarrhea or nausea (better GI tolerability)
EMBER-2/Phase I[19]	Imlunestrant 800 mg OD (N=28)	ER ↓ 70%, PR ↓ 82%, Ki-67 ↓ 72%, CCCA: 35% (highest)	TEAE ≥1: 68% Higher GI toxicity vs other arms: Diarrhea 32%, Nausea 14% Grade ≥3 TEAE: 1 pt (4%) (headache, nausea, blepharospasm) No discontinuations

** ER – Estrogen Receptor, PR – Progesterone Receptor, Ki-67 – Proliferation Marker Ki-67, CCCA – Complete Cell Cycle Arrest*

Drug interactions

Strong CYP3A inhibitors markedly increase IMLUNESTRANT levels and require dose reduction or avoidance of IMLUNESTRANT while strong CYP3A inducers decrease imlunestrant levels and increase dosage of IMLUNESTRANT required (16). Additionally, because IMLUNESTRANT inhibits P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) so it can increase the concentration of sensitive substrates like digoxin (P-gp substrate) and rosuvastatin (BCRP) which further lead to drug related toxicities so such combinations should generally be avoided (16).

Clinical development program

Tables 2, 3 and 4 represent the characteristics of various phase 1/2/3 clinical trials conducted to evaluate the efficacy and safety of IMLUNESTRANT in breast cancer patients.

Regulatory status

Imlunestrant has been approved by US Food and Drug Administration on 25th September 2025 for ER+/HER2- ESR1-mutated advanced or metastatic breast cancer patients in adults (16).

Table 4: Summary of EMBER 3 trial

Study ID / Phase	*Intervention Arm (N) & Regimen*	*Efficacy Outcomes*	*Safety Outcomes*
EMBER-3 / Phase 3[17]	Imlunestrant 400 mg OD (N = 331) vs Standard Therapy (Fulvestrant or Exemestane) (N = 330)	ESR1-mutated subgroup: Median PFS 5.5 months vs 3.8 months with standard therapy RMST at 19.4 months: 7.9 vs 5.4 months (Δ = 2.6 months; P<0.001) Overall population: Median PFS 5.6 vs 5.5 months (HR 0.87, P=0.12 → Not Significant) 18-months OS: 78.6% vs 71.8%	Grade ≥3 AEs: 17.1% vs 20.7% Most common AEs: Fatigue (22.6%) vs 13.3%, Diarrhea (21.4%) vs 11.7%, Nausea (17.1%) vs 13%, Serious AEs: 10.4% vs 11.4 % Discontinuation: 4.3% vs 1.2%
EMBER-3/ Phase 3[17]	Imlunestrant 400 mg OD + Abemaciclib 150 mg BD (N = 213) vs Imlunestrant 400 mg OD (N = 331)	Median PFS 9.4 months vs 5.5 months (HR 0.57, P<0.001) in all randomized population Prior CDK4/6 inhibitors subgroup: PFS 9.1 months vs 3.7 months (HR 0.51)	Grade ≥3 AEs: 48.6% (highest) vs 17.1% Most common: Diarrhea (86% total; 8.2% Grade ≥3), Neutropenia (48%; 19.7% Grade ≥3) Anaemia (43%; 7.7% Grade ≥3) Serious AEs: 16.8% Discontinuation: 6.3%

**ESR1 is the gene that encodes Estrogen Receptor-α (ERα), RMST – Restricted Mean Survival Time, HR- Hazard Ratio, CDK- Cyclin dependent kinases*

Conclusion

Imlunestrant is a strong and well-tolerated oral SERD that offers a useful new option for ER+/HER2- breast cancer, especially when the disease becomes resistant to earlier hormonal treatments or develops ESR1 mutations. It effectively breaks down the estrogen receptor, slows tumor growth and shows consistent benefit both alone and in combination with other targeted drugs. Side effects are generally mild and manageable. When combined with treatments like CDK4/6 inhibitors, it provides even better and longer-lasting disease control. Overall, IMLUNESTRANT adds an important new choice to improve outcomes in advanced ER+/HER2- breast cancer.

Ethical Approval

Ethical approval was not required as this study is based entirely on previously published literature and does not involve human participants or patient data.

Informed consent
Informed consent was not required as this study does not include patient data or identifiable information.

Conflict of interest
The authors declare no conflicts of interest.

Author contributions
Conceptualization: RA, NM, JK, **Literature review:** RA, **Formal analysis:** RA, **Writing–original draft:** RA, **Writing–review & editing:** RA, NM, JK, **Visualization / Figures:** RA, **Supervision:** NM, JK

Data availability statement
No new data was generated or analysed in this study.

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