Population-level outcomes of imlunestrant in patients with advanced breast cancer using a simulated dataset

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Abstract

Introduction

70% of all breast cancer patients have ER+/HER2- metastatic breast cancer. Imlunestrant has been proposed, through the EMBER studies, as a replacement to standard concurrent endocrine therapy treatments to CDK4/6 inhibitors. Having been tested exclusively in clinical trials, real-world evidence studies are necessary to supplement clinical trial weaknesses and validate results in real-world diverse patient populations.

Methods

This retrospective cohort study used de-identified health and administrative data simulated using Claude.ai to identify adults with ER+/HER2- metastatic breast cancer who initiated either imlunestrant or standard endocrine therapy between September 2025 to May 2026. The primary endpoint as progression free survival. Secondary endpoints were various adverse events. Kaplan-Meier and multivariable Cox models were used to compare survival outcomes between groups.

Results

Propensity score matching yielded a final study cohort of 3,180 patients. Imlunestrant significantly prolonged median progression free survival (imlunestrant: 5.2 months, 95% confidence intervals 4.9 to 5.7; standard endocrine therapy: 4.8 months, 4.5 to 5.2; p = 0.02) and significantly decreased the risk of disease progression (adjusted hazard ratio 0.90, 95% confidence interval 0.84 to 0.97; p-value 0.005). The safety analysis found imlunestrant-recipients experienced significantly greater unadjusted incidences of low-grade fatigue, diarrhea, abdominal pain and decreased appetite.

Discussion

Our results suggest imlunestrant may be superior to existing standard endocrine therapy options in preventing disease progression amongst patients with ER+/HER2- metastatic breast cancer. Imlunestrant has similar safety outcomes to existing standard endocrine therapy options with the exception of the increased incidences of several lower-grade events.

1. INTRODUCTION

Approximately 70% of all breast cancer patient have estrogen receptor-positive (ER+) / human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer(mBC)[1]. Current preferred first-line treatment involves the use of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors combined with endocrine therapy[2]. Abemaciclib, as an example, is a potent CDK4/6 inhibitor that has shown profound benefits in patients across all therapeutic contexts with endocrine therapy[3–5].

Fulvestrant is the only estrogen receptor (ER) degrader, meaning it directly antagonizes ERs as well as aromatase inhibitors to block estrogen production, that has been approved as a monotherapy and as part of combination therapy[4]. However, fulvestrant has its substantial disadvantages. These include poor oral bioavailability limiting dose and dose-dependent efficacy, the perceived pain and burden of injections, and its limitations in patients with ESR1 mutations[6–10]. New oral selective ER degraders, like imlunestrant, have been developed with efficacy and patient experience by means of ease of administration in mind.

Imlunestrant, a next-generation and brain-penetrating oral selective ER degrader and pure ER antagonist that continuously inhibits ERs, even in ERS1-mutated breast cancer[11]. Imlunestrant has been tested extensively in clinical trials. In the phase 1 EMBER study, imlunestrant demonstrated low-grade toxicity effects, favorable pharmacokinetics and antitumor activity in patients with ER+/HER2- breast cancer alone and in combination with abemaciclib[12]. The EMBER-3 study found imlunestrant alone significantly increased progression-free survival in patients with ESR1 mutations, but not the overall population, whereas imlunestrant-abemaciclib together significantly improved progression-free survival regardless of ESR1-mutation status[13].

However, clinical trial evidence is not without its weaknesses. The generalizability of clinical trial results to real-world populations are limited by strict eligibility criteria, small sample sizes and shortened follow-ups[14–18]. These considerations increase the value of real-world evidence in complementing clinical trial evidence, validating clinical trial results and demonstrating how real-world populations respond.

This is a mock publication. This publication is meant to serve the following goals: simulate a dataset using artificial intelligence, specifically Claude.ai; apply data cleaning and statistical analysis techniques on this simulated dataset; and to practice manuscript writing.

2. MATERIALS AND METHODS

2.1 Study design

An observational, retrospective population-based study of adults aged 18+ with ER+/HER2- breast cancer who initiated imlunestrant treatment between 25 September 2025 to 25 May 2026 was conducted. This study used the *Reporting of studies Conducted using Observational Routinely-collected Data* (RECORD) guidelines. This statement is presented in Table S1.

2.2 Data sources

In this simulation paper, Claude was used to simulate de-identified health and administrative data. In real-world practice, linked administrative and health databases using unique coded identifiers would be used. This data could be gathered from organizations like ICES, an independent and non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze healthcare and demographic data, without consent, for health system evaluation and improvement.

The details of the databases used, definitions, data sources, variables and reporting details would usually be listed here in supplemental tables. The same can be said for codes used to define therapies or diagnoses. The simulated dataset will be available for use in an associated github repo.

2.3 Patient population

Women (of any menopausal status) or men 18 years of age and older who had locally confirmed ER+/HER2- breast cancer were eligible. Key exclusions include any duplicate records, any records with missing values, patients who were under the age of 18, and those whose date of disease progression occurred at or before the date of imlunestrant treatment initiation.

2.4 Exposure

The exposure of interest is the oral reception of imlunestrant (400 mg once daily) against any standard endocrine monotherapy, like exemestane or fulvestrant. If using real-world data, specific codes used to identify the exposure would be listed in supplemental material.

2.5 End points

The primary endpoint is investigator-assessed progression-free survival with imlunestrant as compared to standard therapy among patients with ESR1 mutations. In the real-world, this would be a complicated task outside of clinical trials. This would involve a team of investigators, working with real-world charts and readings from patients who are or are not receiving imlunestrant, determining when the disease had progressed. Progression-free survival is defined as the length of time from the date of imlunestrant treatment initiation to the date of death or reaching the maximum follow-up date.

The secondary endpoint would be safety-related endpoints. These include patient-reported outcomes like fatigue, diarrhea, nausea, arthralgia, abdominal pain, vomiting, and decreased appetite; and laboratory measurements like aspartate aminotransferase increase, alanine aminotransferase increase, anemia, thrombocytopenia, neutropenia, leukopenia and hypercreatinemia. Laboratory measurements were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 and were graded as low-grade (grades 1-2) or severe-grade (grades 3-4).

2.6 Statistical analysis

Eligible participants were matched 1:1 using a propensity score conditioned upon age, sex and race. Baseline characteristics of the propensity-score matched cohort were presented descriptively, with comparisons between treatment groups assessed using standardized differences. Kaplan-Meier survival functions and log-rank tests were used to estimate the unadjusted probabilities for progression-free survival. A multivariable Cox model was used to estimate the adjusted hazard ratio for progression-free survival. Covariates included age, sex, ethnicity, ECOG performance, ESR1 mutation status, receipt of a previous CDK4/6 inhibitor, and presence of visceral metastases.

A standardized mean difference (SMD) of > 0.10 or a p-value < 0.05 were considered statistically significant[19,20]. Complete case analysis was used to address missing data in this study. All statistical analyses were performed using RStudio (Posit Software, PBC, Boston, MA).

3. RESULTS

3.1 Patient population

A total of 5,000 patients, aged 18+ who received imlunestrant or another endocrine therapy from 25 September 2025 to 25 May 2026 diagnosed with ER+/HER2- mBC, were identified (Figure 1). Patients were excluded as a result of complete case analysis or duplicate records (n = 1,716 patients), or propensity score matching (n= 104 patients). This resulted in 3,180 eligible patients after propensity score matching. An analysis of the distributional and covariate balance of the propensity score matched cohort did not reveal any significant differences between them (Figure S1, Figure S2).

Consequently, there were no significant differences between the two exposure groups (Table 1). The average age of patients receiving imlunestrant was 60.60 years [standard deviation (SD) 10.30) compared to the 59.98 years (SD 10.36) in the standard ET group. Of the 3,180 patients, 99.5% were female. The ethnic makeup of the propensity score matched cohort was 59.0% Caucasian, 29.5% Asian, 3.0% Black, and 8.5% other ethnicities.

3.2 Progression free survival

Amongst the 1,553 patients who received imlunestrant, the median progression free survival was 5.2 months [95% confidence intervals (CI) 4.9 to 5.7). This was significantly longer than the median progression free survival of the standard ET group (median 4.8 months, 95% CI 4.5 to 5.2). These results can be seen in Figure 2.

The multivariable Cox analysis (Table 3) revealed a significantly lower risk of disease progression amongst patients receiving imlunestrant compared to patients receiving standard ET [adjusted hazard ratio (aHR) 0.90; 95% CI 0.84 to 0.97; p-value 0.005).

3.3 Adverse Events

The safety analysis included 3,180 patients. Several significant differences were found between the imlunestrant and standard ET groups. Imlunestrant-recipients experienced significantly greater unadjusted incidences of low-grade fatigue (SMD 0.333), low-grade diarrhea (SMD 0.222), low-grade abdominal pain (SMD 0.151), and low-grade decreased appetite (SMD 0.179). Any other safety signals were not significantly different between the two.

4. DISCUSSION

In summary, imlunestrant significantly prolonged median progression free survival and significantly decreased the risk of disease progression compared to patients receiving ET. However, patients receiving imlunestrant can expect to experience significantly greater unadjusted incidences of low-grade fatigue, diarrhea, abdominal pain and decreased appetite.

4.1 Comparison with other studies

This simulation study was conducted to validate and verify the results of Jhaveri et al. (2025) in a real-world, population-based study using de-identified health and administrative databases. That study found a median progression free survival of 5.6 months with imlunestrant compared to 5.5 months with standard ET, representing an insignificant difference (p-value 0.12). Although their adverse event analysis did not include any significance testing, there were numerical differences between imlunestrant and standard therapy patients in terms of any grade fatigue (imlunestrant vs. standard ET: 22.6% vs. 13.3%); any-grade diarrhea (21.4% to 11.7%), and any-grade nausea (17.1% to 13.0%).

Interestingly, our study found a significant difference in progression free survival between the two exposure groups in favor of imlunestrant. This conflicts with the results found in Jhaveri et al. (2025). Our safety analyses, although assessed differently, suggest similar differences in adverse events.

4.2 Strengths and limitations

Our analysis confers several strengths. First, this simulation study is meant to represent a true population-based representation of a real-world diverse patient cohort. Many other real-world studies in other cancer domains purport the use of population-based data. However, the data in these studies are often retrieved from institutions where only specific groups of patients, not entire populations of patients, were selected. Second, our use of propensity score matching isolates the effect of imlunestrant by accounting for pre-existing baseline differences between the two exposure groups. This drastically reduces the selection bias within our sample, therefore allowing for more confidence causal inferences.

This study has some limitations. First, the use of retrospective data affects our ability to measure other clinical variables of interest. While propensity score matching is strong in reducing bias from **known** confounders, it does not account for unknown confounders. Therefore, our results may be subject to unmeasured confounding. Second, our safety analysis involved unadjusted descriptive comparisons that should be interpreted in the context of potential residual confounding. Finally, our choice of endpoint acts as a proxy for overall survival. Given the recency of imlunestrant's approval and its use in the American medical system, several more years of follow-up may motivate an overall survival analysis for imlunestrant.

Future research may include prospective real-world studies incorporating other key clinical covariates, patient-reported outcomes, and multivariable adverse event analysis to better contextualize the comparative effectiveness of imlunestrant. Other analyses, like economic analyses, may be helpful in supporting decision-making for medical oncologists in the selection of a concurrent ETs alongside CDK4/6 inhibitors.

5. CONCLUSION

This study provides a real-world comparative analysis of imlunestrant with respect to progression-free survival and several safety endpoints. Our findings suggest imlunestrant significantly prolongs median overall survival and significantly reduces the risk of disease progression in patients with ER+/HER2- mBC. The findings of this comparative study, in addition to the EMBER studies, may be helpful in the selection of concurrent ETs alongside CDK4/6 inhibitors.

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Author Contributions

Charles Jia (CJ). Conceptualization: CJ. Data curation: CJ. Data analysis: CJ. Writing – original draft: CJ. Writing – review and editing: CJ.

Data Availability

A .csv formatted version of the data used within this study can be found on the associated github repository linked here.

Disclosures

All authors report no disclosures

Table 1. Baseline characteristics amongst patients treated with either imlunestrant or standard endocrine therapy for patients with ER+/HER2- metastatic breast cancer from 2025 to 2026 (n = 3,180)

		Total (n = 3,180 patients)	**Imlunestrant (n = 1,553)**	**Standard ET (n = 1,627)**	**SMD**
Age (mean, SD)		60.28 (10.33)	60.60 (10.30)	59.98 (10.36)	0.059
Sex (n, %)	Female	3,164 (99.5%)	1,545 (99.5%)	1,619 (99.5%)	0.003
	Male	16 (0.5 %)	8 (0.5 %)	8 (0.5%)	
Ethnicity (n, %)	Asian	939 (29.5%)	443 (28.5%)	496 (30.5%)	0.054
	Black	95 (3.0%)	47 (3.0%)	48 (3.0%)	
	Caucasian	1,875 (59.0%)	936 (60.3%)	939 (57.7%)	
	Other	271 (8.5%)	127 (8.2%)	144 (8.9%)	
ECOG performance score (n, %)		1,071 (33.7%)	491 (31.6%)	580 (35.6%)	0.085
ESR1 mutation (n, %)		1,260 (39.6%)	614 (39.5%)	646 (39.7%)	0.003
Received a previous CDK4/6 inhibitor (n, %)		1,877 (59.0%)	946 (60.9%)	931 (57.2%)	0.075
Presence of visceral metastases (n, %)		1,773 (55.8%)	858 (55.2%)	915 (56.2%)	0.020

Abbreviations: ET = endocrine therapy; SMD = standardized mean differences; ECOG = Eastern Cooperative Oncology Group; CDK4/6 = Cyclin-dependent kinase 4 and 6.

Table 2. Progression free survival medians and confidence intervals from a univariable Kaplan-Meier analysis amongst patients treated with either imlunestrant or standard endocrine therapy for patients with ER+/HER2- metastatic breast cancer from 2025 to 2026 (n = 3,180)

Exposure	Number of patients	Events	Median PFS	95% LCL	95% UCL
Imlunestrant	1553	1553	5.2	4.9	5.7
Standard ET	1627	1627	4.8	4.5	5.2

Abbreviations: ET = endocrine therapy; PFS = progression free survival; LCL = lower confidence limit; UCL = upper confidence limit.

Table 3. Adjusted hazard ratios from a multivariable Cox model for disease progression amongst patients treated with either imlunestrant or standard endocrine therapy for patients with ER+/HER2- metastatic breast cancer from 2025 to 2026 (n = 3,180)

Variable	Comparator	aHR	95% LCL	95% UCL	p-value
Exposure	Imlunestrant vs. Standard ET	0.90	0.84	0.97	0.005
Age	---	1.00	1.00	1.00	0.8
Sex	Male vs. Female	1.25	0.76	2.04	0.4
Race	Black vs. Asian	0.90	0.73	1.12	0.4
	White vs. Asian	0.96	0.89	1.04	0.3
	Other vs. Asian	0.93	0.81	1.06	0.3
ECOG Performance Score	1+ vs. 0	0.96	0.89	1.04	0.3
ESR1 Mutation Status	Yes vs. No	1.19	1.11	1.28	<0.001
Received Previous CDK4/6 inhibitor	Yes vs. No	1.01	0.94	1.09	0.7
Presence of Visceral Metastases	Yes vs. No	1.00	0.94	1.08	> 0.9

Abbreviations: ET = endocrine therapy; aHR = adjusted hazard ratio; LCL = lower confidence limit; UCL = upper confidence limit.

Table 4. Univariable adverse analysis amongst patients treated with either imlunestrant or standard endocrine therapy for patients with ER+/HER2- metastatic breast cancer from 2025 to 2026 (n = 3,180)

		Total (n = 3,180 patients)	**Imlunestrant (n = 1,553)**	**Standard ET (n = 1,627)**	**SMD**
Fatigue	Normal	2557	1145	1412	0.333
	Low-grade	623	408	215	0.333
Diarrhea	Normal	2680	1244	1436	0.225
	Low-grade	498	307	191	0.222
	Severe-grade	NR	NR	NR	NR
Nausea	Normal	2694	1288	1406	0.097
	Low-grade	482	261	221	0.090
	Severe-grade	NR	NR	NR	NR
Arthritis	Normal	2692	1312	1380	0.009
	Low-grade	484	237	247	0.002
	Severe-grade	NR	NR	NR	NR
Abdominal	Normal	2948	1408	1540	0.153
Pain	Low-grade	231	144	87	0.151
	Severe-grade	NR	NR	NR	NR
Decreased	Normal	3009	1437	1572	0.181
Appetite	Low-grade	170	115	55	0.179
	Severe-grade	NR	NR	NR	NR
Decreased	Normal	2791	1379	1412	0.061
Aspartate	Low-grade	371	165	206	0.064
Aminotransferase	Severe-grade	18	9	9	0.004
Decreased	Normal	2865	1405	1460	0.025
Alanine	Low-grade	302	142	160	0.024

Aminotransferase	Severe-grade	13	6	7	0.007
Anemia	Normal	2802	1370	1432	0.006
	Low-grade	348	169	179	0.004
	Severe-grade	30	14	16	0.008
Neutropenia	Normal	3035	1468	1567	0.085
	Low-grade	113	67	46	0.080
	Severe-grade	32	18	14	0.030
Leukemia	Normal	3040	1485	1555	0.002
	Low-grade	115	53	62	0.021
	Severe-grade	25	15	10	0.040
Hypercreatinemia	Normal	3100	1506	1594	0.064
	Low-grade	78	47	31	0.072
	Severe-grade	NR	NR	NR	NR

*Due to best-practice privacy guidelines, I did not report cells < 6. These cells are labeled not reportable (NR) given the risk of re-identification, if this study occurred in the real-world.

Abbreviations: ET = endocrine therapy; SMD = standardized mean differences; NR = not reportable.