A Preoperative Window-of-Opportunity Study of Oral SERD, Imlunestrant, in Newly Diagnosed ER-Positive, HER2-Negative Early Breast Cancer: Results from the EMBER-2 Study

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ABSTRACT

Purpose: Imlunestrant is an oral selective estrogen receptor degrader with favorable safety and preliminary efficacy in patients with advanced breast cancer. Pharmacodynamic (PD) biomarker data can optimize drug dosing; in this study, we present PD data from the EMBER-2 study.

Patients and Methods: Postmenopausal women with untreated, operable estrogen receptor (ER)–positive, HER2-negative early breast cancer were randomized to 400 versus 800 mg of imlunestrant daily for ~2 weeks before surgery. A single arm study tested a daily dose of 200 mg. PD biomarker changes (ER, progesterone receptor, Ki-67 by IHC, and mRNA expression of ER-related genes) were evaluated in paired tumor samples (pre-/posttreatment). Safety and pharmacokinetics were also assessed.

Results: Among evaluable paired samples ($n = 75$), PD profiles demonstrated consistent ER targeting between 400- and 800-mg doses, with less toxicity at the 400-mg dose. Although inducing the lowest rate of complete cell-cycle arrest, PD and pharmacokinetic results were similar for the 200-mg dose.

Conclusions: EMBER-2 combined with existing phase I data has identified 400 mg as the optimal imlunestrant dose.

Introduction

Treatment options for patients with breast cancer are determined by estrogen receptor (ER) and HER2 status (1, 2). Seventy-five percent of breast cancers express ER, a key driver of breast cancer initiation and progression. In ER^+ breast cancer, endocrine therapy (ET) is the foundation of treatment for patients with any stage of ER^+ breast cancer (3–6). ET reduces ER activity by direct ER modulation (tamoxifen and raloxifene), enzymatic inhibition of aromatase (anastrozole, letrozole, and exemestane), or receptor degradation by selective estrogen receptor degraders (SERD), such as fulvestrant or elacestrant (7). However, resistance to ET can occur through multiple mechanisms, including acquired driver mutations such as ESR1. ET resistance leads to worsened clinical outcomes and decreased overall survival (8). Thus, optimization of ER inhibition by overcoming ET resistance remains an important therapeutic goal.

Preoperative window-of-opportunity (WOO) trials are an efficient way to evaluate molecular drug response and pharmacodynamics (PD). Several WOO studies have demonstrated feasibility in the PD

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Translational Relevance

This window-of-opportunity pharmacodynamic study confirms proof of mechanism of imlunestrant, demonstrating an impact on key biomarkers in estrogen receptor (ER)–positive, HER2-negative early breast cancer. Results confirmed that imlunestrant delivers potent ER degradation and downregulation of the ER target genes along with evidence of complete cell-cycle arrest across all dose levels, particularly at the optimal dose (400 mg).

assessment of ET by measuring ER and progesterone receptor (PR) modulation. These studies evaluated the downstream effects, including inhibition of proliferation, as measured by the nuclear proliferation marker Ki-67. The change in the Ki-67 index can serve as a surrogate endpoint of treatment benefit in early breast cancer (9). Additionally, evaluation of Ki-67 pre- and posttherapy can assess a drug's ability to induce complete cell-cycle arrest (CCCA), which correlates with early breast cancer recurrence-free survival (10, 11).

The PD data from WOO trials in early breast cancer can also predict drug impact in advanced breast cancer. As an example, the fulvestrant WOO trial comparing different fulvestrant doses revealed that the PD impact was dose dependent (12). The subsequent phase III CONFIRM study in advanced breast cancer mirrored these results, demonstrating that higher fulvestrant doses significantly improved progression-free survival compared with lower doses (13, 14).

Imlunestrant is a next-generation oral SERD specifically designed to deliver continuous ER target inhibition throughout the dosing period (15). In the phase I EMBER trial, imlunestrant showed favorable safety and preliminary efficacy in patients with either ESR1 mutant or wild-type ER^+ advanced breast cancer after disease progression on prior ET (16). Imlunestrant monotherapy was tolerated across all five dose levels (200–1,200 mg). Although there were no dose-limiting toxicities in dose escalation and the MTD was not reached, there were more toxicities with doses above 400 mg. Overall, adverse events (AE) were mainly low grade and manageable; however, there were some differences in the frequency of low-grade side effects with 400 mg versus higher doses that could potentially affect long-term adherence to imlunestrant (16).

The EMBER-2 study assessed PD, pharmacokinetics (PK), biological effects, and safety of imlunestrant at 400- and 800-mg dose levels in patients with ER^+ treatment-naïve early breast cancer. Patients were randomized to receive 400 or 800 mg for about 2 weeks. Combined data from the EMBER and EMBER-2 trials determined the optimal and recommended imlunestrant dose of 400 mg for future registrational trials. The 200-mg cohort was added later to evaluate the PD effects of a dose reduction option.

Currently, there are two ongoing registrational trials of imlunestrant. The phase III EMBER-3 trial (NCT04975308) is evaluating the efficacy of imlunestrant monotherapy (compared with investigator's choice ET) and imlunestrant plus abemaciclib as second-line treatment of advanced breast cancer. The phase III EMBER-4 trial (NCT05514054) is evaluating imlunestrant monotherapy [compared with standard-of-care (SOC) ET] as adjuvant treatment in patients with high-risk early breast cancer after 2 to 5 years of ET.

Patients and Methods

Study design

EMBER-2 (J2J-MC-JZLB, NCT04647487) was a global, multicountry, phase I, open-label, noncontrolled, randomized preoperative window study of imlunestrant in postmenopausal women with stage I to III ER^+, $HER2^-$ early breast cancer who were scheduled for surgery with curative intent or repeat biopsy if neoadjuvant treatment was planned. Patients were stratified according to histology of the diagnostic biopsy [invasive ductal carcinoma (IDC) vs. invasive lobular carcinoma vs. other].

Initially, patients were randomly assigned 1:1 to either 400- or 800-mg cohorts. After completing the randomized portion of the study, EMBER-2 was amended to add a single-arm 200-mg cohort to which patients were nonrandomly assigned.

Study population

Eligible patients were postmenopausal women of ≥18 years of age with histologically confirmed invasive breast carcinoma: stage I to III, ≥1 cm in largest diameter by ultrasound, ER^+ (>50% or Allred score >5), and $HER2^-$ [according to American Society of Clinical Oncology/College of American Pathologists (CAP) guidelines] per local assessment. The patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ function. Patients with bilateral invasive, metastatic, or inflammatory breast cancer; previously treated breast cancer; or a serious concomitant systemic or cardiac condition were not eligible.

The study protocol was approved by the appropriate institutional review boards and ethics committees and conducted in accordance with Good Clinical Practice of the Declaration of Helsinki. All patients provided written informed consent.

Study intervention

Following informed consent and initial biopsy, patients started imlunestrant at their assigned dose (200, 400, or 800 mg) orally daily for approximately 2 weeks before surgical resection or a posttreatment biopsy. Patients were required to take imlunestrant until the surgical procedure. Dose modifications were not allowed.

Imlunestrant was administered at approximately the same time daily, and patients were instructed not to consume any food at least 1 hour before and at least 2 hours after administration. Pre- and posttreatment tumor samples were evaluated for PD biological makers.

The pretreatment (baseline) tumor tissue acquired was diagnostic archival tissue if collected within 6 weeks of consent; tumor tissue from a new biopsy was required if archival tissue was unavailable/exhausted, or collected >6 weeks before consent, or while the patient was taking hormone replacement therapy. Posttreatment tumor tissue was collected at treatment day 15 (−2 to +7 days).

Sparse PK sampling was conducted at two time points (predose and approximately 3–4 hours postdose) after the first dose and again at steady state (SS) on treatment day 15 (−2 to +7 days).

Patient compliance with study intervention was assessed at each visit and at all doses, by direct questioning and by counting returned tablets and/or capsules. Patients must have received 80% of assigned doses to be considered compliant with study.

Analytic methods

RT-PCR

RNA was extracted from pre- and posttreatment formalin-fixed, paraffin-embedded tumor tissues using the Qiagen AllPrep Kit by Almac

Diagnostic Services. qRT-PCR was performed using Almac Diagnostic Services off-the-shelf Thermo Fisher qPCR assays including 11 ER-regulated genes and five housekeeping genes: *PGR* (Hs01556702_m1), *WISP2* (Hs01031984_m1), *PDZK1* (Hs00275727_m1), *RASGRP1* (Hs00996734_m1), *GREB1* (Hs00536409_m1), *AREG* (Hs00950669_m1), *TFF1* (Hs00907239_m1), *STON1* (Hs00538997_m1), *NBEA* (Hs00396223_m1), *GATA3* (Hs00231122_m1), *XBP1* (Hs00231936_m1), *GAPDH* (Hs02758991_g1), β-actin (Hs03023943_g1), *RPLPO* (Hs00420895_gH), *GUSB* (Hs00939627_m1), and *TFRC* (Hs00951083_m1). Assays were repeated, each in triplicate.

Ct values

Ct values were generated using a QuantStudio Dx system in conjunction with QuantStudio Test Development Software (v1.0.1). Mean and total SD required for estimating imprecision were derived from the linear mixed model with ΔCt as a dependent variable and run as a random-effect model. Before analysis, Tukey outlier detection was performed per sample. Data were normalized to the mean of the most stable among the five housekeeping genes (*RPLPO* and *TFRC*) and analyzed using the $2^{-\Delta\Delta Ct}$ method (17). The ER gene module consisted of 11 genes transcriptionally regulated by ER: *PGR*, *GREB1*, *PDZK1*, *TFF1*, *RASGRP1*, *AREG*, *WISP2*, *GATA3*, *XBP1*, *STON1*, and *NBEA* (Almac Diagnostic Services). The ER gene module was calculated using the weighted mean of gene expression for each gene. The absolute value of change in mRNA expression between pre- and posttreatment tumor samples of select ER-regulated genes and the ER gene module was tested using the paired *t* test, and the reported *P* values were two-tailed.

Endpoints

The primary endpoint was the change in ER expression between pre- and posttreatment tumor samples. The change was measured using an IHC *H*-score (0–300) that captured the percentage and intensity of ER^+ stained tumor cells (antibody SP1, manual scoring by CellCarta). The *H*-score was calculated based on four differential staining intensities of 0 (negative), 1 (weak), 2 (moderate), and 3 (strong). *H*-score = (0 × % of negative cells) + (1 × % of weak positive cells) + (2 × % of moderate positive cells) + (3 × % strong positive cells).

Secondary endpoints included assessment of change in PR expression by IHC *H*-score (0–300) that captured the percentage and intensity of PR tumor cell staining (antibody 1E2, manual scoring by CellCarta as described for ER), the change in the percentage of Ki-67 staining–positive tumor cells (Ki-67 index, antibody 30-9, image analysis–based scoring by CellCarta), and safety, tolerability, and PK evaluations. Exploratory and other endpoints included imlunestrant tumor biodistribution and characterization of further imlunestrant biological effects on ER and/or other cancer-related biomarkers and patient compliance.

Statistical analyses

For IHC studies, the geometric mean of change from baseline in the ER and PR *H*-score was calculated using t-statistic (18). The percent change in *H*-score of ER and PR expression and the 90% confidence interval (based on *t*-statistic) were summarized for each cohort. The geometric mean of change in percentage of Ki-67-expressing positive cells and its 90% confidence interval (based on *t*-statistic) were summarized for each cohort, per international guidelines (19). Subgroup analyses were performed in patients with higher (>5%) baseline Ki-67%.

CCCA was evaluated in patients with baseline Ki-67 ≥5% and is defined as Ki-67 ≤2.7% posttreatment (20).

The safety population included all patients who received study treatment. Safety data were summarized by treatment arms. AE were graded according to the NCI Common Terminology Criteria for AE v5.0 and coded using Medical Dictionary for Regulatory Activities. The PK population included patients who received at least one full dose of imlunestrant and had at least one postbaseline evaluable PK sample. The PD-evaluable population consisted of patients who completed treatment and had evaluable pre- and posttreatment samples.

Data availability

Eli Lilly and Company provides qualified scientific researchers access to all deidentified individual participant data collected during the trial, after anonymization, except PK or genetic data. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment. Eli Lilly and Company retains the right to assess and approve the request at its sole discretion. For details on submitting a request, see the instructions provided at www.vivli.org.

Results

Patients

From April 2021 to November 2022, 59 postmenopausal women with untreated, surgically resectable, ER^+, $HER2^-$ (locally assessed) early breast cancer were randomized 1:1 to receive 400 mg versus 800 mg of imlunestrant orally daily for ~2 weeks before surgery (**Fig. 1**). Upon completion of the randomized portion of the trial, an additional single arm was added using the same treatment schedule; it enrolled 28 patients treated with 200 mg of imlunestrant daily (one patient discontinued treatment before completing the treatment period). Of the total 87 patients enrolled across the study, 86 patients received treatment and were considered evaluable for safety assessment (one patient randomized to the 800-mg dose did not receive therapy). Of the 83 patients who completed therapy, 75 patients had adequate paired samples for evaluation of PD endpoints and 79 had adequate blood samples for PK evaluation (**Fig. 1**).

Baseline characteristics were similar between the treatment arms (**Table 1**). The median age was 64 years (range, 50–83 years). Most patients (95%) had stage I or II disease, and 87% had histopathologic grade of 1 or 2 at initial diagnosis. High-grade tumors and stage III disease were balanced across all dosage arms. The majority of patients had a ductal histologic subtype (IDC) and were both ER^+ and PR^+. Across all treatment arms, 6% of tumors had a baseline Ki-67 index of <5%, 43% had a baseline Ki-67 index of 5% to 19%, and more than half of the baseline samples (51%) had a baseline Ki-67 index of >19%.

Treatment

The median time on treatment was similar in the three treatment arms with a mean of 16 days (range, 13–23) for the PD-evaluable population (**Table 2**). In the safety population, 79% of patients in

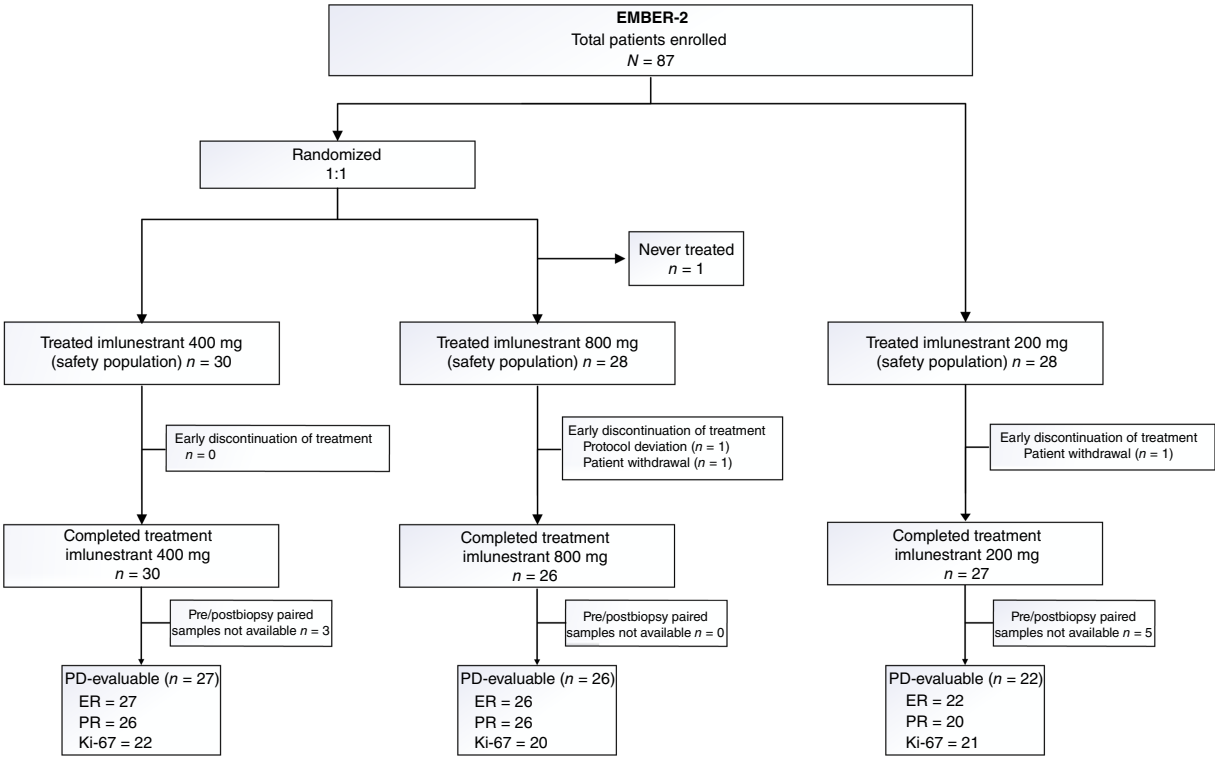


Figure 1.
CONSORT diagram.

the 200-mg cohort, 77% in the 400 mg cohort, and 82% in the 800 mg cohort reported no missed doses. With the exception of one patient at the 400-mg dose level, all others were considered compliant.

Biomarkers

Fifty-three randomized patients were considered evaluable for PD endpoints (400 mg, $n = 27$; 800 mg, $n = 26$). Single-agent imlunestrant induced ER degradation and PR downregulation (81% decrease in geometric mean collectively for both ER and PR), which was similar between the 400- and 800-mg doses (**Fig. 2A**; **Table 2**). The absolute change in ER or PR from baseline is depicted in **Fig. 2B**, with most tumors showing a substantial decrease in both ER and PR levels as measured by IHC. Consistent with imlunestrant-mediated degradation of ER, 11 ER-regulated genes were modulated in response to treatment, including decreased *PGR* (**Fig. 3**). *PGR* RNA expression levels also correlated well with PR protein expression measured by IHC (Spearman $\rho = 0.8$; P value <0.001), showing consistency between RNA and protein expression. Importantly, we compared the 400- and 800-mg cohorts to identify any significant difference between IDC and invasive lobular (invasive lobular carcinoma) histologic subtypes and found no difference in imlunestrant's ability to degrade ER or have a downstream impact (**Fig. 2A**).

As a measure of the anticancer effect, Ki-67 was used to determine imlunestrant's impact on cell proliferation. Reductions in Ki-67 geometric mean at the 400- and 800-mg doses were 71% and 72%, respectively; however, CCCA rates were numerically lower in the 400-mg dosing cohort (23%) than in the 800-mg dosing cohort (35%).

Once accrual to the 400- and 800-mg cohorts was complete, a third cohort ($n = 28$) was accrued and dosed with imlunestrant 200 mg daily for ~2 weeks to determine the PD impact of this reduced dose. Of these, 22 patients were evaluable for PD endpoints. Similar reductions in ER, PR, and Ki-67 were seen at the 200-mg dose (**Fig. 2A** and **B**; **Table 2**); however, the 200-mg dose induced the lowest rate of CCCA (15%) of all the levels tested. Gene expression analyses were not performed on these samples.

PK results

SS plasma predose imlunestrant concentrations increased with doses over the 200- to 800-mg dose range and were similar to those previously observed in the EMBER trial (16). At 400 mg, almost all patients had SS trough concentrations exceeding the EC_{80} concentrations in breast cancer xenograft models, and the literature reported fulvestrant SS C_{max}. SS tumor concentrations were also available in 10 patients across the 200- to 800-mg dose range. The data showed that SS tumor concentrations on day 15 were approximately 15-fold (range, 5–31-fold) higher when compared with predose plasma concentrations on the same day (Supplementary Fig. S1).

Safety

Table 3 shows treatment-emergent AE (TEAE) and AE considered to be treatment-related by the investigator. Most patients (66.3%) experienced at least one TEAE (mainly grade 1). Of note, diarrhea

Table 1. Patient and disease characteristics.

Characteristic	200 mg *N* = 28	400 mg *N* = 30	800 mg *N* = 29	Total *N* = 87
Median age, years (range)	63 (50–74)	64 (50–83)	65 (50–83)	64 (50–83)
ECOG PS—0, *n* (%)	27 (96)	30 (100)	23 (79)	80 (92)
Histologic subtype, *n* (%)				
IDC	16 (57)	20 (67)	22 (76)	58 (67)
ILC	9 (32)	10 (33)	7 (24)	26 (30)
Other	3 (11)	0	0	3 (3)
Stage, *n* (%)				
Stage I	13 (46)	20 (67)	15 (52)	48 (55)
Stage II	14 (50)	8 (27)	13 (45)	35 (40)
Stage III	1 (4)	2 (7)	1 (3)	4 (5)
Histopathologic grade[a], *n* (%)				
Grade 1	4 (14)	6 (20)	8 (28)	18 (21)
Grade 2	18 (64)	20 (67)	20 (69)	58 (67)
Grade 3	3 (11)	3 (10)	1 (3)	7 (8)
Unavailable	3 (11)	1 (3)	0	4 (5)
PR^+ status per central review, *n*/*N*[b] (%)	18/20 (90)	25/26 (96)	24/26 (92)	67/72 (93)
Baseline Ki-67 per central review, *n*/*N*[c] (%)				
<5%	1/21 (5)	0/22 (0)	3/20 (15)	4/63 (6)
≥5% to <20%	7/21 (33)	10/22 (45)	10/20 (50)	27/63 (43)
≥20%	13/21 (62)	12/22 (55)	7/20 (35)	32/63 (51)
Median baseline Ki-67 distribution (min-max)	21 (4–97)	27 (9–69)	13 (3–49)	21 (3–97)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IDL, invasive lobular carcinoma; *n*, number of patients; *N*, number of patients in population.
[a]According to local review.
[b]Among the PR-evaluable population.
[c]Among the Ki-67–evaluable population.

and nausea were more frequent in the 800-mg cohort. In general, TEAE associated with the 200-mg dose were similar to those seen with the 400-mg dose.

The incidence of grade 3 TEAE was similar across all dose levels. None were considered related to imlunestrant by the investigator. One patient in the 800-mg cohort experienced three

Table 2. Relative reduction of ER, PR, and Ki-67 after treatment.

Parameter	200 mg *n*/*N* = 22/28	400 mg *n*/*N* = 27/30	800 mg *n*/*N* = 26/28	Total *n*/*N* = 75/86
Median time on treatment, days (range)	17 (14–23)	16 (13–23)	15 (13–22)	16 (13–23)
Geometric mean change (90% CI) in PD biomarkers				
ER[a]	−89% (−96 to −72%)	−82% (−91 to −60%)	−70% (−78 to −59%)	−81% (−87 to −72%)
PR[a]	−85% (−97 to −37%)	−76% (−90 to −38%)	−82% (−92 to −60%)	−81% (−89 to −66%)
Ki-67[a]	−69% (−79 to −54%)	−71% (−80 to −57%)	−72% (−81 to −59%)	−70% (−76 to −63%)
Baseline Ki-67 >5% *n*, %, (90% CI)	20 −70% (−80 to −56%)	22 −71% (−80 to −57%)	17 −78% (−84 to −70%)	59 −73% (−78 to −67%)
Baseline Ki-67 ≥15% *n*, %, (90% CI)	16 −73% (−83 to −56%)	13 −71% (−82 to −53%)	8 −75% (−83 to −63%)	37 −73% (−79 to −64%)
Baseline Ki-67 ≥20% *n*, %, (90% CI)	13 −77% (−87 to −59%)	12 −72% (−83 to −53%)	7 −78% (−84 to −68%)	32 −75% (−81 to −67%)
CCCA[b] (%)	3/20 (15%)	5/22 (23%)	6/17 (35%)	14/59 (24%)

Abbreviations: CI, confidence interval; *n*, number of patients; *N*, number of patients in population.
[a]See **Fig. 1** for the PD-evaluable population for each biomarker.
[b]CCCA among patients ($n = 59$) with baseline Ki-67 ≥5%.

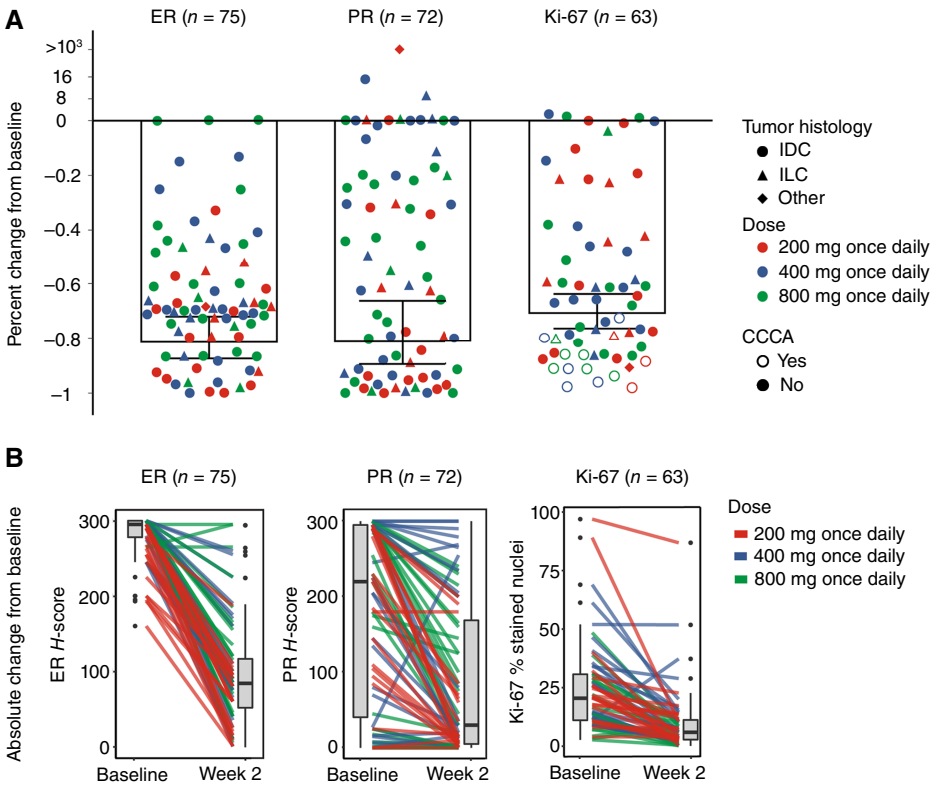
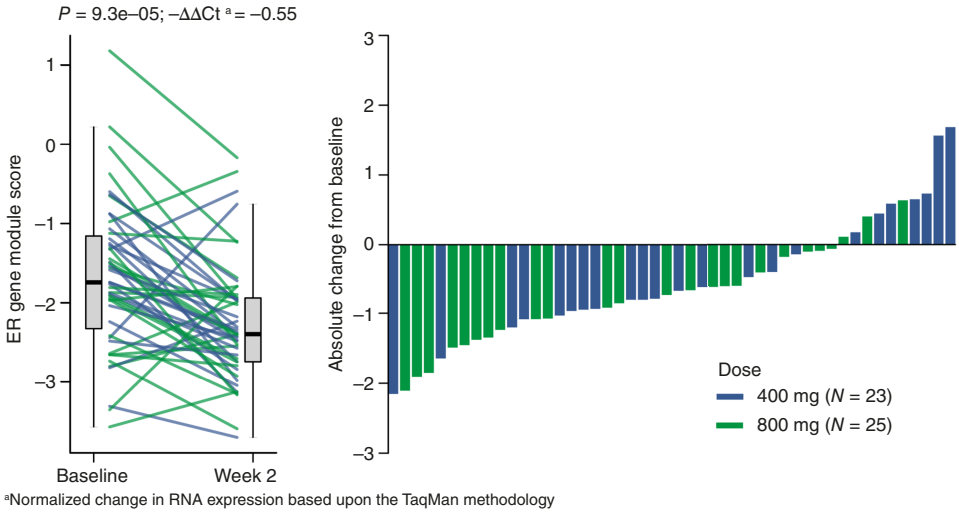


Figure 2.

A, Relative reduction of ER, PR, and Ki-67 after treatment. **B,** Absolute change in ER and PR *H*-score and Ki-67 % stained nuclei after treatment.

separate grade 3 TEAE: headache, nausea, and blepharospasm. Three patients (3.5%) reported ≥1 TEAE of grade 3 or higher. There were no discontinuations due to AE. Treatment-related AE (TRAE) were reported in 33% of patients. Overall, the most commonly reported TRAEs were fatigue (9%), diarrhea (8%), hot flushes (7%), and nausea (7%). At the 400-mg dose, the most common TRAEs were fatigue (13%) and hot flushes (7%), and at the 800-mg dose, the most common TRAEs were diarrhea (18%) and nausea (11%). No TRAEs of diarrhea or nausea occurred at the optimal dose (400 mg).

In total, four patients experienced serious adverse events (SAE), of which only two experienced grade 3 SAE. All were deemed not related to study treatment, and three were related to wound problems. They were known related complications of the subsequent surgical procedure, including mastitis, wound dehiscence, postprocedural hemorrhage, and postprocedural hematoma.



[a]Normalized change in RNA expression based upon the TaqMan methodology

Figure 3.

Relative reduction in ER transcription activity after treatment.

Table 3. TEAE and TRAE, as assessed by the investigator, reported in ≥5% of all patients.

AE term	200 mg		400 mg		800 mg		Total	
	N = 28		*N* = 30		*N* = 28		*N* = 86	
	Grade		Grade		Grade		Grade	
n (%)	All	≥3	All	≥3	All	≥3	All	≥3
Patients with ≥1 TEAE	21 (75)	1 (4)	17 (57)	1 (3)	19 (68)	1 (4)	57 (66)	3 (4)[a]
Diarrhea	3 (11)	0	3 (10)	0	9 (32)	0	15 (17)	0
Fatigue	2 (7)	0	6 (20)	0	4 (14)	0	12 (14)	0
Hot flush	4 (14)	0	2 (7)	0	2 (7)	0	8 (9)	0
Nausea	3 (11)	0	1 (3)	0	4 (14)	1 (4)	8 (9)	1 (1)
Breast pain	2 (7)	0	2 (7)	0	2 (7)	0	6 (7)	0
Headache	2 (7)	0	2 (7)	0	2 (7)	1 (4)	6 (7)	1 (1)
Arthralgia	1 (4)	0	1 (3)	0	2 (7)	0	4 (5)	0
Patients with ≥1 TRAE	9 (32.1)	0 (0)	8 (26.7)	0 (0)	11 (39.3)	0 (0)	28 (32.6)	0 (0)
Fatigue	2 (7)	0 (0)	4 (13.3)	0 (0)	2 (7.1)	0 (0)	8 (9)	0 (0)
Diarrhea	2 (7)	0 (0)	0 (0)	0 (0)	5 (18)	0 (0)	7 (8)	0 (0)
Hot flush	2 (7)	0 (0)	2 (6.7)	0 (0)	2 (7)	0 (0)	6 (7)	0 (0)
Nausea	3 (11)	0 (0)	0 (0)	0 (0)	3 (11)	0 (0)	6 (7)	0 (0)

Abbreviations: *n*, number of patients; *N*, number of patients in population.
[a]All unrelated events; $n = 1$ at 200 mg (mastitis and wound dehiscence); $n = 1$ at 400 mg (postprocedural hematoma); $n = 1$ at 800 mg (nausea, blepharospasm, and headache).

Discussion

ER is a key driver for most breast cancers, and ET is one of the most effective SOC treatment options for ER^+ disease (21). However, novel ER-directed treatments are still needed to prevent disease recurrence or progression and to reduce therapy-related side effects.

Modern drug development efforts to select the optimal biological dose now extend well beyond MTD identification in phase I trials. Rather, it is recognized that optimization of drug dosing early in development is the key to minimizing toxicity while maintaining efficacy, particularly for therapies intended for longer duration use in the adjuvant setting, where adherence to therapy is paramount (22).

WOO trials have played a key role in biologically validating on-target drug effects through measurement of downstream target effects, such as inhibition of cancer cell proliferation (23). Furthermore, several trials have shown that achieving a low proliferation state, that is, Ki-67 <10% or inducing CCCA (Ki-67 <2.7%), with 2 weeks of preoperative ET is associated with favorable long-term outcomes (24). WOO studies are also important in the selection of the most appropriate dose of drugs that do not reach an MTD in traditional phase I dose-escalation trials. Taken together, these observations have been leveraged to optimize drug dosing using short WOO trials evaluating the biological effects of ET at different doses. To this end, the PD results from the EMBER-2 study (25), combined with the safety, efficacy, and PK results from the first-in-human EMBER study (16), determined the optimal dose of imlunestrant to be 400 mg once daily orally. The 400- and 800-mg doses were previously deemed tolerable and showed preliminary efficacy in the phase Ia/b EMBER study. Slightly higher rates of gastrointestinal (GI) toxicity were reported with the 800-mg dose of imlunestrant (16). Imlunestrant is now being evaluated at this 400-mg daily dose versus SOC ET in the phase III EMBER-3 study in advanced breast cancer (NCT04975308) and as adjuvant therapy in the phase III EMBER-4 study in early breast cancer (NCT05514054).

In EMBER-2, single-agent imlunestrant induced substantial ER degradation and PR downregulation (81% decrease in geometric mean collectively for both ER and PR), which was similar between the 400- and 800-mg imlunestrant dose levels (ER, 82% vs. 70%; PR, 76% vs. 82%, respectively), proving that imlunestrant achieved an on-target effect. To further measure downstream impact, gene expression of 11 ER-regulated genes, including *PGR*, also showed a decrease in ER activity at week 2. Additionally, the impact of imlunestrant on tumor cell proliferation was measured using Ki-67 IHC and found to be consistent between the two doses (71% and 72% reductions in Ki-67 geometric mean, respectively). Notably, CCCA rates were numerically lower in the 400-mg (23%) than in the 800-mg dosing cohort (35%). These data should be interpreted with caution given the sample size limitations and that more than a third of the patients in the 800-mg cohort were not evaluable for CCCA (compared with 19% in the 400-mg cohort).

Evaluation of safety data from EMBER-2 did not reveal any new or unexpected safety findings. Overall, imlunestrant used for a short treatment duration was well tolerated. The most frequently reported TEAE were fatigue, diarrhea, hot flushes, and nausea. The majority of TEAE were of low grade, manageable, and did not result in discontinuations. As previously seen in the phase Ia/b EMBER trial (16), the incidence of GI toxicity was higher in the 800-mg cohort than in the 400-mg cohort. There was no evidence of bradycardia or QT prolongation as well as of visual changes or ophthalmic toxicity. There was no evidence of bradycardia, QT prolongation, visual changes, or ophthalmic toxicity.

Together, these data suggest similar biological effects between the 400- and 800-mg doses of imlunestrant with no valid reason to subject patients to the higher 800-mg dose. These results are

clinically meaningful, as the slightly lower rates of GI toxicity seen with the 400-mg dose may not only improve quality of life but also improve treatment adherence, which has been associated with better outcomes in patients with early breast cancer receiving adjuvant ET (26, 27).

In the phase Ia/b EMBER trial, dose reductions due to TRAEs were rare. Only two patients with advanced breast cancer treated with single-agent imlunestrant at 400 mg and in three patients in the combination cohorts with abemaciclib required dose reductions (16).

Once accrual to the randomized portion of the EMBER-2 study was completed, a third cohort of patients was accrued and dosed with imlunestrant 200 mg daily for ~2 weeks to determine the PD impact. It was important to understand the biological effects of this lower (200-mg) dose of imlunestrant. In the phase III EMBER-3 and EMBER-4 studies, based on the data from the 200-mg cohort in EMBER-2, dose reduction to 200 mg is permitted. In rare cases, dose reduction may be necessary to support treatment adherence.

The 200-mg dose of imlunestrant was well tolerated with a side effect profile similar to that of the 400-mg dose. Although similar reductions in ER, PR, and Ki-67 were seen at the 200-mg imlunestrant dose, the 200-mg dose induced the lowest rate of CCCA (15%) of all the dose levels tested. Notably in the EMBER trial, when compared with the 400-mg dose, the 200-mg dose failed to induce an objective response and had a comparatively lower clinical benefit rate along with PK exposures below the *in vivo* efficacious (EC_{80}) range in the majority of treated patients. While acknowledging the small sample size at the 200-mg dose level, the PD data suggest that the 200-mg dose retains biological effects, thus supporting this as a potential dose reduction from the more optimal 400-mg daily starting dose based on the totality of data, across dose levels, from the EMBER and EMBER-2 trials.

Overall PK analyses from the EMBER and EMBER-2 trials were consistent. Specifically at SS, imlunestrant trough plasma concentrations increased proportionally with imlunestrant doses ranging from 200 to 800 mg, with all doses exceeding SS fulvestrant C_{max} and doses of ≥400 mg once daily exceeding the EC_{80} range achieved in preclinical xenograft studies. Furthermore, tumor concentrations of imlunestrant were approximately 15-fold (range, 5–31-fold) higher when compared with trough SS plasma concentrations, indicating adequate tumor penetration.

Within the tumor, imlunestrant binding is expected to lead to ER degradation and lower ER levels while also inhibiting ER activity, as observed by the decreased expression of PR and changes in ER-regulated gene transcription. Although direct cross-trial comparisons have limitations, an imlunestrant-mediated decrease in ER and PR levels, −81% for both, is numerically deeper compared with decreased ER and PR expression previously observed with other SERD approved or in development. With fulvestrant, the changes in expression for ER and PR were −36.3% and −68.7%, respectively; with amcenestrant 200 mg, they were −68.3% and −74.4%, respectively; with giredestrant, they were −72% and −58%, respectively; and with camizestrant 75 mg, −62.7% to –66.9% was observed for ER only (12, 28–30).

Additionally, it is important to measure the downstream impact of ER degradation. The observed decrease in the tumor Ki-67 index following imlunestrant treatment (−71%) is comparable with previous observations with fulvestrant (−75.4%), tamoxifen (−59.5%), and anastrozole (−76.0%; refs. 12, 31). Similar trends were observed in WOO trials with the recently approved elacestrant, as well as other SERD in development (28–30, 32).

Furthermore, in EMBER-2, CCCA was achieved in 24% of treated tumors across all imlunestrant dose levels studied, comparable with similar WOO trials, in which 27% ($n = 6$) were observed with elacestrant (32), 20% ($n = 107$) with giredestrant, and 12% observed with amcenestrant (28, 32, 33). Notably, there are important limitations to these cross-trial comparisons, including key differences in baseline Ki-67 eligibility and treatment durations across both the older WOO trials of approved ET and more recent studies of investigational ET.

Collectively, the data from EMBER and EMBER-2 determined the optimal dose of imlunestrant to be 400 mg daily. This dosing strategy demonstrated biological efficacy in EMBER-2 and clinical benefit in patients with heavily pretreated advanced breast cancer enrolled in the EMBER trial. This dose is currently being tested for efficacy and safety in two randomized phase III trials for the treatment of patients with ER^+, $HER2^-$ breast cancer in the metastatic (EMBER-3) and adjuvant settings (EMBER-4).

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Disclaimer

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