Imlunestrant, an Oral Selective Estrogen Receptor Degrader, as Monotherapy and in Combination With Targeted Therapy in Estrogen Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Phase Ia/Ib EMBER Study

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ABSTRACT

PURPOSE Imlunestrant is a next-generation oral selective estrogen receptor (ER) degrader designed to deliver continuous ER target inhibition, including in *ESR1*-mutant breast cancer. This phase Ia/b trial determined the recommended phase II dose (RP2D), safety, pharmacokinetics, and efficacy of imlunestrant, as monotherapy and in combination with targeted therapy, in ER-positive (ER+) advanced breast cancer (ABC) and endometrial endometrioid cancer. The ER+/human epidermal growth factor receptor 2–negative (HER2–) ABC experience is reported here.

METHODS An i3+3 dose-escalation design was used, followed by dose expansions of imlunestrant as monotherapy or in combination with abemaciclib with or without aromatase inhibitor (AI), everolimus, or alpelisib. Imlunestrant was administered orally once daily and with the combination partner per label.

RESULTS Overall, 262 patients with ER+/HER2– ABC were treated (phase Ia, n = 74; phase Ib, n = 188). Among patients who received imlunestrant monotherapy (n = 114), no dose-limiting toxicities or discontinuations occurred. At the RP2D (400 mg once daily), patients (n = 51) reported grade 1-2 nausea (39.2%), fatigue (39.2%), and diarrhea (29.4%). Patients at RP2D had received previous cyclin-dependent kinase 4/6 inhibitor (CDK4/6i; 92.2%), fulvestrant (41.2%), and chemotherapy (29.4%) for ABC and achieved a median progression-free survival (mPFS) of 7.2 months (95% CI, 3.7 to 8.3). Among patients who received imlunestrant + abemaciclib (n = 42) and imlunestrant + abemaciclib + AI (n = 43), most (69.4%) were treatment-naïve for ABC; all were CDK4/6i-naïve. Patients treated with imlunestrant + everolimus (n = 42)/alpelisib (n = 21) had received previous CDK4/6i (100%), fulvestrant (34.9%), and chemotherapy (17.5%) for ABC. No new safety signals or interactions with partnered drugs were observed. The mPFS was 19.2 months (95% CI, 13.8 to not available) for imlunestrant + abemaciclib and was not reached for imlunestrant + abemaciclib + AI. The mPFS with imlunestrant + everolimus/alpelisib was 15.9 months (95% CI, 11.3 to 19.1)/9.2 months (95% CI, 3.7 to 11.1). Antitumor activity was evident regardless of *ESR1* mutation status.

CONCLUSION Imlunestrant, as monotherapy or in combination with targeted therapy, had a manageable safety profile with evidence of preliminary antitumor activity in ER+/HER2– ABC.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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CONTEXT

Key Objective

To assess the safety, pharmacokinetics (PKs), and preliminary efficacy of the next-generation selective estrogen receptor (ER) degrader imlunestrant, as monotherapy and in combination with targeted therapy, in patients with ER-positive advanced breast cancer.

Knowledge Generated

At the recommended phase II dose of 400 mg once daily, imlunestrant had favorable safety, PKs, and encouraging preliminary antitumor activity in cyclin-dependent kinase 4/6 inhibitor (CDK4/6i)–pretreated patients as monotherapy and in combination with everolimus/alpelisib. In CDK4/6i-naïve patients, imlunestrant + abemaciclib and imlunestrant + abemaciclib + aromatase inhibitor had an 18-month progression-free survival of 60.7% and 73.4%, respectively.

Relevance *(K.D. Miller)*

Optimal use of the ER degrader fulvestrant has been limited by the need for intramuscular administration and questions about optimal dosing, especially in obese patients. Imlunestrant provides an oral option with significant activity in previously treated patients, and ongoing phase III trials will determine its role in our therapeutic armamentarium.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

INTRODUCTION

Endocrine therapy (ET), alone or in combination with targeted therapy, is the standard-of-care treatment of estrogen receptor–positive (ER+) advanced breast cancer (ABC).[1-3] ET acts on estrogen synthesis (aromatase inhibitors [AIs]: anastrozole, letrozole, exemestane) or targets the ER directly through selective modulation (selective ER modulators: tamoxifen) or by antagonizing ER transcriptional activity and promoting its degradation via ER immobilization (selective estrogen receptor degraders [SERDs]: fulvestrant and elacestrant).[4]

Since the introduction of tamoxifen in the late 1960s, optimization of ET has incrementally improved outcomes for patients with ER+ breast cancer.[5-7] Fulvestrant established efficacy compared with an AI in ET-naïve patients with ABC, and an optimal dose was established in ET-pretreated patients with ABC, with a hazard ratio (HR) of approximately 0.8.[8-11] However, fulvestrant has some pharmacologic disadvantages that negatively affect patient experience and efficacy. Specifically, fulvestrant is poorly soluble, is not orally absorbed, and requires intramuscular administration[12,13] that is often painful and burdensome to patients.[14,15] Furthermore, efficacy is limited in patients with ET resistance from activating *ESR1* mutations, the gene encoding ERα.[16] The recently approved oral SERD elacestrant demonstrated clear superiority (HR, 0.55 [95% CI, 0.39 to 0.77]) compared with investigator's choice of ET (fulvestrant or AI) in patients with ABC harboring *ESR1* mutations.[17]

Combining ET with phosphoinositide 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway inhibitors (alpelisib or everolimus) or cyclin-dependent kinase 4/6 inhibitors (CDK4/6i: abemaciclib, palbociclib, or ribociclib) is effective in overcoming ET resistance.[6,18,19] The use of CDK4/6i in combination with ET has had a dramatic impact on patient outcomes for both ET-sensitive and ET-resistant patients with ER+ ABC.[20] Furthermore, in ET-pretreated patients with ABC, abemaciclib + fulvestrant was shown to be effective regardless of *ESR1* mutation status, with numerically greater improvement in median progression-free survival (mPFS) in patients harboring *ESR1*-mutant tumors compared with wild-type (20.7 *v* 15.3 months).[21]

These data provide compelling rationale for the development of novel SERDs that can be administered as monotherapy or in combination, to improve efficacy and patient experience (via oral administration), regardless of *ESR1* mutation status.

Imlunestrant is a next-generation, brain-penetrating, oral SERD with pure antagonistic properties, resulting in sustained inhibition of ER-dependent gene transcription and cell growth. Preclinically, imlunestrant has favorable pharmacokinetic (PK) properties, is efficacious in both *ESR1*-mutant and wild-type tumor models, and demonstrates enhanced efficacy when in combination with targeted therapy.[22,23]

Presented here is the ER+/human epidermal growth factor receptor 2–negative (HER2–) ABC experience focused on patients who received imlunestrant as monotherapy and in combination with abemaciclib with or without AI,

everolimus, or alpelisib from, to our knowledge, the first-in-human EMBER study.

METHODS

Study Design

EMBER (ClinicalTrials.gov identifier: NCT04188548) is a global, open-label, dose-escalation (phase Ia) trial of imlunestrant followed by multiple dose-expansion cohorts (phase Ib) exploring imlunestrant as monotherapy and in combination with targeted therapy. Eligible patients had ER+ (HER2− and HER2+) ABC or recurrent, persistent, or metastatic ER+ endometrial endometrioid cancer (EEC). Recruitment occurred in eight countries and 76 centers from December 2019 to March 2023.

Phase Ia followed an i3+3 design with five dose levels (200-1,200 mg once daily) evaluated. This design is ideal in trial safety with the ability to identify the true maximum tolerated dose (MTD) compared with the classical 3 + 3 design.[24] Initially, 3-6 patients were sequentially evaluated for dose-limiting toxicities (DLTs) during cycle (C) 1 (28 days) at each dose level. Thereafter, approximately 20 patients were allowed to backfill each dose level cohort.

Phase Ib evaluated imlunestrant as monotherapy and in combination with other therapeutic agents (part A: ER+/HER2− ABC, imlunestrant + abemaciclib with or without AI; part B: ER+/HER2− ABC, imlunestrant and imlunestrant + everolimus/alpelisib; part C: ER+/HER2+ ABC, imlunestrant + trastuzumab with or without abemaciclib; part D: ER+ EEC, imlunestrant and imlunestrant + abemaciclib; part E: ER+/HER2+ ABC, imlunestrant + trastuzumab + pertuzumab). Data from parts A and B (ER+/HER2− ABC cohorts) are presented in this study report. Part A randomly assigned patients to treatment cohorts using prespecified stratification factors, and Part B accrued cohorts by physician's choice (Data Supplement, Fig S1, online only).

The primary objective was to determine the recommended phase II dose (RP2D) of imlunestrant as monotherapy and in combination with other targeted therapy. Key secondary objectives included assessment of safety, tolerability, PK, overall response rate (ORR), clinical benefit rate (CBR), and PFS per RECIST v1.1. Exploratory objectives included *ESR1* mutation analysis and evaluation of tumor biomarkers (details are given in the Data Supplement, Methods: Assessment).

The study was approved by the ethical/institutional review board and conducted following the Declaration of Helsinki and the International Council for Harmonisation-Good Clinical Practice guidelines and applicable regulatory requirements. All patients provided written informed consent.

Patients

Eligible patients included those with ER+/HER2− ABC and previous sensitivity to ET or untreated de novo ABC. ER+ was defined as ≥1% ER+ tumor nuclei as determined by immunohistochemistry.[25] Up to three previous therapies were permitted in phase Ia. Abemaciclib cohorts (parts A) enrolled CDK4/6i-naïve patients and allowed one previous therapy. Imlunestrant and imlunestrant + everolimus/alpelisib cohorts (parts B) permitted up to two previous therapies and enrolled CDK4/6i-pretreated patients. Locally determined (tissue and/or plasma) *PIK3CA* mutation was required for the alpelisib cohort. Men and premenopausal women received concomitant gonadotropin-releasing hormone agonists. All patients had an Eastern Cooperative Oncology Group performance status of 0-1.

Key exclusion criteria included symptomatic central nervous system metastasis, concomitant systemic disorders, visceral crisis, or inflammatory breast cancer. Complete eligibility criteria are available in the protocol (online only). Study procedures and assessments are available in the Data Supplement.

Statistical Analysis

Analysis populations are defined in the Data Supplement (Table S1). The safety population included patients who received ≥one dose of imlunestrant. ORR (defined as the proportion of patients with a best overall response [BOR] of complete response [CR] and partial response [PR]) was evaluated in patients with measurable disease. CBR (defined as the proportion of patients with a BOR of CR, PR, or stable disease for ≥24 weeks) and PFS were analyzed in the safety population. Curves were estimated using the Kaplan-Meier method. Median and 95% CIs were calculated using the log-log method.

RESULTS

Patients and Treatment

As of March 2023, a total of 378 patients were treated in EMBER. In phase Ia, 81 patients were treated (ER+/HER2− ABC, n = 74; ER+ EEC, n = 7). In phase Ib, 297 patients were treated (ER+/HER2− ABC, n = 188; ER+/HER2+ ABC, n = 45; ER+ EEC, n = 64; Fig 1). This study report focuses on all patients with ER+/HER2− ABC (n = 262) treated across phase Ia (n = 74) and phase Ib (n = 188).

Among patients with ER+/HER2− ABC, 114 patients received imlunestrant (all dose levels), 51 received the selected RP2D of 400 mg once daily. Of 148 patients who received imlunestrant in combination with targeted therapy, 85 received imlunestrant + abemaciclib with or without an AI, 42 received imlunestrant + everolimus, and 21 received imlunestrant + alpelisib.

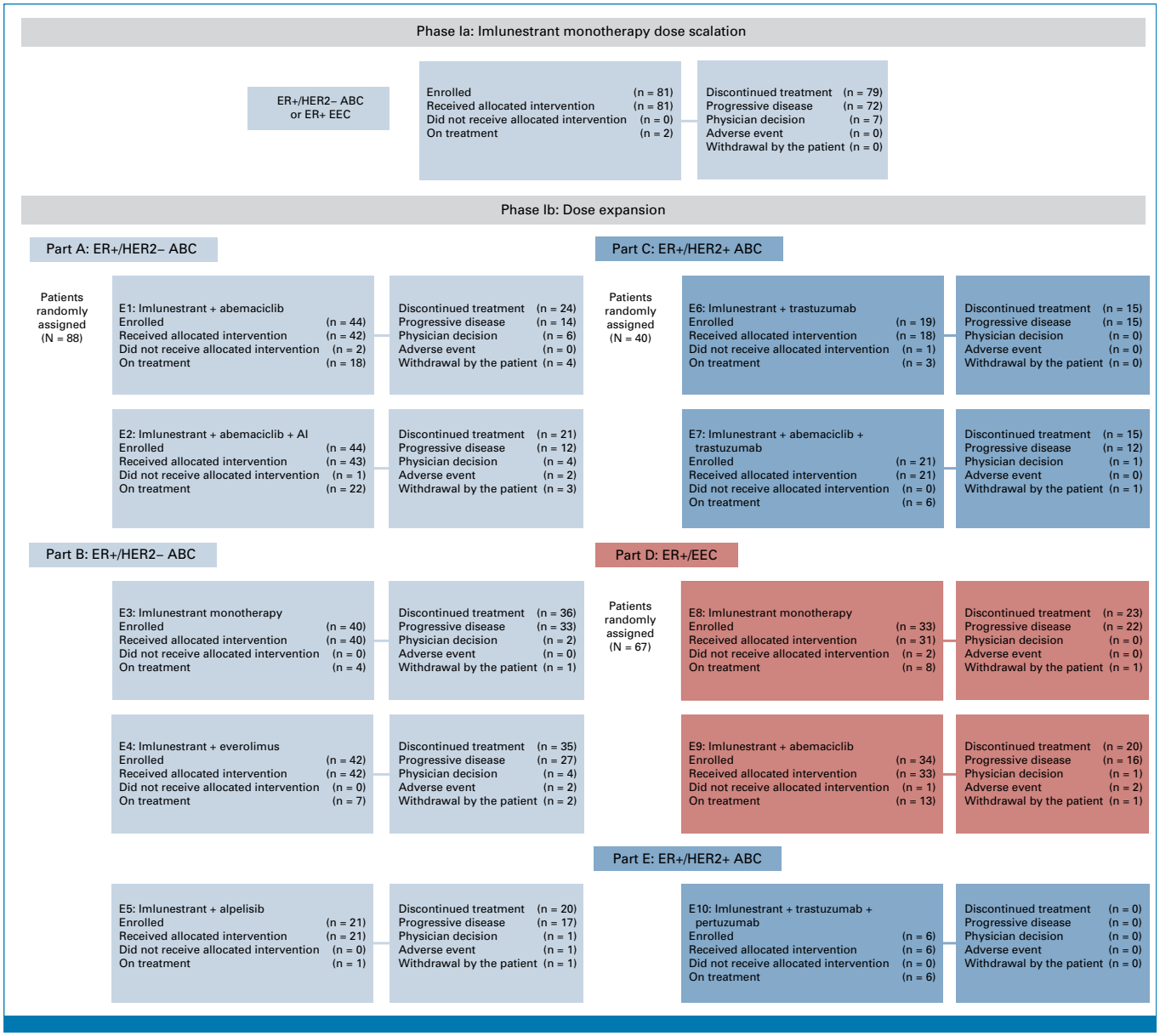

FIG 1. CONSORT diagram. ABC, advanced breast cancer; EEC, endometrial endometrioid cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

In EMBER, pretreated patients received imlunestrant as a second- or later-line treatment. Patients treated with imlunestrant (all dose levels) had a median of two previous anticancer therapies for ABC (Data Supplement, Table S2); those treated at the RP2D had a median of one previous therapy including previous CDK4/6i (92.2%), fulvestrant (41.2%), and chemotherapy (29.4%; Table 1). Among patients who received imlunestrant + abemaciclib with or without AI, most (69.4%) had not received previous ABC treatment, and all were CDK4/6i-naïve. Among patients who received imlunestrant + everolimus/alpelisib, all had received previous ABC treatment, including CDK4/6i (100%), fulvestrant (34.9%), and chemotherapy (17.5%; Data Supplement, Table S3).

Given the pretreated nature of patients who received imlunestrant at RP2D or imlunestrant + everolimus/alpelisib, a significant proportion of patients were found to have an *ESR1* mutation (plasma detected) at baseline (56.0%, 47.6%/47.4%, respectively; details of testing for *ESR1* mutations are given in the Data Supplement, Methods: Assessment). *ESR1* mutation rate was expectedly lower in the CDK4/6i-naïve patients who received imlunestrant + abemaciclib with or without AI (7.3% and 10.0%; Table 1). Per inclusion criteria, all patients had ER expression ≥1%, with most having tumors with an ER score of ≥10% (Table 1; Data Supplement, Table S3).

Safety

Imlunestrant Monotherapy

Across five doses (200-1,200 mg once daily) evaluated during dose escalation, no DLTs were observed and an MTD

TABLE 1. Baseline Demographics and Disease Characteristics in Patients With ER+/HER2− ABC Who Received Imlunestrant Monotherapy at the RP2D or in Combination With Abemaciclib With or Without AI

	Monotherapy	Combination Therapy	
Characteristic	Imlunestrant RP2D (n = 51)	Imlunestrant + Abemaciclib (n = 42[a])	Imlunestrant + Abemaciclib + AI (n = 43[b])
Age, years, median (range)	63 (34-95)	59 (33-86)	53 (31-76)
Race, No. (%)[c]			
White	42 (82.4)	27 (64.3)	28 (65.1)
Asian	6 (11.8)	8 (19.0)	10 (23.3)
Black or African American	2 (3.9)	2 (4.8)	0
American Indian or Alaska Native	1 (2.0)	1 (2.4)	0
Native Hawaiian or other Pacific Islander	0	1 (2.4)	0
Multiple	0	0	1 (2.3)
Menopausal status, No. (%)			
Postmenopausal	42 (82.4)	30 (71.4)	28 (65.1)
Premenopausal	9 (17.6)	12 (28.6)	14 (32.6)
ER score, n/N (%)			
≥10%	31/33 (93.9)[d]	39/42 (92.9)	35/38 (92.1)
PgR−, No. (%)	14 (27.5)	14 (33.3)	10 (23.3)
Baseline ECOG PS, No. (%)			
0	30 (58.8)	26 (61.9)	31 (72.1)
1	21 (41.2)	16 (38.1)	12 (27.9)
ESR1 mutations detected at baseline, n/N (%)[e]	28/50 (56.0)	3/41 (7.3)	4/40 (10.0)
PIK3CA mutations detected at baseline, n/N (%)[e,f]	22/50 (44.0)	10/41 (24.4)	11/40 (27.5)
Visceral metastasis, No. (%)	33 (64.7)	21 (50.0)	27 (62.8)
Untreated de novo metastatic, No. (%)	0	7 (16.7)	9 (20.9)
Measurable disease at baseline, No. (%)	34 (66.7)	28 (66.7)	34 (79.1)
No. of previous therapies in any setting, median (range)	3 (1-9)	1 (0-4)	1 (0-3)
No. of previous therapies for ABC, median (range)	1 (0-8)	0 (0-1)	0 (0-1)
Previous therapy for ABC, No. (%)	50 (98.0)	12 (28.6)	14 (32.6)
Endocrine therapy	50 (98.0)	7 (16.7)	11 (25.6)
AI	40 (78.4)	4 (9.5)	7 (16.3)
Fulvestrant	21 (41.2)	2 (4.8)	2 (4.7)
Tamoxifen	7 (13.7)	1 (2.4)	3 (7.0)
CDK4/6 inhibitor	47 (92.2)	0	0
PI3K/AKT/mTOR inhibitor	6 (11.8)	0	1 (2.3)
Chemotherapy	15 (29.4)	4 (9.5)	4 (9.3)

NOTE. Imlunestrant in combination regimens was administered at the RP2D of monotherapy unless otherwise specified.
Abbreviations: ABC, advanced breast cancer; AI, aromatase inhibitor; AKT, protein kinase B; CDK4/6, cyclin-dependent kinase 4/6; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; PgR, progesterone receptor-negative; PI3K, phosphoinositide 3-kinase; RP2D, recommended phase II dose.
[a]Four patients received imlunestrant 800 mg once daily.
[b]One patient received imlunestrant 800 mg once daily.
[c]Where values do not add up to 100%, remaining data are missing.
[d]Included patients from cohort E3 of phase Ib.
[e]Per central assessment of ctDNA (Guardant360 assay).
[f]ctDNA not detected in two patients and *PIK3CA* variant not detected in one patient.

TABLE 2. TEAEs in Patients With ER+/HER2− ABC Who Received Imlunestrant Monotherapy at the RP2D or in Combination With Abemaciclib With or Without AI

	Monotherapy, No. (%)		Combination Therapy, No. (%)			
	Imlunestrant RP2D (n = 51)		Imlunestrant + Abemaciclib (n = 42)		Imlunestrant + Abemaciclib + AI (n = 43)	
Parameter	All	G ≥3	All	G ≥3	All	G ≥3
Patients with dose reduction because of TEAEs	2 (3.9)	1 (2.0)	14 (33.3)	7 (16.7)	18 (41.9)	6 (14.0)
Treatment discontinuations because of TEAEs	0		1 (2.4)[a]		3 (7.0)[b]	
Patients with ≥one TEAE[c]	47 (92.2)	10 (19.6)	41 (97.6)	25 (59.5)	42 (97.7)	21 (48.8)
GI disorders						
Nausea	20 (39.2)	1 (2.0)	25 (59.5)	0	27 (62.8)	0
Diarrhea	15 (29.4)	1 (2.0)	40 (95.2)	5 (11.9)	35 (81.4)	3 (7.0)
Vomiting	5 (9.8)	0	14 (33.3)	0	16 (37.2)	0
Abdominal pain[d]	4 (7.8)	0	15 (35.7)	1 (2.5)	15 (34.9)	1 (2.3)
Constipation	4 (7.8)	0	6 (14.3)	0	6 (14.0)	0
Hematologic, biochemical, and lymphatic system disorders						
Anemia	4 (7.8)	0	13 (31.0)	5 (11.9)	16 (37.2)	2 (4.7)
Hyperglycemia	5 (9.8)	0	3 (7.1)	1 (2.5)	3 (7.0)	0
Neutropenia	3 (5.9)	2 (3.9)	18 (42.9)	6 (14.3)	19 (44.2)	8 (18.6)
Thrombocytopenia	3 (5.9)	0	3 (7.1)	0	7 (16.3)	1 (2.3)
Leukopenia	1 (2.0)	0	7 (16.7)	2 (4.8)	9 (20.9)	3 (7.0)
Hypokalemia	1 (2.0)	0	7 (16.7)	0	4 (9.3)	1 (2.3)
Liver disorders						
AST increased	8 (15.7)	0	7 (16.7)	2 (4.8)	11 (25.6)	2 (4.7)
ALT increased	5 (9.8)	0	5 (11.9)	2 (4.8)	9 (20.9)	3 (7.0)
Renal and urinary disorders						
Urinary tract infection	4 (7.8)	0	6 (14.3)	1 (2.5)	6 (14.0)	1 (2.3)
Blood creatinine increased	1 (2.0)	0	12 (28.6)	1 (2.4)	9 (20.9)	1 (2.3)
Chronic kidney disease	0	0	4 (9.5)	1 (2.4)	3 (7.0)	0
Brain disorders						
Headache	6 (11.8)	0	12 (28.6)	0	8 (18.6)	0
Dizziness	2 (3.9)	0	7 (16.7)	0	7 (16.3)	1 (2.3)
Respiratory, thoracic, and mediastinal disorders						
Cough	7 (13.7)	0	7 (16.7)	0	9 (20.9)	0
Dyspnea	5 (9.8)	1 (2.0)	3 (7.1)	0	3 (7.0)	2 (4.7)
COVID-19	3 (5.9)	1 (2.0)	9 (21.4)	0	11 (25.6)	0
Pain						
Arthralgia	10 (19.6)	0	7 (16.7)	0	10 (23.3)	0
Back pain	4 (7.8)	0	6 (14.3)	0	4 (9.3)	1 (2.3)
Pain in extremity	3 (5.9)	0	5 (11.9)	0	5 (11.6)	0
Myalgia	1 (2.0)	0	4 (9.5)	0	0	0
Skin and subcutaneous disorders						
Pruritus	5 (9.8)	0	4 (9.5)	0	2 (4.7)	0
Rash[e]	4 (7.8)	0	8 (19.0)	0	9 (20.9)	0
Alopecia	3 (5.9)	0	13 (31.0)	0	8 (18.6)	0
Others						
Fatigue	20 (39.2)	2 (3.9)	18 (42.9)	3 (7.1)	25 (58.1)	1 (2.3)
Decreased appetite	7 (13.7)	0	10 (23.8)	0	9 (20.9)	0
Hot flashes	6 (11.8)	0	6 (14.3)	0	6 (14.0)	0
Hypertension	4 (7.8)	1 (2.0)	6 (14.3)	2 (4.8)	3 (7.0)	2 (4.7)
Insomnia	3 (5.9)	0	6 (14.3)	0	6 (14.0)	0

(continued on following page)

TABLE 2. TEAEs in Patients With ER+/HER2− ABC Who Received Imlunestrant Monotherapy at the RP2D or in Combination With Abemaciclib With or Without AI (continued)

	Monotherapy, No. (%)		Combination Therapy, No. (%)			
	Imlunestrant RP2D (n = 51)		Imlunestrant + Abemaciclib (n = 42)		Imlunestrant + Abemaciclib + AI (n = 43)	
Parameter	All	G ≥3	All	G ≥3	All	G ≥3
Blood alkaline phosphatase increased	3 (5.9)	0	4 (9.5)	2 (4.8)	3 (7.0)	0
Weight decreased	2 (3.9)	0	4 (9.5)	0	4 (9.3)	0
Pyrexia	2 (3.9)	0	5 (11.9)	1 (2.4)	1 (2.3)	0
Vision blurred	2 (3.9)	0	5 (11.9)	0	1 (2.3)	0
Gastroesophageal reflux disease	1 (2.0)	0	4 (9.5)	0	5 (11.6)	0
Flatulence	1 (2.0)	0	5 (11.9)	0	3 (7.0)	0
Dysgeusia	0	0	7 (16.7)	0	4 (9.3)	0
Lacrimation increase	0	0	4 (9.5)	0	3 (7.0)	0
Nail disorder	0	0	4 (9.5)	0	1 (2.3)	0
Ejaculation failure[f]	0	0	0	0	1 (100.0)	0

NOTE. Selected grouped terms are provided in the footnote, all other grouped terms are listed in the Data Supplement.
Abbreviations: ABC, advanced breast cancer; AI, aromatase inhibitor; ER, estrogen receptor; G, grade; HER2, human epidermal growth factor receptor 2; RP2D, recommended phase II dose; TEAE, treatment-emergent adverse event.
[a]One patient discontinued abemaciclib alone.
[b]One patient discontinued abemaciclib alone, and two patients discontinued imlunestrant + abemaciclib + AI.
[c]TEAEs occurring in ≥10% of patients in any treatment arm.
[d]The grouped term of abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, and GI pain.
[e]The grouped term of TEAE included rash, rash vesicular, rash maculopapular, rash morbilliform, rash pruritic, rash pustular, rash erythematous, and dermatitis acneiform.
[f]Denominator adjusted for male-specific events.

was not reached. Dose optimization on the basis of PK, pharmacodynamic (PD), and biologic factors was performed following the US Food and Drug Administration guidelines.[26] The RP2D was determined as 400 mg once daily on the basis of an optimal safety, efficacy, and PK/PD profile observed in the EMBER and EMBER-2 trials (a window-of-opportunity study that evaluated the biologic [PK/PD] effect of imlunestrant across dose levels).[27]

At the RP2D, the most common treatment-emergent AEs (TEAEs) were primarily grade 1-2 nausea (39.2%), fatigue (39.2%), and diarrhea (29.4%; Table 2; all imlunestrant dose levels are presented in the Data Supplement, Table S4). Grade ≥3 TEAEs were observed in 19.6% of patients (Table 2), and 9.8% was treatment-related AEs (TRAEs; Data Supplement, Table S5). Dose reductions occurred in 3.9% of patients, and no patient discontinued treatment because of toxicity (Table 2; all dose levels are presented in the Data Supplement, Table S6).

Imlunestrant in Combination With Targeted Therapy

The most common TEAEs in the imlunestrant + abemaciclib and imlunestrant + abemaciclib + AI cohorts were diarrhea (95.2% and 81.4%, respectively), nausea (59.5% and 62.8%), fatigue (42.9% and 58.1%), and neutropenia (42.9% and 44.2%; Table 2). In the everolimus cohort, these were diarrhea (57.1%), fatigue (47.6%), and aspartate aminotransferase increase (38.1%), and in the alpelisib cohort, these were diarrhea (85.7%), rash (66.7%), and hyperglycemia (61.9%). Combination therapy with alpelisib was associated with the highest rate of grade 3 toxicity (81.0%), predominately rash (47.6%), hyperglycemia (9.5%), and diarrhea (9.5%; Data Supplement, Table S7; TRAEs are presented in the Data Supplement, Table S8). Dose reductions were most frequently observed in the imlunestrant + abemaciclib + AI (41.9%) and alpelisib (47.6%) cohorts and were mostly of abemaciclib (71.9%) and alpelisib (70.0%) alone (Data Supplement, Table S9). Discontinuations because of TEAEs occurred in 2.4% and 7.0% of the patients who received imlunestrant + abemaciclib with or without AI, respectively (Table 2), but were more common with imlunestrant + everolimus (9.5%) and imlunestrant + alpelisib (38.1%; Data Supplement, Table S7).

PKs

PK parameters were summarized across all patients who received imlunestrant with intensive PK sampling (200-1,200 mg once daily; n = 89, 82 of whom were patients with ER+/HER2− ABC) during phase Ia/Ib. A dose-proportional increase in the maximum plasma concentration (C_{max}) and $AUC_{0-\infty}$ of imlunestrant was observed on the basis of statistical analyses, with similar PK parameters across formulations. The median t_{max} was around 4 hours, and the geometric mean half-life of imlunestrant ranged from 25 to 30 hours (Data Supplement, Table S10), which

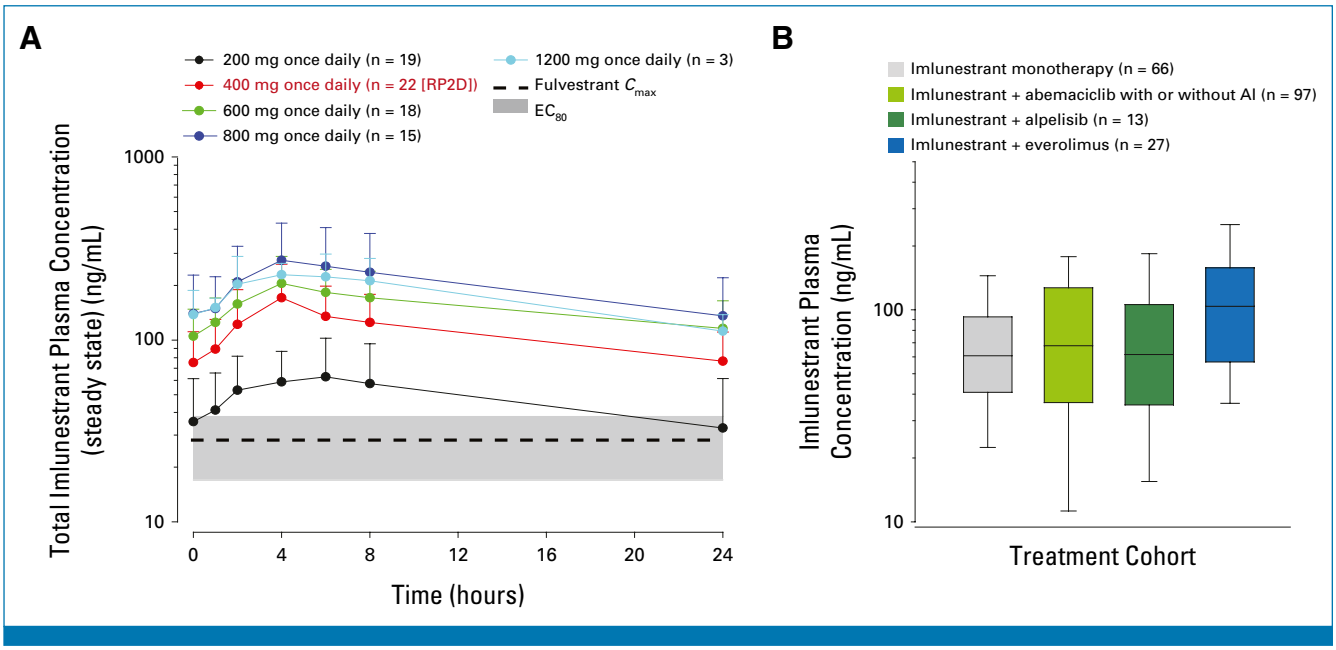

FIG 2. Imlunestrant plasma concentration in patients who received imlunestrant monotherapy or in combination with targeted therapy. Patients with ABC and EEC were included together in the PK summaries since no PK differences existed between these patients. (A) Imlunestrant plasma concentration-time profiles on day 15 after multiple oral imlunestrant doses of 200-1,200 mg once daily in patients with intensive PK sampling who received monotherapy during phase Ia or Ib. (B) Steady-state average total plasma concentrations of imlunestrant trough concentrations across different cohorts. The shaded area represents the EC_{80} range (18-38 ng/mL) derived from preclinical breast cancer xenograft studies. The dotted black line represents the fulvestrant steady-state total C_{max} of 28 ng/mL and unbound C_{max} of 0.0056 ng/mL. ABC, advanced breast cancer; AI, aromatase inhibitor; C_{max}, maximum plasma concentration; EC, effective concentration; EEC, endometrial endometrioid cancer; PK, pharmacokinetics; RP2D, recommended phase II dose.

supports once daily dosing. Steady-state total plasma concentrations of imlunestrant at doses of ≥200 mg once daily exceeded the in vivo effective concentration $(EC)_{80}$ range derived from preclinical breast cancer xenograft studies and the literature-reported fulvestrant steady-state C_{max} (Fig 2A). However, at doses of ≥400 mg once daily, exposures exceeded the EC_{80} range throughout the dosing interval and sustained biologically relevant concentrations. Imlunestrant PKs were not affected by abemaciclib, AIs, everolimus, or alpelisib (Fig 2B). Importantly, there were no drug-drug interactions identified with any partner drugs.

Concentration-corrected QT interval by Fridericia (QTcF) analyses conducted in 76 patients (imlunestrant, all dose levels) with matched PK and showed no effects of imlunestrant concentrations on the QTc interval, with the upper bound of the 95% CI of the mean delta corrected QT interval (QTc) <10 ms at C_{max} of 400 mg (95% CI, −0.86 to 4.29).

Efficacy

Imlunestrant Monotherapy

Among the 114 patients treated with imlunestrant (all dose levels), the CBR was 42.1%, the mPFS was 4.3 months (95% CI, 3.6 to 7.1), and the ORR was 7.9%. The median treatment duration was 3.8 months (range, 0.2-30.2). Among subgroups of interest, fulvestrant-pretreated patients (n = 59) had a mPFS of 3.8 months (95% CI, 1.9 to 6.4) and CDK4/6i-pretreated patients receiving imlunestrant as second-line treatment (n = 48) had a mPFS of 6.5 months (95% CI, 3.7 to 8.3; Data Supplement, Fig S2 and Table S11).

At the RP2D (n = 51), the CBR was 54.9%, the mPFS was 7.2 months (95% CI, 3.7 to 8.3), and the ORR was 11.8% (n = 34; Fig 3; Table 3). Similar efficacy was observed in subgroups of interest, with the mPFS of 7.5 months (95% CI, 1.9 to 11.1) and 7.1 months (95% CI, 3.5 to 8.1) in fulvestrant-pretreated patients (n = 21) and CDK4/6i-pretreated patients receiving imlunestrant as second-line treatment (n = 26), respectively (Data Supplement, Fig S3 and Table S11).

Imlunestrant in Combination With Targeted Therapy

Among patients who received imlunestrant + abemaciclib (n = 42), the ORR was 32.1%, the CBR 71.4%, the mPFS was 19.2 months (95% CI, 13.8 to not available [NA]), and the 18-month PFS was 60.7% (95% CI, 39.6 to 76.5). In patients who received imlunestrant + abemaciclib + AI (n = 43), the ORR was 61.8%, the CBR was 79.1%, mPFS was not reached, and the estimated 18-month PFS was 73.4% (95% CI, 55.5 to 85.0; Fig 3; Table 3). It is worth noting that 16 patients in the abemaciclib arms had untreated de novo metastasis, among whom the CBR was 71.4% (n = 5 of 7) with imlunestrant +

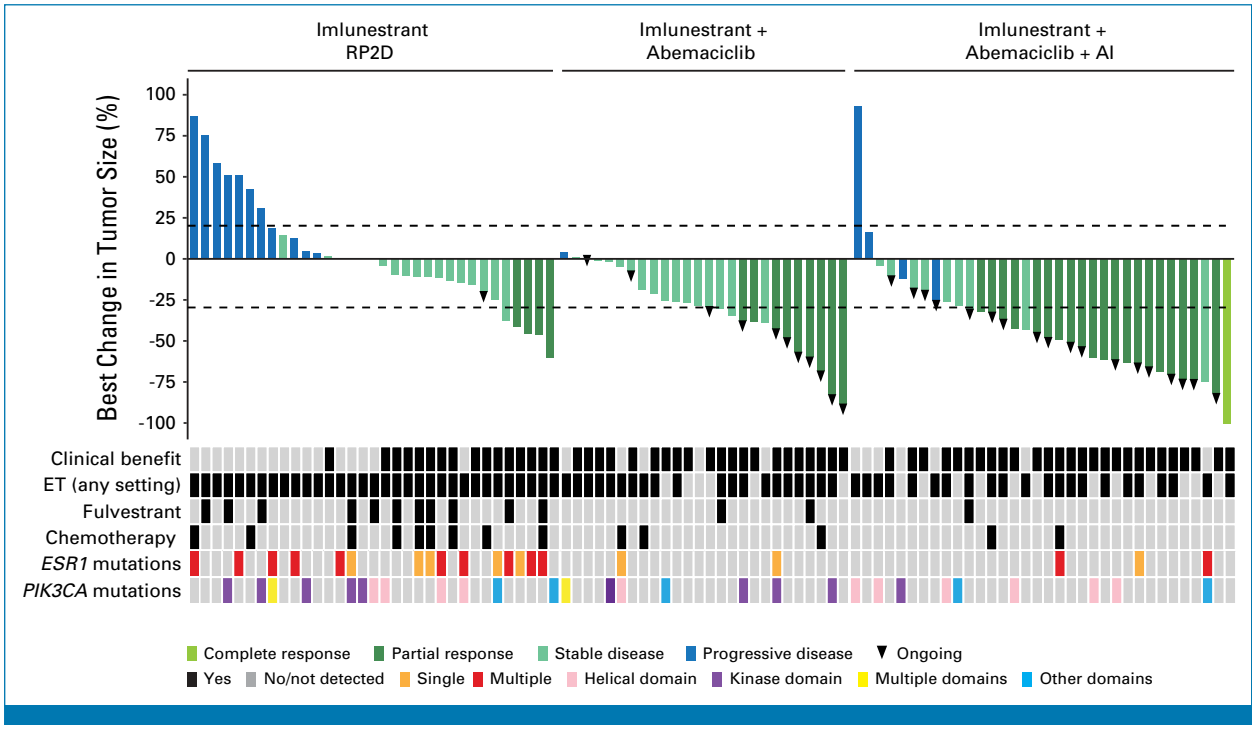

FIG 3. Tumor response in patients with ER+/HER2– ABC who received imlunestrant monotherapy at the RP2D or in combination with abemaciclib with or without AI. Waterfall plot for best percentage change in tumor size in patients with measurable disease who received imlunestrant monotherapy at the RP2D (n = 34), imlunestrant + abemaciclib (n = 28), and imlunestrant + abemaciclib + AI (n = 34). Each bar represents one patient. ABC, advanced breast cancer; AI, aromatase inhibitor; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; RP2D, recommended phase II dose.

abemaciclib and 88.9% (n = 8 of 9) with imlunestrant + abemaciclib + AI (Data Supplement, Table S12).

Among patients who received imlunestrant + everolimus (n = 42), the ORR was 21.4%, the CBR 61.9%, and the mPFS was 15.9 months (95% CI, 11.3 to 19.1), whereas in patients who received imlunestrant + alpelisib (n = 21), the ORR was 58.3%, the CBR was 61.9%, and the mPFS was 9.2 months (95% CI, 3.7 to 11.1). The median treatment duration was 11.8 months (range, 0.5-23.0) and 6.1 months (range, 1.5-

TABLE 3. Efficacy in Patients With ER+/HER2– ABC Who Received Imlunestrant Monotherapy at the RP2D or in Combination With Abemaciclib With or Without AI

	Monotherapy	Combination Therapy	
Parameter	Imlunestrant RP2D (n = 51)	Imlunestrant + Abemaciclib (n = 42)	Imlunestrant + Abemaciclib + AI (n = 43)
ORR, n/N (%)[a]	4/34 (11.8)	9/28 (32.1)	21/34 (61.8)
CBR, No. (%)	28 (54.9)	30 (71.4)	34 (79.1)
Treatment duration, months, median (range)	6.5 (0.3-25.9)	13.9 (0.2-26.3)	14.0 (1.8-23.0)
TTR, months, median (range)	3.6 (1.6-5.4)	5.5 (1.6-10.9)	3.7 (1.7-8.5)
PFS, months, median (95% CI)	7.2 (3.7 to 8.3)	19.2 (13.8 to NA)	NA (18.9 to NA)
ESR1 mutation	7.1 (3.7 to 8.2)	NE	NE
ESR1 mutation not detected	5.6 (1.8 to 8.4)	NE	NE
12-month PFS, % (95% CI)	22.2 (11.3 to 35.3)	74.2 (56.2 to 85.7)	80.7 (65.1 to 89.9)

Abbreviations: ABC, advanced breast cancer; AI, aromatase inhibitor; BOR, best overall response; CBR, clinical benefit rate (BOR of CR and PR or stable disease for ≥ 24 weeks); CR, complete response; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NA, not available; NE, not estimated because of small numbers; ORR, overall response rate (BOR of CR and PR); PFS, progression-free survival; PR, partial response; RP2D, recommended phase II dose; TTR, time to response.
[a]ORR evaluable for patients who have measurable disease at baseline.

14.7) for imlunestrant + everolimus/alpelisib, respectively (Data Supplement, Figs S3 and S4 and Table S12).

Exploratory Efficacy Analyses by Baseline *ESR1* Mutation Status (circulating tumor DNA detected)

Imlunestrant Monotherapy

Among evaluable patients treated with imlunestrant (all dose levels; n = 109), the mPFS was 5.4 months (95% CI, 3.7 to 7.5) and 3.7 months (95% CI, 1.9 to 8.1) in those with (n = 53) and without (n = 56) a detectable *ESR1* mutation, respectively. At the RP2D (n = 50 evaluable), the mPFS was 7.1 months (95% CI, 3.7 to 8.2) and 5.6 months (95% CI, 1.8 to 8.4) in patients with (n = 28) and without (n = 22) an *ESR1* mutation, respectively (Data Supplement, Fig S3 and Table S13).

Imlunestrant in Combination With Targeted Therapy

Exploratory analyses by baseline *ESR1* mutation status were conducted in the ET-pretreated cohorts (imlunestrant + everolimus/alpelisib, n = 61 evaluable) where approximately half the patients had tumors harboring a detectable *ESR1* mutation.

Patients with a detectable *ESR1* mutation (n = 20) treated with imlunestrant + everolimus had a longer mPFS compared with those without the mutation (n = 22; 16.8 months [95% CI, 12.0 to 21.9] *v* 13.7 months [95% CI, 3.5 to NA], respectively; Data Supplement, Fig S3). Similarly, patients with *ESR1* mutation (n = 9) treated with imlunestrant + alpelisib had a longer mPFS compared with those without a detectable *ESR1* mutation (n = 10; 10.7 months [95% CI, 1.6 to NA] *v* 7.8 months [95% CI, 1.5 to NA], respectively; Data Supplement, Fig S3). The low proportion (8.6%) of patients with *ESR1* mutation who received imlunestrant + abemaciclib with or without AI precluded the exploratory clinical analyses of these cohorts.

Correlation of Circulating Tumor DNA Dynamics With Disease Response

In patients with serial circulating tumor DNA (ctDNA) available (imlunestrant, all dose levels, n = 89; imlunestrant + abemaciclib with or without AI, n = 41), clinical benefit and objective response were associated with deep declines in ctDNA levels (all somatic mutations) at C2D1 (Figs 4A and 4B). Patients who achieved a molecular response (decline ≥50% ctDNA) had longer PFS than those who did not (Figs 4C and 4D). Similar observations were noted for the imlunestrant + everolimus/alpelisib cohorts (Data Supplement, Fig S5) although the number of evaluable patients was limited.

For the 60 patients with an *ESR1* mutation who received imlunestrant (n = 53) or imlunestrant + abemaciclib with or without AI (n = 7), the two most frequent *ESR1* mutations were *Y537* (61.7% [n = 37 of 60]) and *D538* (61.7% [n = 37 of 60]; Fig 4E). In patients with an *ESR1* mutation and serial ctDNA available (n = 45 imlunestrant, n = 5 imlunestrant + abemaciclib with or without AI), multiple mutations per patient were observed. Of the *ESR1* mutations detected at baseline, 74.2% (72 of 97) cleared completely or declined (≥50%) at C2D1 (Fig 4F).

DISCUSSION

The phase Ia/Ib EMBER study tested doses of imlunestrant from 200 to 1,200 mg once daily, with no DLTs observed and no treatment discontinuations because of toxicity. Imlunestrant demonstrated a favorable safety profile of low-grade and manageable TEAEs, similar to other drugs in the class, with the notable absence of ocular or cardiac side effects and effect of imlunestrant on the QTc interval at all dose levels. At the 400 mg once daily dose, imlunestrant exhibited a low incidence of GI toxicities (mostly grade 1-2), sustained exposures above the EC_{80} range and the fulvestrant C_{max}, and encouraging preliminary efficacy (CBR 54.9%, mPFS 7.2 months [95% CI, 3.7 to 8.3]) in pretreated patients with ER+/HER2− ABC. These data supported selection of 400 mg once daily as the RP2D.

Nearly all patients received previous CDK4/6i, and almost half received previous fulvestrant. Clinical benefit was similar for both, at 53.2% and 61.9%, respectively. While noting the limitations of cross-trial comparisons, the efficacy of imlunestrant at RP2D compares favorably with recent trials of fulvestrant (phase III: mPFS 1.9 months)[17] and elacestrant (phase I: CBR 42.6% [RP2D], mPFS 4.5 months[28]; phase III: CBR 18.4%, mPFS 2.8 months).[17] In addition, it is comparable with other oral SERDs in development such as giredestrant (phase II: mPFS 5.6 months)[29] and camizestrant (phase II: mPFS 7.2 months [75 mg once daily]).[30]

EMBER also explored the combination of imlunestrant with targeted therapy. Overall, the combination safety profiles were consistent with previous reports of these targeted therapies with standard-of-care ET.[31-38] Incidences of GI toxicities, fatigue, and neutropenia with imlunestrant + abemaciclib with or without AI were comparable with those in MONARCH 2 (fulvestrant + abemaciclib)[31] and MONARCH 3 (AI + abemaciclib),[32] suggesting no additive toxicity effect. Side effects were predictable and manageable with concomitant medications and/or dose adjustments.[39] Diarrhea, fatigue, and elevated hepatic transaminases were observed with imlunestrant + everolimus.[33,34,36] Notably, the highest grade 3 toxicity rates occurred with imlunestrant + alpelisib, and similar to those in SOLAR-1 (fulvestrant + alpelisib), these were mainly hyperglycemia and rash,[40] with a higher rate of grade 3 rash observed in EMBER. Prophylactic measures were recommended,[41] but not mandatory. Dose modification rates were also generally consistent with those in previous reports of targeted therapies.[35-37,42-44]

Overall, robust preliminary efficacy was observed with imlunestrant combination regimens. In CDK4/6-naïve patients, the

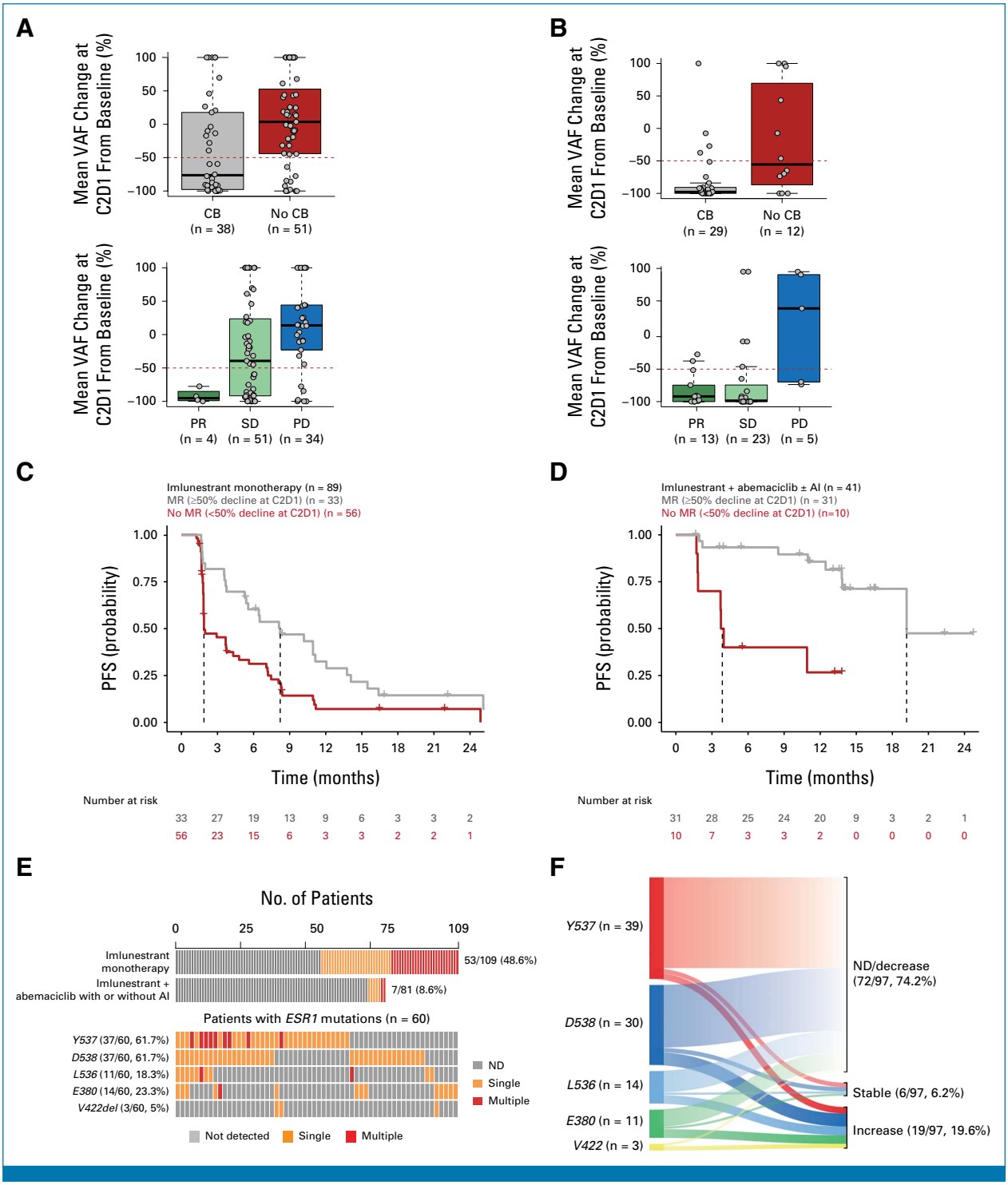

FIG 4. Circulating tumor DNA dynamics in patients with ER+/HER2− ABC who received imlunestrant monotherapy (all dose levels) or in combination with abemaciclib with or without AI. Mean VAF % change of all somatic mutations at C2D1 compared with baseline according to the clinical benefit and best overall response in patients who received (A) imlunestrant (n = 89) or (B) imlunestrant + abemaciclib with or without AI (n = 41). (C and D) PFS according to MR (≥50% decline in VAF at C2D1) or no MR (<50%-0% decline in VAF at C2D1). (E) Landscape of *ESR1* mutations detected at baseline. (F) Dynamic change in *ESR1* mutations at baseline and at C2D1 in response to imlunestrant (n = 45) and imlunestrant + abemaciclib with or without AI (n = 5). Multiple *ESR1* mutations (n = 97) were observed per patient. The Guardant360 assay was used to perform ctDNA somatic mutation analysis. ABC, advanced breast cancer; AI, aromatase inhibitor; C2D1, cycle 2 day 1; CB, clinical benefit; CR, complete response; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MR, molecular response; ND, not detected; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; VAF, variant allele frequency.

18-month PFS rates were 60.7% and 73.4% with imlunestrant + abemaciclib and imlunestrant + abemaciclib + AI, respectively. While several ongoing trials are evaluating SERDS in combination with CDK4/6-/PI3K-/AKT-/mTOR inhibitors,[6] to our knowledge, EMBER is the first study to demonstrate the feasibility and tolerability of an oral SERD + a CDK4/6i and AI triplet combination. Overall, the GI toxicity with imlunestrant + abemaciclib was not worse than previously reported with fulvestrant + abemaciclib. However, clinical trials combining imlunestrant with other CDK4/6i would be necessary to establish safe dosing, ensuring that there is no exacerbation of known toxicities, and evaluate the efficacy of these combinations.

ESR1 mutations, especially *Y537S* and *D538G*, have been linked to acquired ET resistance, particularly to AIs.[45] Indeed, up to 50% of patients with ER+/HER2− ABC treated with ET will develop an *ESR1* mutation.[16] However, this rate may be underestimated because of the limitations of ctDNA testing, particularly for acquired subclonal variants.[46,47] Thus, serial ctDNA testing may be warranted for detection of *ESR1* mutations to identify patients with ER-dependent disease where the SERD benefit may be enhanced.[48] Although elacestrant demonstrated a significant improvement in PFS versus investigator's choice of ET (fulvestrant or AI) in the overall population and those with *ESR1* mutations, elacestrant is only approved for use in patients with ER+/HER2−, *ESR1*-mutated ABC, where the greatest benefit (HR, 0.55 [95% CI, 0.39 to 0.77]; P = .0005) was appreciated.[17,49]

In largely CDK4/6i-pretreated patients (92.2% and 100%, respectively), imlunestrant at the RP2D or imlunestrant + everolimus/alpelisib showed antitumor activity regardless of *ESR1* mutation status. Although efficacy was enriched in patients with an *ESR1* mutation (mPFS 7.1 months imlunestrant RP2D; 16.8 months/10.7 months imlunestrant + everolimus/alpelisib, respectively), it was also evident in those without a detectable *ESR1* mutation (mPFS 5.6 months in imlunestrant RP2D; 13.7 months/7.8 months in imlunestrant + everolimus/alpelisib, respectively). While these observations are limited by the exploratory nature of these analyses in small sample sizes, it has been consistently observed that SERD benefit is enriched in patients with *ESR1* mutations.[28,50]

Notably, 74.2% of *ESR1* mutations detected at baseline completely cleared or declined by ≥50% on C2D1 in response to imlunestrant and imlunestrant + abemaciclib with or without AI. Overall, patients who achieved a molecular response had the longest PFS with imlunestrant, as monotherapy or in combination with targeted therapy. By contrast, *ESR1* mutation reduction at C2D1 of imlunestrant was not associated with longer PFS, indicating that modulation of *ESR1* mutation variants, independent of other variants, may simply serve as an indicator of imlunestrant target engagement.

Our study is limited by the short follow-up duration, preventing conclusions about treatment-naïve patients with ABC included in the abemaciclib cohorts, particularly in the small number of patients with de novo ABC. Although it is sufficient to establish the preliminary efficacy of imlunestrant monotherapy and combination therapy, longer follow-up is needed, particularly for a better understanding of safety with chronic dosing along with the overall impact on patient outcomes. In addition, because of the nature of phase I studies, the reported cohorts are limited by small sample sizes.

In conclusion, imlunestrant at the RP2D of 400 mg orally once daily had a manageable safety profile with mostly low-grade, reversible, GI symptoms, suggesting potential suitability for chronic administration. Also notable with imlunestrant was its favorable PK profile with sustained steady-state exposures above the fulvestrant C_{max} and encouraging preliminary antitumor activity as monotherapy and in combination with other targeted therapies. Taken together, these results show promise for imlunestrant as an oral alternative to fulvestrant and support the ongoing development of imlunestrant in phase III studies as monotherapy or in combination with abemaciclib for ET-pretreated patients with ABC (EMBER-3; ClinicalTrials.gov identifier: NCT04975308) and as adjuvant monotherapy for early-stage BC (EMBER-4; ClinicalTrials.gov identifier: NCT05514054).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/jco.23.02733. Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, except PK or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. Once the data is available, there is currently no set expiration date for data requests. 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. For details on submitting a request, see the instructions provided at www.vivli.org.

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Imlunestrant, an Oral Selective Estrogen Receptor Degrader, as Monotherapy and in Combination With Targeted Therapy in Estrogen Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Phase Ia/Ib EMBER Study

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