ORIGINAL ARTICLE

Imlunestrant with or without Abemaciclib in Advanced Breast Cancer

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ABSTRACT

BACKGROUND

Imlunestrant is a next-generation, brain-penetrant, oral selective estrogen-receptor (ER) degrader that delivers continuous ER inhibition, even in cancers with mutations in the gene encoding ERα (*ESR1*).

METHODS

In a phase 3, open-label trial, we enrolled patients with ER-positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer that recurred or progressed during or after aromatase inhibitor therapy, administered alone or with a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor. Patients were assigned in a 1:1:1 ratio to receive imlunestrant, standard endocrine monotherapy, or imlunestrant–abemaciclib. Primary end points were investigator-assessed progression-free survival with imlunestrant as compared with standard therapy among patients with *ESR1* mutations and among all patients and with imlunestrant–abemaciclib as compared with imlunestrant among all patients who had undergone randomization concurrently.

RESULTS

Overall, 874 patients underwent randomization, with 331 assigned to imlunestrant, 330 to standard therapy, and 213 to imlunestrant–abemaciclib. Among 256 patients with *ESR1* mutations, the median progression-free survival was 5.5 months with imlunestrant and 3.8 months with standard therapy. The estimated restricted mean survival time at 19.4 months was 7.9 months (95% confidence interval [CI], 6.8 to 9.1) with imlunestrant and 5.4 months (95% CI, 4.6 to 6.2) with standard therapy (difference, 2.6 months; 95% CI, 1.2 to 3.9; P<0.001). In the overall population, the median progression-free survival was 5.6 months with imlunestrant and 5.5 months with standard therapy (hazard ratio for progression or death, 0.87; 95% CI, 0.72 to 1.04; P=0.12). Among 426 patients in the comparison of imlunestrant–abemaciclib with imlunestrant, the median progression-free survival was 9.4 months and 5.5 months, respectively (hazard ratio, 0.57; 95% CI, 0.44 to 0.73; P<0.001). The incidence of grade 3 or higher adverse events was 17.1% with imlunestrant, 20.7% with standard therapy, and 48.6% with imlunestrant–abemaciclib.

CONCLUSIONS

Among patients with ER-positive, HER2-negative advanced breast cancer, treatment with imlunestrant led to significantly longer progression-free survival than standard therapy among those with *ESR1* mutations but not in the overall population. Imlunestrant–abemaciclib significantly improved progression-free survival as compared with imlunestrant, regardless of *ESR1*-mutation status. (Funded by Eli Lilly; EMBER-3 ClinicalTrials.gov number, NCT04975308.)

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*A list of the members of the EMBER-3 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Estrogen receptor (ER)–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer is the most common subtype of breast cancer and is treated with endocrine therapy.[1] Enhancements to endocrine therapy have incrementally improved outcomes by means of continued ER targeting by different mechanisms. These mechanisms include selective ER modulators and selective ER degraders that directly antagonize ER as well as aromatase inhibitors that block estrogen production and that can subsequently lead to resistance by means of mutation in the gene encoding ERα (*ESR1*).[2,3] New oral selective ER degraders may effectively target these *ESR1* mutations.[4,5]

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have been a critical addition to endocrine therapy and are commonly combined with aromatase inhibitors as first-line therapy for ER-positive, HER2-negative advanced breast cancer.[6] Abemaciclib, a potent CDK4/6 inhibitor that is administered on a continuous schedule, has shown a profound benefit across all therapeutic contexts, including adjuvant therapy and advanced disease management.[6-9] Abemaciclib has also shown a benefit in patients who have disease progression while they are receiving CDK4/6 inhibitor therapy.[10]

Fulvestrant is the only selective ER degrader that has been broadly approved both as monotherapy and as part of combination therapy, in which it is most commonly combined with inhibitors of phosphatidylinositol 3-kinase (PI3K), AKT, and mammalian target of rapamycin (mTOR) or of CDK4/6.[8,11-13] Despite its broad use, fulvestrant has substantial disadvantages. Poor oral bioavailability necessitates intramuscular administration, which limits its dose and thereby its dose-dependent efficacy.[14-16] Furthermore, the injections can be painful and burdensome to patients, mainly requiring in-office administration, and oral options may be preferred.[17,18] The efficacy of fulvestrant is also limited in patients with *ESR1* mutations.[14] Given these limitations, new oral selective ER degraders have been developed with the goal of improving both efficacy and patient experience by means of ease of administration. Critical to these efforts is the identification of selective ER degraders that have a favorable safety profile, which would permit both adjuvant development and use in combination therapy, a necessary approach for advanced disease.

Imlunestrant is a next-generation, brain-penetrant, oral selective ER degrader and pure ER antagonist that delivers continuous ER inhibition, even in *ESR1*-mutated breast cancer.[19,20] In the phase 1 EMBER study, imlunestrant, as monotherapy and in combination with abemaciclib, showed mainly low-grade toxic effects, favorable pharmacokinetics, and encouraging antitumor activity in patients with ER-positive, HER2-negative advanced breast cancer.[21] Here, we present the primary analysis results of the EMBER-3 trial, in which we investigated the efficacy of imlunestrant, as monotherapy and in combination with abemaciclib, in patients with ER-positive, HER2-negative advanced breast cancer whose disease had recurred or progressed during or after treatment with an aromatase inhibitor administered alone or with a CDK4/6 inhibitor.

METHODS

TRIAL DESIGN

In this open-label, phase 3 trial, we initially randomly assigned patients in a 1:1 ratio to receive either oral imlunestrant (at a dose of 400 mg once daily; imlunestrant group) or the investigator's choice of standard endocrine monotherapy (oral exemestane [25 mg once daily] or fulvestrant [500 mg, administered as an intramuscular injection on days 1 and 15 of cycle 1 and on day 1 of subsequent 28-day cycles]; standard-therapy group). The trial was amended early in the enrollment process to a 1:1:1 randomization with the addition of a group that received imlunestrant (400 mg once daily) plus oral abemaciclib (150 mg twice daily) (imlunestrant–abemaciclib group). Premenopausal women, perimenopausal women, and men received a gonadotropin-releasing hormone agonist. Randomization was stratified according to previous CDK4/6 inhibitor treatment (yes vs. no), the presence or absence of visceral metastases, and geographic region (East Asia vs. North America or western Europe vs. other).

PATIENT POPULATION

Women (with any menopausal status) or men 18 years of age or older who had locally confirmed ER-positive, HER2-negative advanced breast cancer were eligible. Patients had to have measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, or nonmeasurable bone-only disease. Patients had

to have disease progression while receiving an aromatase inhibitor (administered alone or with a CDK4/6 inhibitor) as neoadjuvant or adjuvant treatment or within 12 months after adjuvant treatment or while receiving first-line treatment for advanced breast cancer. No other previous therapy for advanced breast cancer was permitted. Patients with visceral crisis, symptomatic or untreated brain metastases, or inflammatory breast cancer were excluded.

END POINTS

The three primary end points were investigator-assessed progression-free survival with imlunestrant as compared with standard therapy among patients with *ESR1* mutations; with imlunestrant as compared with standard therapy among all patients; and with imlunestrant–abemaciclib as compared with imlunestrant among all patients who had undergone randomization concurrently. The end point of progression-free survival with imlunestrant as compared with standard therapy among patients with *ESR1* mutations was changed from a secondary end point to a primary end point by means of a protocol amendment in August 2022.

Overall survival for the three between-group comparisons listed above were key secondary end points. Other secondary end points included progression-free survival as assessed by means of blinded independent central review, overall response, and safety. Details of post hoc analyses are provided in the Supplementary Appendix.

ASSESSMENTS

Tumor assessments (according to RECIST, version 1.1) with the use of computed tomography or magnetic resonance imaging were performed at baseline (within 28 days before randomization), every 8 weeks for the first 12 months, and then every 12 weeks until the occurrence of progression. Data on adverse events (assessed according to the Common Terminology Criteria for Adverse Events, version 5.0, of the National Cancer Institute) were collected until 30 days after the last dose of trial drug.

ESR1-mutation status was centrally determined in blood samples that had been obtained before treatment administration. Patients who had at least one *ESR1* mutation classified as "oncogenic" or "likely oncogenic"[22] were included in the subgroup of patients with *ESR1* mutations (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

TRIAL OVERSIGHT

The trial protocol, which is available at NEJM.org, was approved by the ethics review board at each site. The trial was conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, and applicable laws and regulations. All the participants provided written informed consent.

The trial was designed by the sponsor (Eli Lilly) in collaboration with the protocol steering committee. The investigators gathered the data. The sponsor monitored the conduct of the trial, received the data, and performed all the analyses. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

The first draft of the manuscript was written by the authors employed by the sponsor, with assistance from a sponsor-funded medical writer. Subsequently, all the authors reviewed the manuscript. The investigators and protocol steering committee worked under confidentiality agreements with the sponsor.

STATISTICAL ANALYSIS

To adjust for multiplicity and control the overall type I error at 0.025 (one-sided), the alpha level for significance was initially split between the progression-free survival comparison of imlunestrant with standard therapy among patients with *ESR1* mutations (0.02) and among all patients (0.005) (Fig. S2). Progression-free survival with imlunestrant–abemaciclib as compared with imlunestrant was to be inferentially tested only if either of the first two primary end points was significant according to the graphical testing procedure.[23] Overall survival for each between-group comparison was to be tested only if the corresponding end point for progression-free survival was significant. Full details of the graphical testing procedure are provided in the protocol and Supplementary Appendix.

The final analysis of progression-free survival comparing imlunestrant with standard therapy in patients with *ESR1* mutations was planned to occur once 192 events (progression or death) had taken place. We calculated that this analysis would

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Imlunestrant		Standard Therapy		Imlunestrant–Abemaciclib
	Patients with *ESR1* Mutations (N=138)	All Patients (N=331)	Patients with *ESR1* Mutations (N=118)	All Patients (N=330)	All Patients (N=213)
Median age (range) — yr	61 (28–85)	61 (28–87)	60 (33–85)	62 (27–89)	62 (36–87)
Female sex — no. (%)	138 (100)	327 (98.8)	118 (100)	329 (99.7)	211 (99.1)
Postmenopausal status — no. (%)	122 (88.4)	278 (84)	105 (89.0)	284 (86.1)	184 (86.4)
Race — no. (%)†					
White	80 (58.0)	186 (56.2)	76 (64.4)	191 (57.9)	111 (52.1)
Asian	35 (25.4)	92 (27.8)	31 (26.3)	96 (29.1)	72 (33.8)
Black	7 (5.1)	11 (3.3)	3 (2.5)	7 (2.1)	8 (3.8)
Other	8 (5.8)	25 (7.6)	4 (3.4)	23 (7.0)	6 (2.8)
Missing data	8 (5.8)	17 (5.1)	4 (3.4)	13 (3.9)	16 (7.5)
Geographic region — no. (%)‡					
East Asia	30 (21.7)	83 (25.1)	26 (22.0)	84 (25.5)	66 (31.0)
North America or western Europe	63 (45.7)	127 (38.4)	54 (45.8)	127 (38.5)	95 (44.6)
Other	45 (32.6)	121 (36.6)	38 (32.2)	119 (36.1)	52 (24.4)
ECOG performance-status score — no. (%)§					
0	85 (61.6)	219 (66.2)	77 (65.3)	208 (63.0)	142 (66.7)
1	53 (38.4)	112 (33.8)	41 (34.7)	122 (37.0)	71 (33.3)
Progesterone receptor–positive disease — no. (%)	109 (79.0)	257 (77.6)	97 (82.2)	260 (78.8)	158 (74.2)
ESR1 mutation — no. (%)¶	138 (100)	138 (41.7)	118 (100)	118 (35.8)	67 (31.5)
PI3K pathway mutation — no. (%)‖	72 (52.2)	129 (39.0)	57 (48.3)	128 (38.8)	88 (41.3)
Measurable disease at baseline — no. (%)	112 (81.2)	262 (79.2)	91 (77.1)	251 (76.1)	167 (78.4)
Site of metastases — no. (%)					
Viscera	84 (60.9)	189 (57.1)	67 (56.8)	177 (53.6)	119 (55.9)
Liver	57 (41.3)	107 (32.3)	47 (39.8)	98 (29.7)	57 (26.8)
Bone only	27 (19.6)	72 (21.8)	30 (25.4)	86 (26.1)	51 (23.9)
Endocrine resistance — no. (%)**					
Primary	0	25 (7.6)	0	36 (10.9)	16 (7.5)
Secondary	138 (100)	305 (92.1)	118 (100)	293 (88.8)	197 (92.5)
Context of most recent endocrine therapy — no. (%)					
As neoadjuvant or adjuvant therapy	29 (21.0)	106 (32.0)	23 (19.5)	113 (34.2)	63 (29.6)
For advanced breast cancer	101 (73.2)	208 (62.8)	91 (77.1)	208 (63.0)	145 (68.1)
Previous CDK4/6 inhibitor — no. (%)					
Overall	93 (67.4)	195 (58.9)	85 (72.0)	189 (57.3)	139 (65.3)
As adjuvant therapy	3 (2.2)	14 (4.2)	3 (2.5)	15 (4.5)	7 (3.3)
For advanced breast cancer	90 (65.2)	181 (54.7)	82 (69.5)	174 (52.7)	132 (62.0)

Table 1. (Continued.)

Characteristic	Imlunestrant		Standard Therapy		Imlunestrant–Abemaciclib
	Patients with *ESR1* Mutations (N=138)	All Patients (N=331)	Patients with *ESR1* Mutations (N=118)	All Patients (N=330)	All Patients (N=213)
Previous CDK4/6 inhibitor therapy — no./total no. (%)					
Palbociclib	64/93 (68.8)	118/195 (60.5)	61/85 (71.8)	130/189 (68.8)	90/139 (64.7)
Ribociclib	22/93 (23.7)	56/195 (28.7)	22/85 (25.9)	50/189 (26.5)	37/139 (26.6)
Abemaciclib	7/93 (7.5)	19/195 (9.7)	2/85 (2.4)	7/189 (3.7)	10/139 (7.2)

* Patients in the standard-therapy group received standard endocrine therapy (exemestane or fulvestrant). Percentages may not total 100 because of rounding. CDK4/6 denotes cyclin-dependent kinase 4 and 6.
† Race was reported by the patients. Data were missing for patients who did not disclose their race.
‡ East Asia included China, Japan, South Korea, and Taiwan. North America and western Europe included Austria, Belgium, the Czech Republic, France, Germany, Greece, Italy, the Netherlands, Spain, and the United States. Other included Argentina, Australia, Brazil, India, Mexico, Russia, Turkey, and Ukraine.
§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
¶ *ESR1* mutation status was centrally assessed with the use of pretreatment circulating tumor DNA (ctDNA). Samples were analyzed by means of Guardant360 CDx (Guardant Health), except in patients from China, for whom the pretreatment samples were analyzed by the OncoCompass Target assay (Burning Rock Biotech).
‖ Phosphatidylinositol 3-kinase (PI3K) pathway mutations included single nucleotide variants and insertions or deletions in the genes *PIK3CA*, *AKT1*, or *PTEN* as analyzed by Guardant360 ctDNA assay. This analysis excluded 40 patients from China and 18 patients with unknown *ESR1*-mutation status.
** Endocrine resistance was assessed according to the European School of Oncology–European Society for Medical Oncology International Consensus Guidelines for advanced breast cancer (ABC guidelines 6 and 7). Data were missing for one patient in the standard-therapy group that included all patients.

have 97% power, assuming a hazard ratio of 0.57 at the significance level of 0.02. The analysis of progression-free survival comparing imlunestrant with standard therapy in all patients was planned to occur once approximately 480 events had taken place. We calculated that this analysis would have 91% power, assuming a hazard ratio of 0.74 at the full significance level after recycling. The final analysis of progression-free survival comparing imlunestrant–abemaciclib with imlunestrant in all patients who had undergone randomization concurrently was planned to occur once 248 events had taken place. We calculated that this analysis would have 80% power, assuming a hazard ratio of 0.7 at the significance level of 0.025.

Progression-free survival and overall survival were estimated with the use of the Kaplan–Meier method and tested with a stratified log-rank test, with stratification according to the randomization factors (although geographic region was excluded from the analysis involving patients with *ESR1* mutations). Hazard ratios and 95% confidence intervals were estimated with the use of the stratified Cox regression model. The proportional-hazards assumption was assessed with the use of the Schoenfeld residual test.[24] If the curves were not parallel and the proportional-hazards assumption was violated, an analysis of restricted mean survival time (the area under the survival curve up to the specific time point) was conducted.[25,26] Subgroup analyses of progression-free survival and overall survival for all three two-group comparisons were conducted according to prespecified factors, including status with regard to *ESR1* mutation (present or absent), and clinically relevant nonprespecified factors. All reported P values are two-sided.

RESULTS

PATIENTS

From October 2021 through November 2023, a total of 874 patients underwent randomization at 195 sites across 22 countries. A total of 331 patients were assigned to the imlunestrant group,

330 to the standard-therapy group, and 213 to the imlunestrant–abemaciclib group. Most patients in the standard-therapy group (292 of 330) received fulvestrant (Fig. S3).

Overall, the characteristics of the patients at baseline were generally balanced among the treatment groups (Table 1). Among all the patients, the median age was 61 years (range, 27 to 89), 55.5% had visceral metastases, and 59.8% had previously received a CDK4/6 inhibitor. A total of 256 patients (38.7%) across the imlunestrant group (138 patients) and standard-therapy group (118 patients) had *ESR1* mutations; the baseline characteristics of these patients were broadly similar to those in the overall population, except for marginally higher percentages of patients with PI3K pathway mutations (50.4%), liver metastases (40.6%), and previous CDK4/6 inhibitor treatment (69.5%). The patient population in this trial was representative of the population of patients with ER-positive, HER2-negative advanced breast cancer who have previously received endocrine therapy with an aromatase inhibitor with or without a CDK4/6 inhibitor (Table S8).

TREATMENT

At the primary analysis (data-cutoff date, June 24, 2024), a total of 183 patients were continuing to receive treatment, including 65 of 331 patients (19.6%) in the imlunestrant group, 43 of 330 (13.0%) in the standard-therapy group, and 75 of 213 (35.2%) in the imlunestrant–abemaciclib group. The median duration of treatment was 5.6 months with imlunestrant, 4.8 months with standard therapy, and 7.7 months with imlunestrant–abemaciclib. The main reason for treatment discontinuation was disease progression (in 239 patients [72.2%] in the imlunestrant group, in 258 [78.2%] in the standard-therapy group, and in 113 [53.1%] in the imlunestrant–abemaciclib group).

EFFICACY

Imlunestrant vs. Standard Therapy

The primary analysis occurred after 211 events (progression or death) were observed among patients with *ESR1* mutations (109 in the imlunestrant group and 102 in the standard-therapy group) and 490 events were observed among all the patients (237 in the imlunestrant group and 253 in the standard-therapy group). Among patients with *ESR1* mutations, the median progression-free survival was 5.5 months (95% confidence interval [CI], 3.9 to 7.4) in the imlunestrant group, as compared with 3.8 months (95% CI, 3.7 to 5.5) in the standard-therapy group (Fig. 1A and Fig. S4). Owing to evidence of nonproportional hazards, which make interpretation of the hazard ratio problematic, a restricted mean survival time analysis was conducted. The estimated restricted mean survival time at 19.4 months was 7.9 months (95% CI, 6.8 to 9.1) in the imlunestrant group as compared with 5.4 months (95% CI, 4.6 to 6.2) in the standard-therapy group (difference, 2.6 months; 95% CI, 1.2 to 3.9; P<0.001) (Fig. 1A). Among all 661 patients in the overall between-group comparison, the median progression-free survival was 5.6 months (95% CI, 5.3 to 7.3) in the imlunestrant group and 5.5 months (95% CI, 4.6 to 5.6) in the standard-therapy group (hazard ratio for progression or death, 0.87; 95% CI, 0.72 to 1.04; P=0.12) (Fig. 1B).

Progression-free survival analyses across all subgroups in patients with *ESR1* mutations are shown in Figure S5. The results of the secondary analyses of progression-free survival according to blinded independent central review and overall response were consistent with those of the primary analysis in patients with *ESR1* mutations (Fig. S6 and Table S1).

In exploratory analyses involving patients without *ESR1* mutations, the median progression-free survival was 5.6 months in the imlunestrant group and 5.7 months in the standard-therapy group (hazard ratio for progression or death, 1.00; 95% CI, 0.79 to 1.27) (Fig. S7). In post hoc analyses, the 12-month cumulative incidence of central nervous system (CNS) progression was 1.5% with imlunestrant and 6.7% with standard therapy among patients with *ESR1* mutations (cause-specific hazard ratio, 0.18; 95% CI, 0.04 to 0.90). Among all patients, the incidence of CNS progression was 1.6% with imlunestrant and 3.0% with standard therapy (cause-specific hazard ratio, 0.47; 95% CI, 0.16 to 1.38) (Fig. S8).

As of the interim overall survival analysis, 31.2% of the patients with *ESR1* mutations had died, as had 23.0% of all patients (Fig. 2A and 2B). The estimated overall survival at 18 months was 77.0% (95% CI, 67.4 to 84.1) in the imlunestrant group and 58.6% (95% CI, 47.2 to 68.3) in the standard-therapy group among patients with *ESR1* mutations (hazard ratio for death, 0.55; 95% CI, 0.35 to 0.86; P=0.008 [not significant; P-value

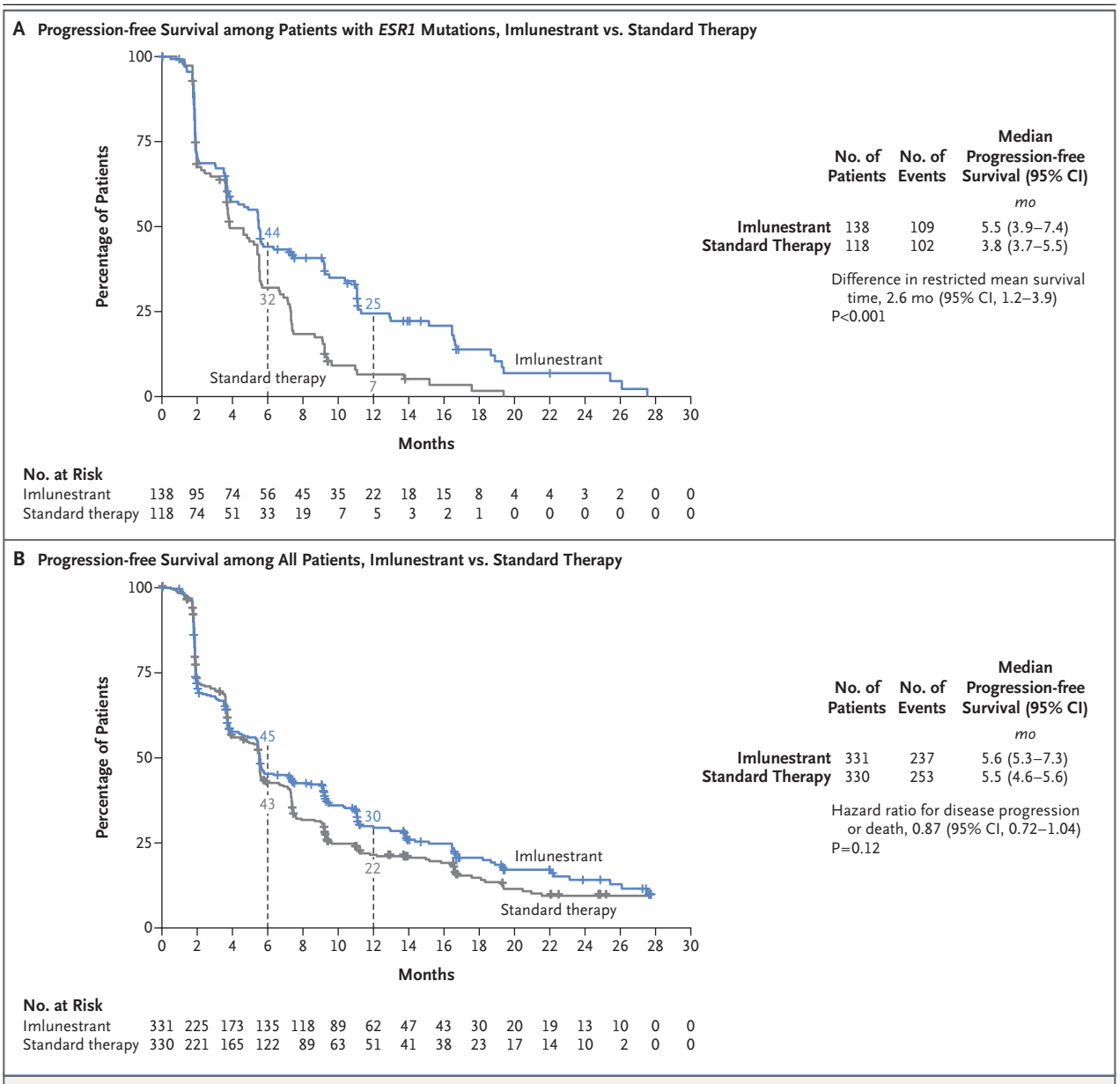


Figure 1. Investigator-Assessed Progression-free Survival with Imlunestrant as Compared with Standard Therapy.

Panel A shows Kaplan–Meier estimates of progression-free survival among patients with *ESR1* mutations. The median follow-up was 16.7 months in the imlunestrant group and 13.8 months in the group that received standard endocrine therapy. Panel B shows Kaplan–Meier estimates of progression-free survival in the overall patient population. The median follow-up was 16.6 months in the imlunestrant group and 16.8 months in the standard-therapy group. In both panels, tick marks indicate censored data.

threshold, 2.2×10^{-10}]) and 78.6% (95% CI, 72.6 to 83.5) in the imlunestrant group and 71.8% (95% CI, 65.4 to 77.2) in the standard-therapy group among all patients (hazard ratio, 0.69; 95% CI, 0.50 to 0.96 [not inferentially tested]) (Fig. 2B). Overall survival among patients without *ESR1* mutations is shown in Figure S9.

Imlunestrant–Abemaciclib vs. Imlunestrant

The primary analysis was conducted after 263 events (progression or death) had occurred (114 in the imlunestrant–abemaciclib group and 149 in the imlunestrant group) among all 426 patients in this between-group comparison who had undergone randomization concurrently (213 patients in

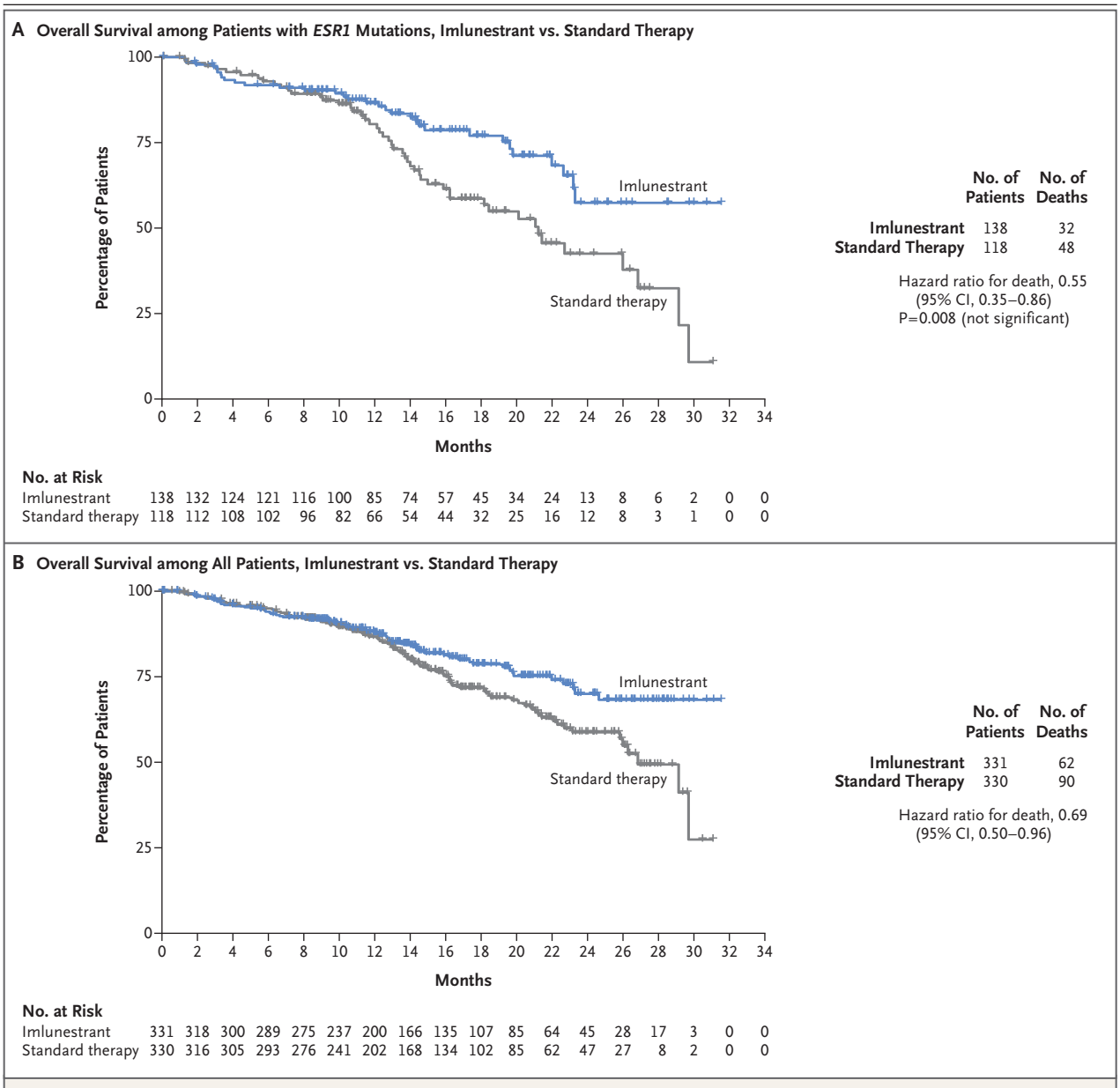


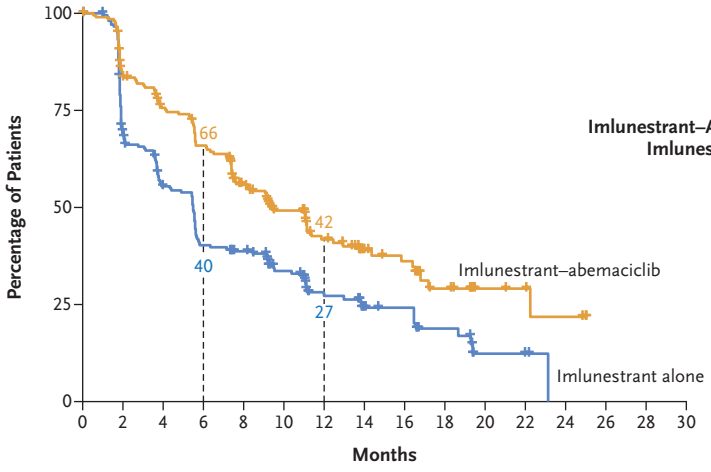
Figure 2. Overall Survival with Imlunestrant as Compared with Standard Therapy.

Shown are Kaplan–Meier estimates of overall survival among patients with *ESR1* mutations (Panel A) and among all patients (Panel B). Statistical significance was not met in the analysis involving patients with *ESR1* mutations (P-value threshold, 2.2×10^{-10}) and was not inferentially tested in the analysis involving all patients. In both panels, tick marks indicate censored data.

each group). The median progression-free survival was 9.4 months (95% CI, 7.5 to 11.9) in the imlunestrant–abemaciclib group, as compared with 5.5 months (95% CI, 3.8 to 5.6) in the imlunestrant group (hazard ratio for progression or death, 0.57; 95% CI, 0.44 to 0.73; P<0.001) (Fig. 3A).

Results in analyses comparing imlunestrant–abemaciclib with imlunestrant were similar across most patient subgroups, regardless of *ESR1*-mutation status or PI3K pathway–mutation status and also in patients who had received CDK4/6 inhibitor treatment previously (Fig. 3B and Figs. S10, S11, and S12). The data regarding overall survival were immature, with 15.0% of the patients having died (hazard ratio for death, 1.34; 95% CI, 0.81 to 2.21; P=0.25) (Fig. S16). Results of the

A Progression-free Survival among All Patients, Imlunestrant–Abemaciclib vs. Imlunestrant Alone

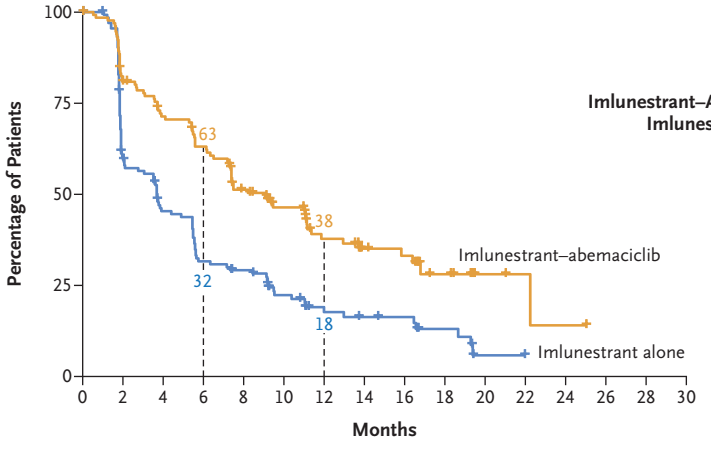


	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant–Abemaciclib	213	114	9.4 (7.5–11.9)
Imlunestrant Alone	213	149	5.5 (3.8–5.6)

Hazard ratio for disease progression or death, 0.57 (95% CI, 0.44–0.73)
P<0.001

No. at Risk																
Imlunestrant–abemaciclib	213	165	141	122	96	72	48	29	25	13	6	5	3	0	0	0
Imlunestrant alone	213	140	106	77	67	48	29	20	18	10	3	2	0	0	0	0

B Progression-free Survival among Patients with Previous CDK4/6 Inhibitor Treatment, Imlunestrant–Abemaciclib vs. Imlunestrant Alone



	No. of Patients	No. of Events	Median Progression-free Survival (95% CI)
			mo
Imlunestrant–Abemaciclib	139	79	9.1 (7.2–11.2)
Imlunestrant Alone	140	109	3.7 (2.1–5.5)

Hazard ratio for disease progression or death, 0.51 (95% CI, 0.38–0.68)

No. at Risk																
Imlunestrant–abemaciclib	139	105	87	76	58	43	29	19	17	8	3	2	1	0	0	0
Imlunestrant alone	140	79	56	39	32	21	13	11	10	6	1	0	0	0	0	0

Figure 3. Investigator-Assessed Progression-free Survival with Imlunestrant–Abemaciclib as Compared with Imlunestrant Alone.

Panel A shows Kaplan–Meier estimates of progression-free survival among all 426 patients in the imlunestrant–abemaciclib and imlunestrant groups who had undergone randomization concurrently. The median follow-up was 13.5 months in the imlunestrant–abemaciclib group and 13.7 months in the imlunestrant group. Panel B shows Kaplan–Meier estimates of progression-free survival among patients who had received cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor treatment previously. The confidence interval shown for the hazard ratio in Panel B was not adjusted for multiplicity and should not be used for inference. In both panels, tick marks indicate censored data.

secondary analyses of progression-free survival according to blinded independent central review and overall response were consistent with those of the primary analysis (Fig. S13 and Table S2).

Results regarding prespecified exploratory end points were generally consistent with those of the primary analyses. In the analysis of imlunestrant–abemaciclib as compared with standard therapy,

Table 2. Adverse Events According to Grade (Safety Population).*

Event	Imlunestrant (N=327)		Standard Therapy (N=324)		Imlunestrant–Abemaciclib (N=208)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)					
Any adverse event	270 (82.6)	56 (17.1)	273 (84.3)	67 (20.7)	204 (98.1)	101 (48.6)
Fatigue†	74 (22.6)	1 (0.3)	43 (13.3)	2 (0.6)	80 (38.5)	10 (4.8)
Diarrhea	70 (21.4)	1 (0.3)	38 (11.7)	0	179 (86.1)	17 (8.2)
Nausea	56 (17.1)	1 (0.3)	42 (13.0)	0	101 (48.6)	4 (1.9)
Arthralgia	46 (14.1)	2 (0.6)	46 (14.2)	1 (0.3)	19 (9.1)	1 (0.5)
Aspartate aminotransferase increase	41 (12.5)	3 (0.9)	41 (12.7)	3 (0.9)	34 (16.3)	5 (2.4)
Back pain	35 (10.7)	2 (0.6)	23 (7.1)	1 (0.3)	10 (4.8)	1 (0.5)
Alanine aminotransferase increase	34 (10.4)	1 (0.3)	33 (10.2)	2 (0.6)	28 (13.5)	10 (4.8)
Anemia†	33 (10.1)	7 (2.1)	41 (12.7)	9 (2.8)	91 (43.8)	16 (7.7)
Abdominal pain†	29 (8.9)	1 (0.3)	18 (5.6)	2 (0.6)	41 (19.7)	4 (1.9)
Vomiting	29 (8.9)	2 (0.6)	16 (4.9)	1 (0.3)	65 (31.2)	1 (0.5)
Decreased appetite	26 (8.0)	1 (0.3)	12 (3.7)	1 (0.3)	41 (19.7)	2 (1.0)
Thrombocytopenia†	18 (5.5)	3 (0.9)	16 (4.9)	4 (1.2)	38 (18.3)	3 (1.4)
Neutropenia†	17 (5.2)	7 (2.1)	15 (4.6)	6 (1.9)	100 (48.1)	41 (19.7)
Leukopenia†	17 (5.2)	2 (0.6)	15 (4.6)	0	54 (26.0)	9 (4.3)
Rash†	9 (2.8)	0	12 (3.7)	0	21 (10.1)	3 (1.4)
Hypercreatinemia†	9 (2.8)	1 (0.3)	7 (2.2)	0	45 (21.6)	2 (1.0)

* The safety population included all the patients who received at least one dose of imlunestrant, fulvestrant, or exemestane or one dose each of imlunestrant and abemaciclib in the imlunestrant–abemaciclib group. The listed events were reported in at least 10% of the patients in any treatment group and are ordered according to the incidence in the imlunestrant group.
† This event was reported as a consolidated term. A detailed list of consolidated terms is provided in the Supplementary Appendix.

the hazard ratio for progression or death was 0.46 (95% CI, 0.36 to 0.60) (Fig. S14). In the analysis of overall survival with imlunestrant–abemaciclib as compared with standard therapy, the hazard ratio for death was 0.90 (95% CI, 0.57 to 1.42) (Fig. S15).

SAFETY

The safety population included 859 patients who initiated treatment. A total of 327 patients in the imlunestrant group, 324 in the standard-therapy group, and 208 in the imlunestrant–abemaciclib group were in the safety population.

Imlunestrant

The most frequently reported adverse events of any grade in the imlunestrant group, as compared with the standard-therapy group, were fatigue (in 22.6% vs. 13.3% of the patients), diarrhea (in 21.4% vs. 11.7%), and nausea (in 17.1% vs. 13.0%), with the majority of these events being of grade 1. Adverse events of grade 3 or higher occurred in 17.1% of the patients who received imlunestrant and in 20.7% of those who received standard therapy — predominantly, anemia (in 2.1% vs. 2.8% of the patients) and neutropenia (in 2.1% vs. 1.9%) (Table 2 and Table S3). The incidence of bradycardia (in 2.1% of the patients in the imlunestrant group and in no patients in the standard-therapy group), dyslipidemia as a grouped term (in 7.3% vs. 8.6%), photopsia (in no patients in either group), and increased levels of triglycerides and cholesterol (as relevant laboratory variables) is shown in Table S4.

Serious adverse events were reported in 10.4% of the patients who received imlunestrant and in 11.4% of those who received standard therapy (Table S5). In each of these two treatment groups, six patients died owing to adverse events, including one death (from right ventricular failure) in

the imlunestrant group that was considered by the investigator to be related to treatment.

Among patients who received imlunestrant, adverse events led to dose interruptions in 10.4% (vs. in 0.6% of those who received standard therapy). Dose reductions occurred in 2.4% of the patients who received imlunestrant and in none of the patients who received standard therapy, and permanent discontinuation occurred in 4.3% and 1.2%, respectively (Table S6).

Imlunestrant–Abemaciclib

The incidence of adverse events was higher in the imlunestrant–abemaciclib group than in the imlunestrant group. The most frequently reported adverse events of any grade were diarrhea (in 86.1% of the patients), nausea (in 48.6%), neutropenia (in 48.1%), and anemia (in 43.8%). Adverse events of grade 3 or higher occurred in 48.6% of the patients — predominantly, neutropenia (in 19.7%), diarrhea (in 8.2%), and anemia (in 7.7%) (Table 2 and Table S7).

Serious adverse events were reported in 16.8% of the patients; three patients had a fatal outcome, with one death (from an unknown cause) being considered by the investigator to be related to treatment. Adverse events led to dose interruptions of imlunestrant, abemaciclib, or both in 55.3% of the patients, dose reductions in 39.4%, and permanent discontinuation in 6.3%.

DISCUSSION

Disease progression after treatment with an aromatase inhibitor, with or without a CDK4/6 inhibitor, remains a formidable challenge in the treatment of ER-positive, HER2-negative advanced breast cancer owing to complex molecular alterations and other drivers of endocrine-therapy resistance. We describe the primary progression-free survival results from the phase 3 EMBER-3 trial of imlunestrant as compared with standard therapy and of imlunestrant–abemaciclib as compared with imlunestrant in patients with ER-positive, HER2-negative advanced breast cancer that had progressed during or after aromatase inhibitor therapy with or without a CDK4/6 inhibitor.

Imlunestrant therapy significantly improved progression-free survival over standard therapy among patients with *ESR1* mutations (between-group difference in restricted mean survival time, 2.6 months; 95% CI, 1.2 to 6.9; P<0.001) but did not reach significance in the overall population (hazard ratio for progression or death, 0.87; 95% CI, 0.72 to 1.04). Imlunestrant–abemaciclib therapy significantly improved progression-free survival over imlunestrant among all patients (hazard ratio, 0.57; 95% CI, 0.44 to 0.73; P<0.001), with a similar treatment effect observed regardless of *ESR1*-mutation status. The safety profile of imlunestrant was similar to that of standard therapy, and the safety profile of imlunestrant–abemaciclib was consistent with the known profile of fulvestrant–abemaciclib.[8,12]

In a finding in line with those of other trials of new selective ER degraders, the benefit of imlunestrant over standard therapy was more pronounced in patients with *ESR1* mutations than in those without *ESR1* mutations.[4,27,28] In a result consistent with preclinical data showing the CNS penetrance and CNS activity of imlunestrant,[19] the percentage of patients with CNS progression was somewhat lower with imlunestrant than with standard therapy among all patients, although small numbers of patients and a lack of mandated serial CNS imaging in all the patients limit interpretation. In the overall population, progression-free survival was not significantly prolonged with imlunestrant. Although we acknowledge differences in the enrolled populations and trial designs, these results closely mirror those reported in the EMERALD trial with elacestrant, a new selective ER degrader with dose-dependent mixed ER agonist–antagonist activity.[4,29,30]

Although new oral selective ER degraders as monotherapy appear to be particularly efficacious in patients with *ESR1* mutations, data from our trial show that their treatment benefit when used in combination with CDK4/6 inhibitors may be more broadly based than when used as monotherapy.[31] Treatment with imlunestrant–abemaciclib led to a significant improvement over imlunestrant alone in the median progression-free survival among all patients (9.4 vs. 5.5 months), which is a substantial advantage in progression-free survival given recent studies in the context of this disease.[4,10,13,32]

The EMBER-3 trial lacked a direct comparison of imlunestrant–abemaciclib with fulvestrant–abemaciclib, and unlike the EMERALD and postMONARCH trials,[4,10] our trial did not require previous treatment with a CDK4/6 inhibitor. However, most patients (65%) in the imlunestrant–abemaciclib group in our trial had received a

CDK4/6 inhibitor previously, and the treatment effect of imlunestrant–abemaciclib (hazard ratio for progression or death, 0.51) in these patients was consistent with that in the overall population, and the median progression-free survival was 9.1 months. In addition, the treatment effect of imlunestrant–abemaciclib was similar in patients with or without *ESR1* or PI3K pathway mutations. The consistency of these results across clinically relevant subgroups is reassuring given that most patients who are eligible for second-line therapy have received a CDK4/6 inhibitor previously and that many available second-line therapies require biomarker selection.[11,33,34] In the context of combination therapy that can effectively target and overcome other (non-*ESR1*) mechanisms of resistance, it is possible that an oral selective ER degrader combined with CDK4/6 inhibition more completely inhibits the ER signaling cascade, which would drive efficacy in populations of patients with *ESR1* mutations and in those without such mutations and would possibly have more synergy than fulvestrant in this context.

Imlunestrant therapy showed favorable safety, with generally low-grade adverse events — mainly fatigue, diarrhea, and nausea, each at relatively low incidences — and low percentages of patients with dose reduction and discontinuation. Preliminary analysis suggests that imlunestrant therapy involves lower risks of bradycardia, dyslipidemia, and photopsia than other new selective ER degraders.[33-35] In the currently ongoing trials of new selective ER degraders as adjuvant therapy, data regarding the long-term safety profiles of and adherence to these therapies will be important.[36-39] Imlunestrant–abemaciclib had a predictable safety profile, which was similar to that seen in previous studies of fulvestrant–abemaciclib.[8,12] The incidence of discontinuation of imlunestrant–abemaciclib (6.3%) also compares favorably with that of available combination regimens, including fulvestrant–alpelisib (26%), fulvestrant–capivasertib (13%), and exemestane–everolimus (19%), each of which had arguably less-predictable and less-manageable toxic effects, such as hyperglycemia, rash, and stomatitis, than imlunestrant–abemaciclib.[11,13,40]

This phase 3 trial involving patients with ER-positive, HER2-negative advanced breast cancer that had progressed during or after aromatase inhibitor therapy with or without a CDK4/6 inhibitor showed significant prolongation of progression-free survival with imlunestrant over standard therapy among patients with *ESR1* mutations, as well as with imlunestrant–abemaciclib over imlunestrant in all patients. Imlunestrant showed mainly low-grade toxic effects as monotherapy and in combination with abemaciclib. Imlunestrant, as monotherapy or in combination with abemaciclib, provides an oral targeted-therapy option after progression during endocrine therapy in patients with ER-positive, HER2-negative advanced breast cancer.

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APPENDIX

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