Abemaciclib Plus Fulvestrant in Advanced Breast Cancer After Progression on CDK4/6 Inhibition: Results From the Phase III postMONARCH Trial

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ABSTRACT

PURPOSE Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) combined with endocrine therapy (ET) are the standard first-line treatment for hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC); however, disease progression occurs in almost all patients and additional treatment options are needed. Herein, we report outcomes of the postMONARCH trial investigating a switch in ET with/without CDK4/6 inhibition with abemaciclib after disease progression on CDK4/6i.

METHODS This double-blind, randomized phase III study enrolled patients with disease progression on previous CDK4/6i plus aromatase inhibitor as initial therapy for advanced disease or recurrence on/after adjuvant CDK4/6i + ET. Patients were randomly assigned (1:1) to abemaciclib + fulvestrant or placebo + fulvestrant. The primary end point was investigator-assessed progression-free survival (PFS). Secondary end points included PFS by blinded independent central review, objective response rate (ORR), and safety.

RESULTS This study randomly assigned 368 patients (abemaciclib + fulvestrant, n = 182 placebo + fulvestrant, n = 186). At the primary analysis (258 events), the hazard ratio (HR) was 0.73 (95% CI, 0.57 to 0.95; nominal $P = .017$), with median PFS 6.0 (95% CI, 5.6 to 8.6) versus 5.3 (95% CI, 3.7 to 5.6) months and 6-month PFS rates of 50% and 37% in the abemaciclib + fulvestrant and placebo + fulvestrant arms, respectively. These results were supported by BICR-assessed PFS (HR, 0.55 [95% CI, 0.39 to 0.77]; nominal $P < .001$). A consistent treatment effect was seen across major clinical and genomic subgroups, including with/without *ESR1* or *PIK3CA* mutations. Among patients with measurable disease, investigator-assessed ORR was improved with abemaciclib + fulvestrant versus placebo + fulvestrant (17% *v* 7%; nominal $P = .015$). No new safety signals were observed, with findings consistent with the known safety profile of abemaciclib.

CONCLUSION Abemaciclib + fulvestrant significantly improved PFS after disease progression on previous CDK4/6i + ET in patients with HR+, HER2– ABC, offering an additional targeted therapy option for these patients.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

The addition of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) to endocrine therapy (ET) has transformed the treatment paradigm for patients with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) breast cancer.[1] Abemaciclib is an oral, potent CDK4/6i with greater selectivity for CDK4 than CDK6, which allows continuous dosing because of less myelosuppression.[2] Abemaciclib plus ET reduces the risk of recurrence for patients with high-risk early breast cancer and improves progression-free survival (PFS) and overall survival (OS) for patients with advanced breast cancer (ABC).[3-8]

The optimal treatment after disease progression on a CDK4/6i-containing regimen remains uncertain. Treatment decisions

CONTEXT

Key Objective

To compare the efficacy of abemaciclib plus fulvestrant versus placebo plus fulvestrant for hormone receptor–positive, human epidermal growth factor receptor 2– advanced breast cancer (ABC) after disease progression on previous CDK4/6i treatment.

Knowledge Generated

Abemaciclib combined with fulvestrant demonstrated efficacy for patients with ABC with progression-free survival (PFS) hazard ratio = 0.73 (95% CI, 0.57 to 0.95; nominal $P = .017$) and median PFS of 6.0 (95% CI, 5.6 to 8.6) versus 5.3 (95% CI, 3.7 to 5.6) months. The safety profile was consistent with that of abemaciclib; no new safety signals were observed.

Relevance *(K.D. Miller)*

While the study reached statistical significance, a <1-month improvement is not clinically significant. With the availability of mTOR, PI3CA, and AKT inhibitors, clinical trials need to consider current practice patterns so results can truly inform practice.*

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

are often influenced by tumor genomic profile, toxicity profiles of available therapies, comorbid conditions, disease characteristics, and patient preferences, and are complicated by lack of head-to-head comparisons. Guidelines recommend switching ET and/or adding a targeted therapy.[1] There remains a significant need for effective and tolerable treatments available to a broad population after disease progression on CDK4/6i, as metastatic breast cancer remains a fatal disease.

If ET resistance drives progression but the disease maintains CDK4/6 pathway dependence, a switch in ET with continued CDK4/6 inhibition could potentially provide benefit.[9,10] Results from phase II studies of CDK4/6i after disease progression on a previous CDK4/6i are mixed; the MAINTAIN trial demonstrated improved PFS when switching ET and the majority of patients switching CDK4/6i (palbociclib to ribociclib), while the PACE and PALMIRA trials showed no improvement with continuation of palbociclib.[11–13]

Herein, we report results from postMONARCH, a phase III trial evaluating CDK4/6 inhibition with abemaciclib with a switch in ET after progression on previous CDK4/6i in patients with HR+, HER2– ABC.

METHODS

Trial Design and Patients

postMONARCH (ClinicalTrials.gov identifier: NCT05169567) was a phase III, global, randomized, double-blind, placebo-controlled study that enrolled 368 patients at 96 centers in 16 countries. Additional details are available in the Protocol (online only).

Patients with locally confirmed HR+, HER2– ABC and radiologic disease progression on a CDK4/6i plus aromatase inhibitor (AI) as initial treatment for advanced disease or recurrence on/after adjuvant CDK4/6i plus ET were eligible. There was no restriction on interval duration after adjuvant CDK4/6i treatment. Adequate organ function, Eastern Cooperative Oncology Group performance status of 0 or 1, and measurable or evaluable disease per RECIST version 1.1 were required.

Intervening systemic therapy between disease recurrence or progression on CDK4/6i and enrollment was not allowed. Previous CDK4/6i treatment in more than one setting, chemotherapy for metastatic disease, previous selective estrogen receptor degraders (SERDs) such as fulvestrant, previous PI3K, mTOR, or AKT inhibitors, visceral crisis, and symptomatic or untreated CNS metastasis were not allowed.

Randomization (1:1) between abemaciclib + fulvestrant or placebo + fulvestrant was stratified according to geography, presence or absence of visceral metastasis (including lung, liver, brain, pleural, or peritoneal involvement), and duration of previous CDK4/6i therapy (greater/less than 12 months in the metastatic setting or recurrence during/after treatment in the adjuvant setting). The sponsor, patients, and investigators were blinded to treatment assignment.

Trial Procedures

Patients received 150 mg abemaciclib or matched placebo twice daily and 500 mg fulvestrant by intramuscular injection once per day on days 1 and 15 of cycle 1, then once every 4 weeks. Men and premenopausal women received a gonadotropin-releasing hormone analog. Dose interruptions/reductions were allowed per protocol. Treatment continued

until disease progression, death, or discontinuation for other reasons.

Tumors were assessed at baseline, every 8 weeks for 12 months, and then every 12 weeks until disease progression, death, or study discontinuation. Investigators reviewed imaging for treatment/discontinuation decisions; images were also assessed by blinded independent central review (BICR).

Adverse events (AEs) were recorded and graded according to the Common Terminology Criteria for Adverse Events version 5.0. Laboratory tests were obtained at screening, during treatment (days 1 and 15 of cycles 1 and 2, then day 1 of every third cycle thereafter), and at treatment end.

Pretreatment plasma samples were collected on day 1 of cycle 1 for baseline circulating tumor DNA (ctDNA) biomarker analysis. Serial plasma samples were collected on day 1 of cycles 2-4, 7, every sixth cycle thereafter, and at progression. Baseline ctDNA was analyzed using the Guardant Infinity assay.

End Points

The primary end point was investigator-assessed PFS per RECIST version 1.1. Key secondary end points included OS, PFS by BICR, objective response rate (ORR), and safety.

Statistical Methods

The study was powered at approximately 80% to detect the superiority of the abemaciclib + fulvestrant arm over the placebo + fulvestrant arm in PFS with an assumed hazard ratio (HR) of 0.70 and cumulative two-sided type I error controlled at 0.05. This required approximately 251 PFS events in the intention-to-treat (ITT) population at the time of the primary analysis. One interim efficacy analysis was planned for PFS, which required approximately 176 events (70% of information fraction). The critical *P* value at interim analysis was determined on the basis of the actual number of events per the O'Brien-Fleming alpha spending function.

The Kaplan-Meier method was used to estimate PFS, including the median and 6-month PFS rate in each arm with 95% CIs. The comparison of PFS curves between treatment arms was conducted by a stratified log-rank test. Patients with no documented progressive disease were censored at the time of their last adequate tumor assessment. The treatment effect was estimated by HRs with corresponding 95% CI using the Cox proportional hazard model stratified by the randomization strata. For the assessment of effect size across subgroups, unstratified Cox proportional hazard models were fit for each subgroup, including the treatment group, subgroup, and their interaction variable.

Safety was summarized by descriptive statistics in participants who received at least one dose of study treatment. Follow-up time was defined as the time from random assignment until death from any cause or the last known alive date under follow-up period.

Trial Oversight

The sponsor, Eli Lilly and Company, designed the trial and was responsible for site monitoring and data collection in collaboration with investigators. This study was performed in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol and all amendments were approved by an ethical review board for each site. A steering committee comprising participating investigators and sponsor representatives oversaw the trial conduct. An independent data monitoring committee reviewed safety and interim efficacy data. All patients provided written informed consent.

RESULTS

Patients

Between March 2022 and June 2023, a total of 368 patients were randomly assigned to the abemaciclib + fulvestrant (n = 182) or placebo + fulvestrant arms (n = 186; Fig 1).

Baseline characteristics were well balanced between arms (Table 1). The median age was 59 years (range, 27-86). At baseline, most patients (n = 221; 60%) had visceral disease (including 38% with liver metastases), while 20% had bone-only disease.

Nearly all patients were enrolled after receiving previous CDK4/6i in the advanced setting; three patients entered the study after adjuvant therapy. Palbociclib (n = 217; 59%) and ribociclib (n = 122; 33%) were the most commonly used previous CDK4/6i; fewer patients received previous abemaciclib (n = 28; 8%). The median duration of previous CDK4/6i therapy in the advanced setting was 20 months (range, 2-110), with most patients (n = 273; 74%) receiving CDK4/6i for ≥12 months.

Treatment

Median follow-up time at the primary analysis was 13 months (IQR, 10-17 months), and 22% versus 17% of patients remained on treatment in the abemaciclib + fulvestrant arm versus the placebo + fulvestrant arm. The most frequent cause of discontinuation was disease progression (63% and 77% of patients enrolled in the abemaciclib + fulvestrant and placebo + fulvestrant arms, respectively).

Efficacy

The study achieved statistical significance at the prespecified interim analysis conducted after 169 investigator-assessed PFS events were observed (70 *v* 99 in abemaciclib + fulvestrant and placebo + fulvestrant arms, respectively; data cutoff: June 15, 2023), resulting in a HR of 0.66 (log-rank *P* = .01; critical *P* value boundary: .013; Appendix Fig A1, online only).

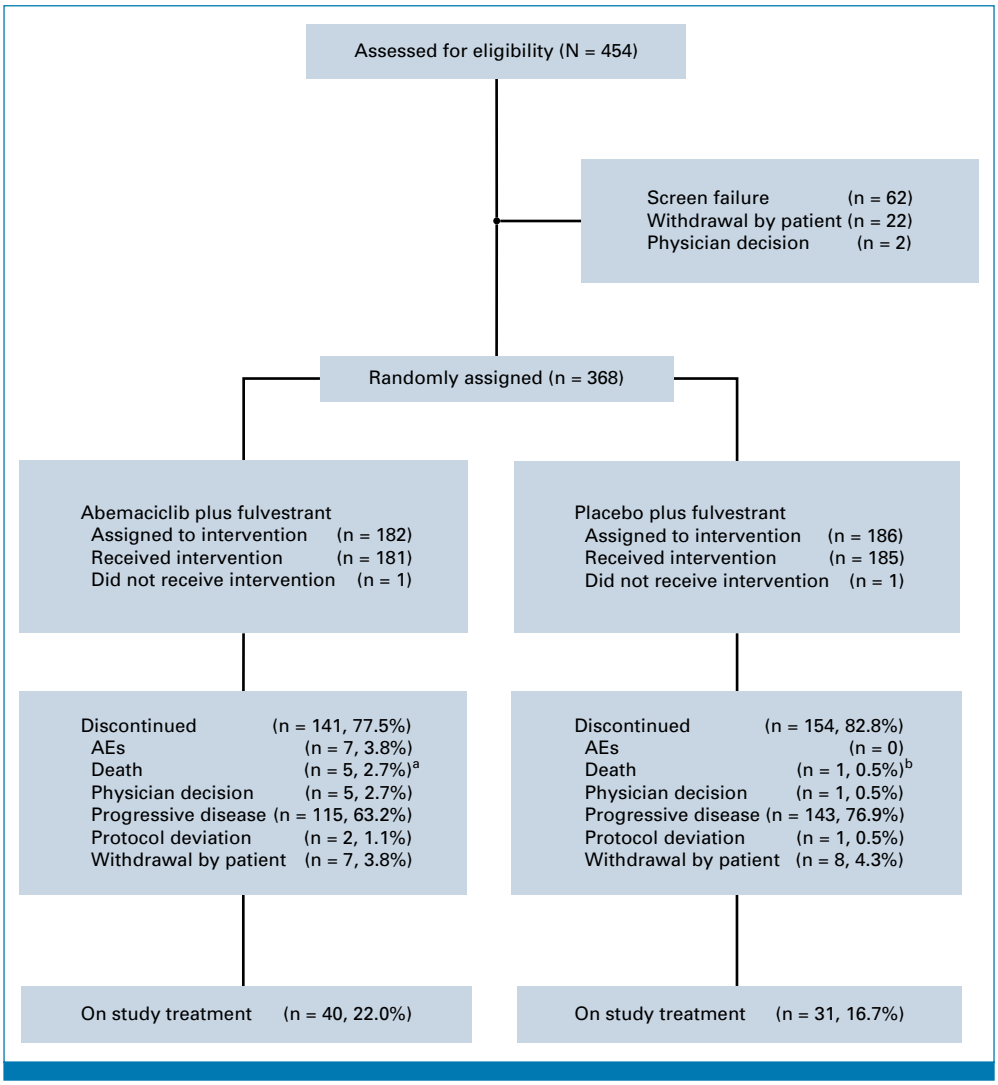

FIG 1. CONSORT diagram. [a]Includes four deaths due to AE and one death due to study disease. [b]Death due to study disease. AE, adverse event.

At the primary analysis, with 258 events (117 *v* 141 in abemaciclib + fulvestrant and placebo + fulvestrant arms, respectively; data cutoff: February 8, 2024), a HR of 0.73 (95% CI, 0.57 to 0.95; nominal $P = .017$) reflected a 27% reduction in the risk of developing a PFS event with the addition of abemaciclib to fulvestrant (Fig 2A). The 6-month PFS rate was 50% versus 37% in the abemaciclib + fulvestrant versus placebo + fulvestrant arms, and the median PFS (mPFS) was 6.0 versus 5.3 months, favoring the abemaciclib + fulvestrant arm (Fig 2A). PFS analyses according to stratification criteria and important demographic and prognostic factors showed a generally consistent abemaciclib treatment effect across evaluated subgroups (Fig 3A, Appendix Fig A2), although some subgroups were limited in sample size.

PFS was also assessed through BICR, with results demonstrating consistent PFS benefit in all patients (mPFS 12.9 months abemaciclib + fulvestrant *v* 5.6 months placebo + fulvestrant; HR, 0.55 [95% CI, 0.39 to 0.77]; nominal $P < .001$; Fig 2B) and across subgroups (Fig 3B). There was notable discordance between the number of BICR- versus investigator-assessed events (60 [51%] and 54 [38%] of investigator-assessed PFS events unconfirmed by BICR in the abemaciclib + fulvestrant and placebo + fulvestrant arms, respectively).

Among patients with measurable disease, ORR was higher with abemaciclib + fulvestrant versus placebo + fulvestrant, both by investigator and BICR assessment (investigator: 17% *v* 7%, nominal $P = .015$; BICR: 23% *v* 8%, nominal $P < .001$; Appendix Tables A1 and A2).

OS data were immature at the time of data cutoff, with 40 deaths (22%) in the abemaciclib + fulvestrant arm and 37 deaths (20%) in the placebo + fulvestrant arm.

Safety

In the safety population (abemaciclib + fulvestrant, n = 181; placebo + fulvestrant, n = 185), median

TABLE 1. Baseline Patient Characteristics

Characteristic	Abemaciclib + Fulvestrant (n = 182)	Placebo + Fulvestrant (n = 186)	Total (N = 368)
Age, years			
Median	58.0	61.0	59.0
<65, No. (%)	126 (69.2)	118 (63.4)	244 (66.3)
Female sex, No. (%)	180 (98.9)	185 (99.5)	365 (99.2)
Region, No. (%)			
Other (including the European Union)	133 (73.1)	134 (72.0)	267 (72.6)
United States	28 (15.4)	28 (15.1)	56 (15.2)
East Asia	21 (11.5)	24 (12.9)	45 (12.2)
Race,[a] No. (%)			
White	140 (82.4)	143 (82.2)	283 (82.3)
Asian	21 (12.4)	26 (14.9)	47 (13.7)
Black or African American	6 (3.5)	3 (1.7)	9 (2.6)
American Indian or Alaska Native	3 (1.8)	2 (1.1)	5 (1.5)
ECOG performance status, No. (%)			
0	104 (57.1)	107 (57.5)	211 (57.3)
1	78 (42.9)	79 (42.5)	157 (42.7)
Hormone receptor status, No. (%)			
ER+	182 (100)	184 (98.9)	366 (99.5)
PR+	144 (79.1)	150 (80.6)	294 (79.9)
Measurable disease, No. (%)	131 (72.0)	127 (68.3)	258 (70.1)
Site of metastasis, No. (%)			
Visceral	112 (61.5)	109 (58.6)	221 (60.1)
Liver	68 (37.4)	71 (38.2)	139 (37.8)
Bone only	32 (17.6)	42 (22.6)	74 (20.1)
Stage IV at initial diagnosis	75 (41.2)	74 (39.8)	149 (40.5)
Previous CDK4/6i setting,[b] No. (%)			
ABC	182 (100)	182 (97.8)	364 (98.9)
Adjuvant	0	3 (1.6)	3 (0.8)
Previous CDK4/6i, No. (%)			
Palbociclib	107 (58.8)	110 (59.1)	217 (59.0)
Ribociclib	61 (33.5)	61 (32.8)	122 (33.2)
Abemaciclib	14 (7.7)	14 (7.5)	28 (7.6)
Duration of previous CDK4/6i, months,[c] No. (%)			
≥12	129 (70.9)	141 (75.8)	270 (73.4)
<12	53 (29.1)	40 (21.5)	93 (25.3)
Duration of previous CDK4/6i,[c] months, median			
All	19	21	20
Palbociclib	19	23	21
Ribociclib	15	18	17
Abemaciclib	26	17	22

Abbreviations: ABC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor(s); ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor.
[a]The denominator for race was 170 for the abemaciclib arm and 174 for the placebo arm.
[b]One patient did not receive previous CDK4/6i and was deemed inadvertently enrolled.
[c]For ABC.

treatment duration was six and five cycles, respectively. Most patients experienced ≥1 AE (Table 2). Grade ≥3 AEs occurred in 55% and 20% of patients in the abemaciclib + fulvestrant and placebo + fulvestrant arms, respectively. Diarrhea was the most frequently observed AE in the abemaciclib + fulvestrant arm, with low frequency (4%) of grade ≥3 events. No new safety signals were identified.

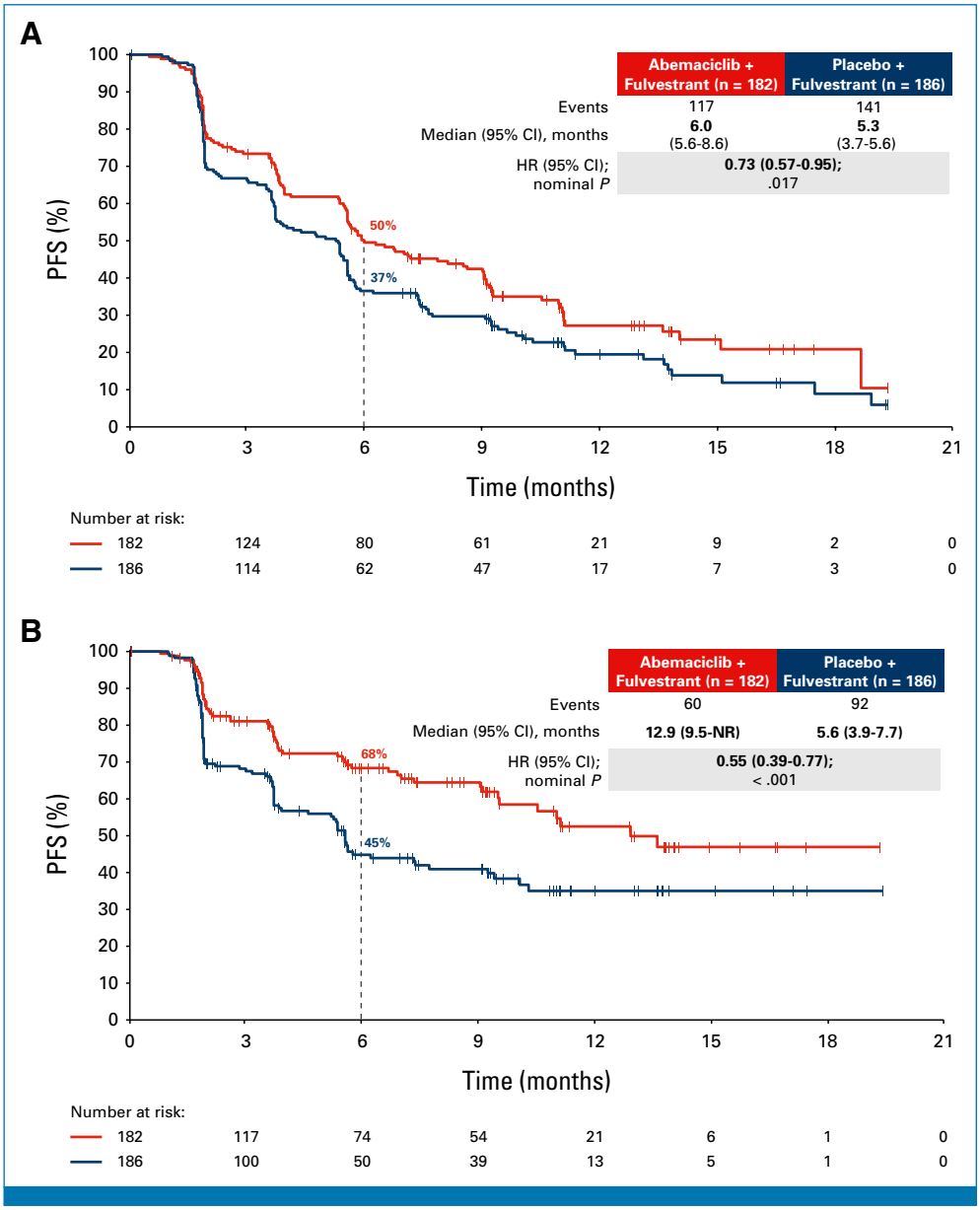

FIG 2. Primary analysis of (A) investigator-assessed and (B) BICR-assessed PFS. BICR, blinded independent central review; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

Serious adverse events (SAEs) were reported in 24% and 11% of patients in the abemaciclib + fulvestrant and placebo + fulvestrant arms, respectively. Pneumonia was the most frequently reported SAE (abemaciclib + fulvestrant arm, 4%; placebo + fulvestrant arm, 2%).

Dose interruptions due to AEs occurred in 55% and 7% of patients in the abemaciclib + fulvestrant and placebo + fulvestrant arms, respectively. Neutropenia was the most common AE leading to abemaciclib dose interruptions (20%). Dose reductions due to AEs occurred in 30% versus 3% of patients in the abemaciclib + fulvestrant versus placebo + fulvestrant arm, with the majority of these (22% *v* 3%) being a reduction in one dose level. Diarrhea was the most common AE leading to abemaciclib dose reductions (9%). AEs led to treatment discontinuation in 6% of patients in the abemaciclib + fulvestrant arm and none in the placebo + fulvestrant arm. AEs leading to death occurred in four patients (2%) in the abemaciclib + fulvestrant arm and two patients (1%) in the placebo + fulvestrant arm. Of these, one death (due to pneumonia) in the abemaciclib + fulvestrant arm was considered by the investigator to be related to study treatment.

Exploratory Biomarker Analysis

Baseline plasma samples for biomarker analyses were available from 87% of patients; all but three had detectable ctDNA at baseline. The ctDNA-evaluable subgroup was largely representative of the ITT population in baseline

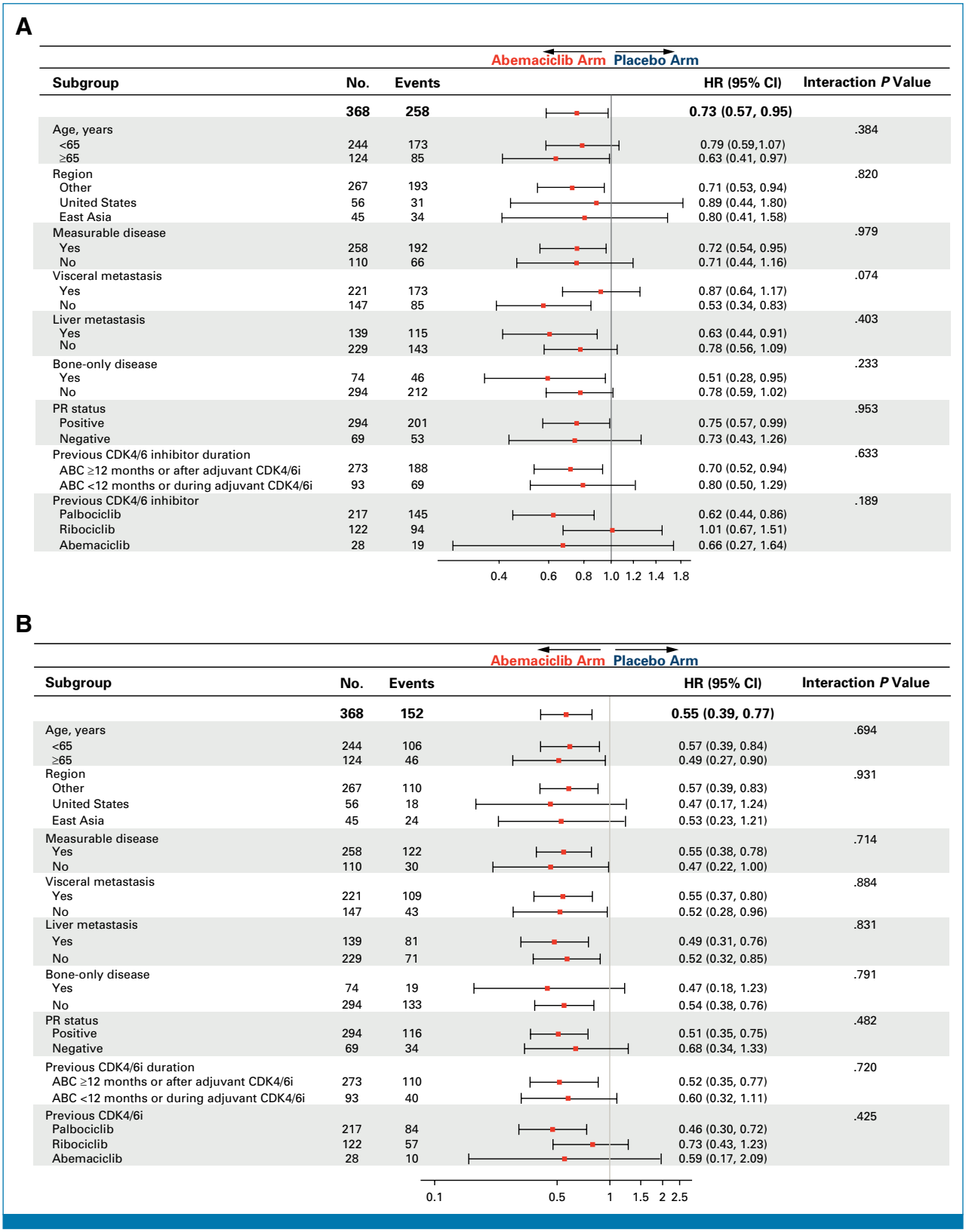

FIG 3. (A) Investigator-assessed and (B) BICR-assessed PFS in clinically relevant subgroups. ABC, advanced breast cancer; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor(s); HR, hazard ratio; PFS, progression-free survival; PR, progesterone receptor.

TABLE 2. Overview of Safety

	Abemaciclib + Fulvestrant (n = 181), No. (%)		Placebo + Fulvestrant (n = 185), No. (%)	
TEAE (≥10% in either arm)	Any Grade	Grade ≥3	Any grade	Grade ≥3
Any	176 (97.2)	100 (55.2)	151 (81.6)	37 (20.0)
Diarrhea	135 (74.6)	7 (3.9)	32 (17.3)	3 (1.6)
Neutropenia[a]	74 (40.9)	45 (24.9)[b]	6 (3.2)	0
Anemia[a]	63 (34.8)	20 (11.0)	28 (15.1)	7 (3.8)
Fatigue[a]	60 (33.1)	5 (2.8)	43 (23.2)	1 (0.5)
Nausea	59 (32.6)	6 (3.3)	34 (18.4)	0
Abdominal pain[a]	43 (23.8)	3 (1.7)	30 (16.2)	0
Vomiting	36 (19.9)	4 (2.2)	11 (5.9)	0
Thrombocytopenia[a]	33 (18.2)	7 (3.9)	11 (5.9)	3 (1.6)
Decreased appetite	33 (18.2)	2 (1.1)	12 (6.5)	0
Leukopenia[a]	32 (17.7)	15 (8.3)	6 (3.2)	0
AST increased	27 (14.9)	10 (5.5)	20 (10.8)	3 (1.6)
ALT increased	23 (12.7)	7 (3.9)	19 (10.3)	3 (1.6)
Arthralgia	21 (11.6)	1 (0.6)	23 (12.4)	1 (0.5)
Blood creatinine increased	20 (11.0)	0	4 (2.2)	0
Cough	19 (10.5)	0	12 (6.5)	0
Other AEs of special interest	Any grade	Grade ≥3	Any grade	Grade ≥3
Venous thromboembolism[a]	9 (5.0)	4 (2.2)[c]	5 (2.7)	1 (0.5)
ILD[a]	5 (2.8)	2 (1.1)[d]	1 (0.5)	0
Dose modifications				
Dose reductions due to AE	55 (30.4)		6 (3.2)	
Discontinuations due to AE	11 (6.1)[e]		0	

Abbreviations: AE, adverse event; ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
[a]Consolidated term.
[b]Includes one event of grade 3 and one event of grade 4 febrile neutropenia.
[c]Includes one event of grade 5 pulmonary embolism.
[d]Includes one event of grade 3 and one event of grade 4 ILD.
[e]Includes four fatal AEs (pneumonia [two patients], hepatic failure [one patient], and pulmonary embolism [one patient]).

characteristics and benefit derived from abemaciclib + fulvestrant (HR, 0.77 [95% CI, 0.59 to 1.00]).

ESR1 mutations were detected in 40% and 51% of the abemaciclib + fulvestrant and placebo + fulvestrant arms, respectively. PI3K pathway mutations were identified in 46% and 52% of the abemaciclib + fulvestrant and placebo + fulvestrant arms, respectively, including 36% and 42% *PIK3CA*, 11% and 10% *PTEN*, and 3% and 6% *AKT1* (Fig 4A). Consistent abemaciclib treatment effect was observed across the most prevalent biomarker subgroups (Fig 4B): HR, 0.79 (95% CI, 0.54 to 1.15) *ESR1* detected versus 0.78 (95% CI, 0.54 to 1.12) not detected; HR, 0.76 (95% CI, 0.50 to 1.14) *PIK3CA* detected versus 0.80 (95% CI, 0.57 to 1.12) not detected. Numerically, benefit was less apparent in patients with *PTEN* or *AKT1* alterations, but the small sample size limits the significance of this observation.

DISCUSSION

The postMONARCH study demonstrated that abemaciclib added to fulvestrant significantly improved PFS in patients with HR+, HER2− ABC after disease progression on/after previous CDK4/6i plus ET. To our knowledge, the postMONARCH trial is the first randomized, placebo-controlled phase III study to demonstrate benefit of continued CDK4/6 inhibition beyond progression on a CDK4/6i. This aligns with the hypothesis that continued suppression of the CDK4/6 pathway delivers ongoing clinical benefit and with some preclinical data indicating that sensitivity to some CDK4/6is may be retained after resistance to others, also highlighting potential differences across the CDK4/6i class.[10,14,15] These results are also consistent with the randomized phase II MAINTAIN study[11] and real-world data.[16–18]

A

Subgroup	Abemaciclib + Fulvestrant, No. (%)	Placebo + Fulvestrant, No. (%)
ctDNA-evaluable population	(n = 161)	(n = 159)
Gene alteration		
ESR1	64 (39.8)	81 (50.9)
AKT1	5 (3.1)	9 (5.7)
PIK3CA	58 (36.0)	67 (42.1)
PTEN	17 (10.6)	16 (10.1)
PIK3CA or *PTEN* or *AKT1*	74 (46.0)	82 (51.6)

B

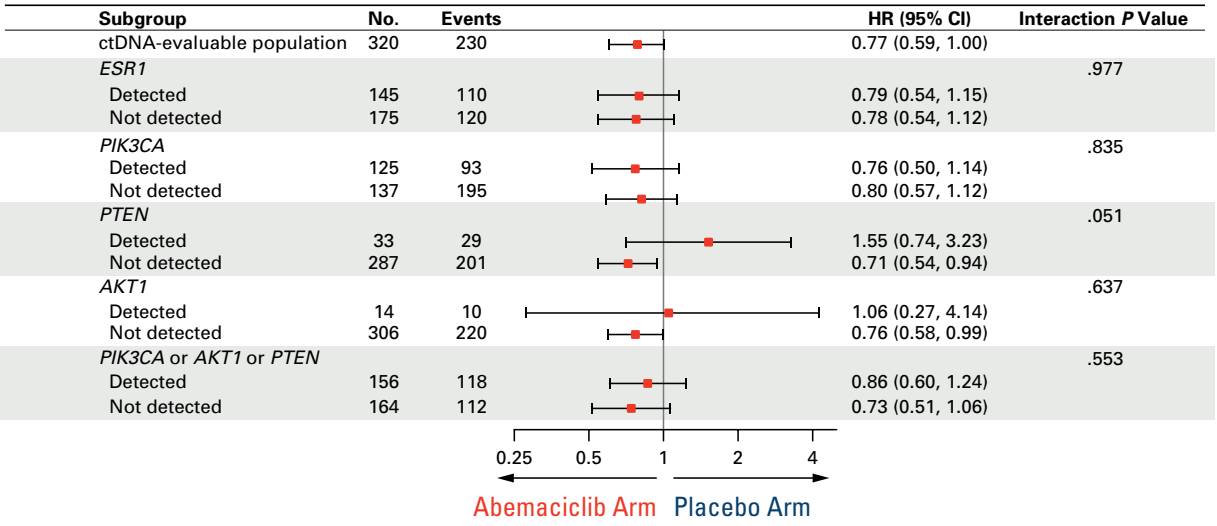

FIG 4. Exploratory biomarker analysis in biomarker-evaluable population. (A) Frequency of gene alterations in *ESR1* and the PI3K pathway. (B) Investigator-assessed PFS. ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival.

postMONARCH included patients with disease progression on a CDK4/6i plus AI as initial treatment for advanced disease or recurrence on/after a CDK4/6i plus ET as adjuvant therapy. Patients were not allowed to have received chemotherapy or more than one line of ET for ABC. As such, postMONARCH enrolled a less heterogeneous population than recent studies including post-CDK4/6i populations, likely accounting, at least in part, for the control arm performing better than expected.[11-13,19-21] Despite this control arm overperformance, abemaciclib added to fulvestrant demonstrated significant benefit in this post-CDK4/6i population. Although absolute mPFS benefit in the ITT population was modest, the overall treatment effect across all time points is better summarized by the HR, which showed a 27% risk reduction for developing a PFS event (HR, 0.73 [95% CI, 0.57 to 0.95]) and landmark analysis such as the 6-month PFS rate (50% *v* 37% with abemaciclib + fulvestrant *v* placebo + fulvestrant). Consistent with this, ORR (17% *v* 7% for patients with measurable disease) was also improved with abemaciclib versus placebo added to fulvestrant.

The investigator results were supported by independent review (BICR), although discordance was noted and most frequently because of investigator declaring progression that was unconfirmed by BICR. At the time of investigator-declared progression, treatment was discontinued. All treatment decisions were made using investigator assessments and clinical judgment; BICR results were unknown to investigators. After treatment discontinuation, no additional scans were mandated. Consequently, there were higher rates of censoring on BICR analyses as fewer patients remained on study eligible for a PFS event. Although discordance is common (Appendix Table A3),[22] and like in postMONARCH, frequently shows shorter investigator-assessed mPFS than BICR, the notably higher rate of discordance observed in the abemaciclib + fulvestrant arm compared with placebo + fulvestrant arm prompted post hoc analyses. Meaningful trends in enrollment geography and disease or patient characteristics were not identified. Several factors can contribute to assessment of progression by the investigator but not by BICR, including direct patient interactions where clinical factors contribute to assessments.

Overall, the abemaciclib treatment effect was largely consistent across subgroups, regardless of investigator or BICR assessment. Some subgroups, such as patients without visceral metastasis (mPFS, 11.1 months) and with bone-only disease (mPFS, 15.1 months), appeared to derive a substantial benefit. Certain subgroups were small, limiting interpretation; for example, only 8% of patients received previous abemaciclib. Only three patients received a CDK4/6i in the adjuvant setting, which precluded analysis. As adjuvant CDK4/6i use increases, benefit from further/repeated CDK4/6i after disease recurrence is an increasingly important question. Although numerically smaller effect size was observed for patients who received previous therapy with ribociclib versus palbociclib, the subgroup was comparatively smaller, the CI was wide, and the specific previous CDK4/6i was not a stratification factor. Additionally, the treatment duration of previous ribociclib was marginally shorter than that of previous palbociclib (median 17 *v* 21 months, respectively), particularly among previous ribociclib patients randomly assigned to the abemaciclib + fulvestrant arm, in whom median previous ribociclib duration was 15 months, potentially suggesting those patients had less CDK4/6i-sensitive disease. Taken together, these data reflect a need for additional study of abemaciclib after previous ribociclib treatment.

Most patients had previously received palbociclib, reflecting its widespread use before the postMONARCH study period. It is, however, acknowledged that prescribing practices of CDK4/6is are evolving because of the lack of OS or invasive disease-free survival benefit observed with palbociclib in the advanced or adjuvant setting, respectively.[23-26] Thus, data from other ongoing phase III studies (EMBER-3; ELAINE-3) of continued abemaciclib after progression on abemaciclib and ribociclib will be important.[27,28]

Exploratory biomarker analyses found that 45% of patients had circulating *ESR1* mutations, consistent with contemporary trials and previous treatment with AI, which is associated with development of these mutations.[20,29,30] Additionally, 49% of patients had tumor PI3K pathway alterations, including 39% with *PIK3CA* mutations. PFS benefit from abemaciclib + fulvestrant was observed regardless of *ESR1* or *PIK3CA* tumor mutations. This is consistent with other data in CDK4/6i-naïve patients, where abemaciclib + ET (AI in MONARCH 3 or fulvestrant in MONARCH 2) was effective regardless of baseline *ESR1* or *PIK3CA* mutations.[31,32] Conversely, in MAINTAIN, patients with detectable *ESR1* mutations did not benefit from ribociclib + fulvestrant versus placebo + fulvestrant (HR, 1.22 [95% CI, 0.59 to 2.49]), although a comparatively smaller trial.[11] A slight imbalance in *ESR1* mutations was observed between arms in postMONARCH (40% abemaciclib + fulvestrant *v* 51% placebo + fulvestrant); more detailed assessment of this, including of specific variants as well as impact of other genomic alterations, is warranted. Although limited by sample size, numerically less benefit was observed with *PTEN* alterations, consistent with previous association with CDK4/6i resistance.[33]

Finally, no new safety signals were identified with abemaciclib + fulvestrant and the discontinuation rate due to AEs was low (6%). Additionally, the grade 3 diarrhea and dose modification rates were lower than in previous studies, likely reflecting increased familiarity with abemaciclib.[7,8] Overall, abemaciclib + fulvestrant had a predictable and manageable toxicity profile.

There is no clear standard of care for disease progression after CDK4/6i therapy and, although combination ET with a targeted therapy is generally recommended before chemotherapy,[1,34] optimal sequencing remains unclear. Although important progress has been made for patients with disease progression on ET, including three approvals in the past 5 years, these targeted therapies are confined to biomarker-selected subgroups (alpelisib for *PIK3CA*-mutated, elacestrant for *ESR1*-mutated, and capivasertib for *PIK3CA*-/*AKT1*-/*PTEN*-altered ABC). Everolimus is a broadly available and used option, but data after CDK4/6i are primarily restricted to real-world analyses and small single-arm studies.[35-39]

The mPFS of 6 months (95% CI, 5.6 to 8.6) in postMONARCH is consistent with recent trials in the post-CDK4/6i setting. Indeed, contemporary trials of targeted therapies have demonstrated mPFS of 3.8-5.5 months in CDK4/6i-pretreated patients, although most had higher toxicity-driven discontinuation rates of 6%-25%.[19-21] Collectively, the observed ≤6-month mPFS from these studies highlight the need for better treatments after CDK4/6i and improved patient selection.[20,29,30] This might be achieved in the future by building upon the postMONARCH regimen with optimization of the ET backbone. This strategy is currently under evaluation in the phase III EMBER-3 study of imlunestrant, a next-generation oral SERD, as monotherapy or in combination with abemaciclib, which will provide additional data for abemaciclib after progression on a CDK4/6i.[27] Finally, triplet regimens of approved or novel therapies with synergistic mechanisms added to an abemaciclib and ET backbone might further improve patient outcomes, provided that combinations are tolerable.[20,29,30]

The postMONARCH trial supports maintaining CDK4/6 inhibition with abemaciclib, while switching the ET backbone, after disease recurrence or progression on a CDK4/6i plus ET. This combination offers an additional targeted therapy option for patients with HR+, HER2− ABC.

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Consulting or Advisory Role: Polyphor, Roche/Genentech, Lilly, Eisai, Macrogenics, Pfizer, Merck, AstraZeneca, Sanofi, Seagen, Sermonix Pharmaceuticals
Speakers' Bureau: Lilly
Research Funding: Eisai (Inst), Polyphor (Inst), Lilly (Inst), Novartis (Inst), Pfizer (Inst), Sanofi (Inst), Zymeworks (Inst), Sermonix Pharmaceuticals (Inst)
Expert Testimony: Seagen
Travel, Accommodations, Expenses: Lilly, Polyphor, Seagen

Montserrat Muñoz
Consulting or Advisory Role: Seagen
Speakers' Bureau: Roche, Roche, Gilead Sciences, Gilead Sciences, Gilead Sciences, Esteve
Expert Testimony: Novartis, Menarini
Travel, Accommodations, Expenses: Roche, Roche, Lilly, Gilead Sciences, Roche, Lilly, Pfizer

Jiun-I Lai
Honoraria: Gilead Sciences, Pfizer, Ono Pharmaceutical, Novartis, Merck
Consulting or Advisory Role: Novartis, Gilead Sciences
Travel, Accommodations, Expenses: Ono Pharmaceutical, Merck

Holly Knoderer
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Stock and Other Ownership Interests: Lilly, ADC Therapeutics, Athenex, Lilly (I)

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Stock and Other Ownership Interests: Lilly

Aarti R. Chawla
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Stock and Other Ownership Interests: Lilly

Bastien Nguyen
Employment: Loxo/Lilly

Yanhong Zhou
Employment: AbbVie (I), Lilly
Stock and Other Ownership Interests: Lilly, AbbVie (I)
Travel, Accommodations, Expenses: Lilly

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Stock and Other Ownership Interests: Lilly

Lacey M. Litchfield
Employment: Lilly
Stock and Other Ownership Interests: Lilly

Lillian Smyth
Employment: Loxo
Leadership: Eli Lilly Kinsale Limited
Stock and Other Ownership Interests: Lilly
Patents, Royalties, Other Intellectual Property: Loxo@Lilly | Eli Lilly and Company

Seth A. Wander
Consulting or Advisory Role: Foundation Medicine, Puma Biotechnology, Veracyte, Lilly, Hologic, Pfizer, Biovica, AstraZeneca, Novartis, Genentech/Roche, Regor Therapeutics
Speakers' Bureau: Lilly, Guardant Health, 2nd.MD
Research Funding: Genentech, Lilly, Pfizer, Regor Therapeutics, Nuvation Bio, Sermonix Pharmaceuticals

No other potential conflicts of interest were reported.

APPENDIX

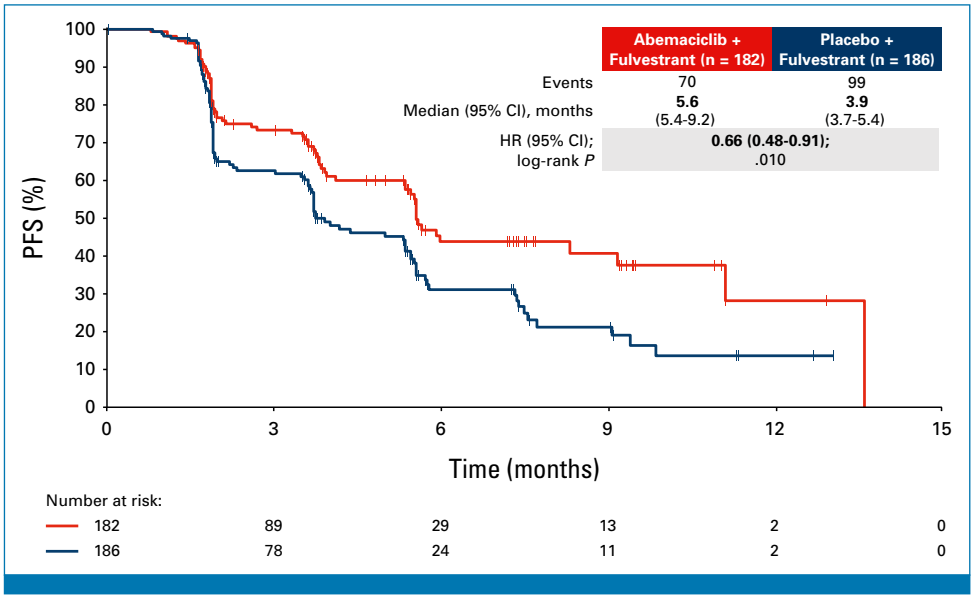

FIG A1. Interim analysis of investigator-assessed PFS. HR, hazard ratio; PFS, progression-free survival.

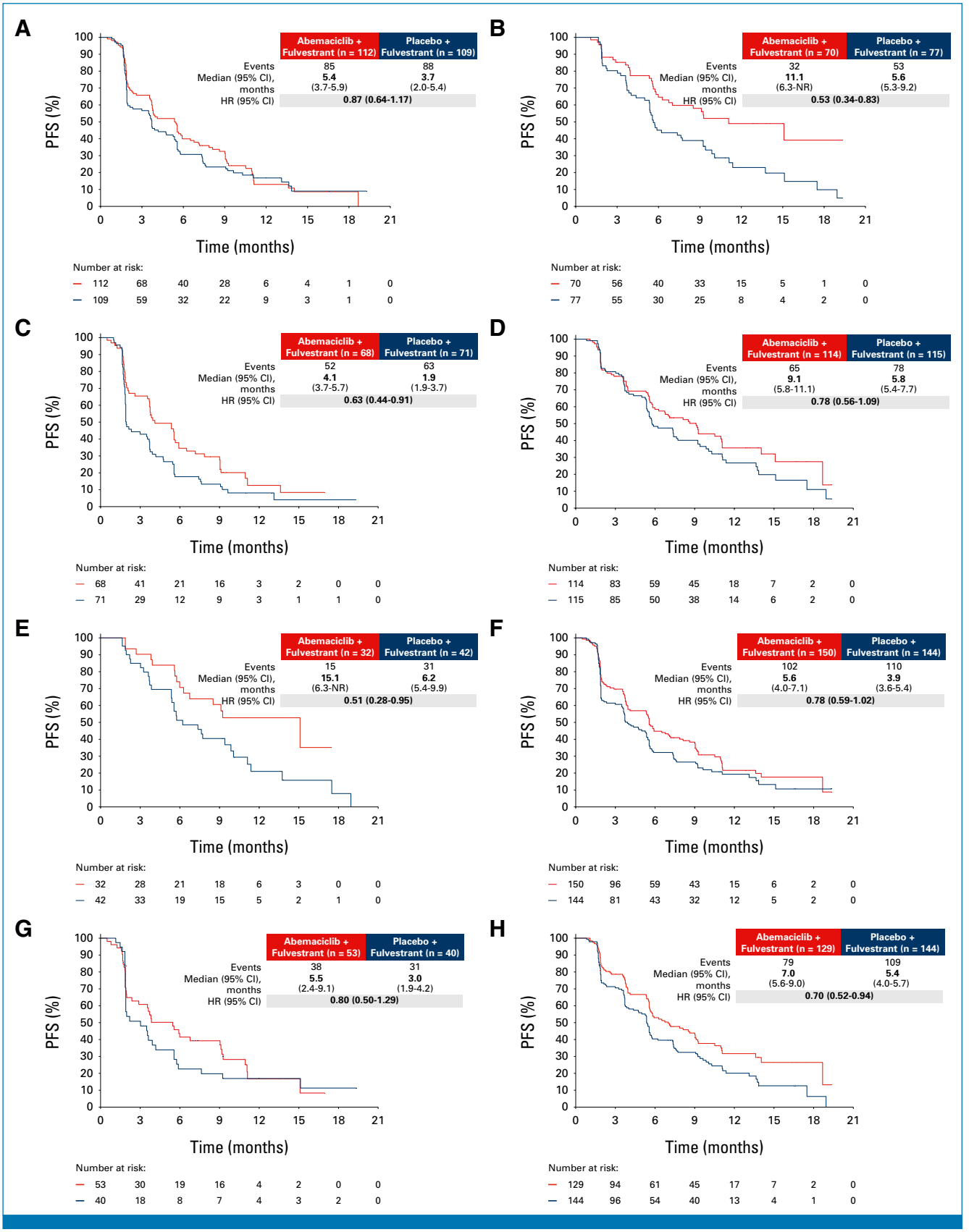

FIG A2. Investigator-assessed PFS for clinically relevant subgroups: (A) patients with visceral metastasis; (B) patients without visceral metastasis; (C) patients with liver metastasis; (D) patients without liver metastasis; (E) patients with bone-only disease; (F) patients without bone-only disease; (G) patients who received previous CDK4/6i for <12 months; and (H) patients who received previous CDK4/6i for ≥12 months. CDK4/6i, cyclin-dependent kinase 4/6 inhibitor(s); HR, hazard ratio; NR, not reached; PFS, progression-free survival.

TABLE A1. Tumor Response in Patients with Measurable Disease at Baseline

Response	Abemaciclib + Fulvestrant (n = 131), No. (%)	Placebo + Fulvestrant (n = 127), No. (%)	Nominal *P* Value
Investigator-assessed			
Best overall response			
Complete response	1 (0.8)	2 (1.6)	
Partial response	21 (16.0)	7 (5.5)	
Stable disease	65 (49.6)	64 (50.4)	
Progressive disease	32 (24.4)	49 (38.6)	
Unknown	12 (9.2)	5 (3.9)	
ORR[a]	22 (16.8)	9 (7.1)	.015
Clinical benefit rate[b]	38 (29.0)	23 (18.1)	.036
BICR-assessed			
Best overall response			
Complete response	6 (4.6)	2 (1.6)	
Partial response	24 (18.3)	8 (6.3)	
Stable disease	53 (40.5)	46 (36.2)	
Progressive disease	20 (15.3)	49 (38.6)	
Unknown	14 (10.7)	8 (6.3)	
ORR[a]	30 (22.9)	10 (7.9)	<.001
Clinical benefit rate[b]	42 (32.1)	19 (15.0)	.002

Abbreviations: BICR, blinded independent central review; ORR, objective response rate.
[a]Defined as a best overall response of complete or partial response.
[b]Defined as a best overall response of complete or partial response or stable disease persisting for ≥6 months.

TABLE A2. Tumor Response in Patients From the Intention-to-Treat Population

Response	Abemaciclib + Fulvestrant (n = 182), No. (%)	Placebo + Fulvestrant (n = 186), No. (%)	Nominal *P* Value
Investigator-assessed			
Best overall response			
Complete response	3 (1.6)	2 (1.1)	
Partial response	21 (11.5)	8 (4.3)	
Stable disease	106 (58.2)	111 (59.7)	
Progressive disease	38 (20.9)	59 (31.7)	
Unknown	14 (7.7)	6 (3.2)	
Overall response rate[a]	24 (13.2)	10 (5.4)	.009
Clinical benefit rate[b]	50 (27.5)	39 (21.0)	.142
BICR-assessed			
Best overall response			
Complete response	7 (3.8)	2 (1.1)	
Partial response	29 (15.9)	9 (4.8)	
Stable disease	61 (33.5)	56 (30.1)	
Progressive disease	25 (13.7)	66 (35.5)	
Unknown	17 (9.3)	14 (7.5)	
Overall response rate[a]	36 (19.8)	11 (5.9)	<.001
Clinical benefit rate[b]	50 (27.5)	23 (12.4)	<.001

Abbreviation: BICR, blinded independent central review.
[a]Defined as a best overall response of complete or partial response.
[b]Defined as a best overall response of complete or partial response or stable disease persisting for ≥6 months.

TABLE A3. Comparison of Investigator- and BICR-Assessed Progression-Free Survival across HR+, HER2– Advanced Breast Cancer Trials

	HR (95% CI)		Discrepancy Rate	
Trial[22]	Investigator	BICR	BICR/Investigator HR	Primary Assessment
MONARCH 3[3] (abemaciclib + letrozole)	0.54 (0.42 to 0.70)	0.47 (0.34 to 0.64)	0.87	Investigator
MONALEESA-2[40] (ribociclib + letrozole)	0.56 (0.43 to 0.72)	0.59 (0.41 to 0.85)	1.05	Investigator
PALOMA-2[41] (palbociclib + letrozole)	0.58 (0.46 to 0.72)	0.65 (0.51 to 0.84)	1.12	Investigator
MONALEESA-7[42] (ribociclib + ET)	0.55 (0.44 to 0.69)	0.43 (0.29 to 0.63)	0.78	Investigator
MONARCH 2[7] (abemaciclib + fulvestrant)	0.55 (0.45 to 0.68)	0.46 (0.36 to 0.58)	0.84	Investigator
MONALEESA-3[43] (ribociclib + fulvestrant)	0.59 (0.48 to 0.73)	0.49 (0.35 to 0.70)	0.83	Investigator
PALOMA-3[44] (palbociclib + fulvestrant)	0.46 (0.36 to 0.59)	0.37 (0.23 to 0.59)	0.80	Investigator
BOLERO-2[45] (everolimus + exemestane)	0.45 (0.38 to 0.54)	0.38 (0.31 to 0.48)	0.84	Investigator
SOLAR-1[46] (alpelisib + fulvestrant)	0.65 (0.50 to 0.85)	0.48 (0.32 to 0.71)	0.74	Investigator
CAPItello-291[21] (capivasertib + fulvestrant)	0.60 (0.51 to 0.71)	0.61 (0.50 to 0.73)	1.02	Investigator
EMERALD[20] (elacestrant)	0.77 (0.63 to 0.95)	0.70 (0.55 to 0.88)	0.91	BICR
postMONARCH (abemaciclib + fulvestrant)	0.73 (0.57 to 0.95)	0.55 (0.39 to 0.77)	0.75	Investigator

Abbreviations: BICR, blinded independent central review; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2–negative; HR, hazard ratio.