Second-Line Endocrine Therapy With or Without Palbociclib Rechallenge in Patients With Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: PALMIRA Trial

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ABSTRACT

PURPOSE Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors plus endocrine therapy (ET) represents the standard first-line treatment for patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HER2-negative) advanced breast cancer (ABC). However, there is no definitive consensus on the preferred second-line treatment option. The PALMIRA trial investigated whether palbociclib rechallenge with an alternative ET would improve the antitumor activity in patients progressing after a first-line palbociclib-containing regimen.

METHODS This international, randomized, open-label, phase II study enrolled 198 patients with hormone receptor–positive/HER2-negative ABC with disease progression after first-line palbociclib plus ET (aromatase inhibitor or fulvestrant). Patients were eligible if they showed clinical benefit to the previous regimen (response or stable disease ≥24 weeks) or had progressed on a palbociclib-based therapy in the adjuvant setting. Patients were randomly assigned (2:1 ratio) to either palbociclib rechallenge plus second-line ET (fulvestrant or letrozole) or second-line ET alone. Stratification factors were previous ET and visceral involvement. The primary end point was investigator-assessed progression-free survival (PFS).

RESULTS Between April 2019 and October 2022, 136 and 62 patients were randomly assigned to palbociclib plus ET or ET alone, respectively. Median investigator-assessed PFS was 4.9 months (95% CI, 3.6 to 6.1) with palbociclib plus ET versus 3.6 months (95% CI, 2.5 to 4.2) with ET alone (hazard ratio, 0.84 [95% CI, 0.66 to 1.07]; $P = .149$). Grade ≥3 treatment-emergent adverse events were higher with palbociclib plus ET (47.4% *v* 10.0%), without new safety signals.

CONCLUSION Palbociclib rechallenge plus an alternative ET did not significantly improve PFS compared with ET alone in patients with hormone receptor–positive/HER2-negative ABC progressing on a first-line palbociclib-based ET regimen.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Targeting endocrine sensitivity until exhaustion is the mainstay of treatment for patients with hormone receptor–positive/human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer (ABC).[1]

The gold standard for first-line therapy consists of the combination of a cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i) with an endocrine agent. This is based on four phase III studies that demonstrated that the addition of a CDK4/6i (palbociclib, ribociclib, or abemaciclib) to an aromatase inhibitor for the treatment of patients with

CONTEXT

Key Objective

To evaluate whether palbociclib rechallenge with an alternative second-line endocrine therapy (ET) would represent an active therapeutic option in patients with disease progression after a first-line palbociclib-based regimen.

Knowledge Generated

Palbociclib rechallenge did not significantly improve median progression-free survival when combined with second-line ET.

Relevance *(K.D. Miller)*

These negative results are consistent with the previously reported PACE trial and differ significantly from trials showing a benefit (albeit modest) from the use of ribociclib or abemaciclib after progression on prior cyclin-dependent kinase inhibitor–containing regimens. Combined with the differing results in the adjuvant setting, preferential use of palbociclib is not justified.*

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

endocrine-sensitive, hormone receptor–positive/HER2-negative ABC significantly improves median progression-free survival (PFS) and overall response rate (ORR) compared with single-agent endocrine therapy (ET).[2-5] Two of these trials have also shown a statistically significant improvement in overall survival (OS).[2,4] Additionally, three other phase III trials have confirmed the benefit of adding a CDK4/6i to fulvestrant among endocrine-sensitive or endocrine-resistant patients in terms of PFS and ORR,[6-8] with two of these trials also demonstrating significant OS benefits.[9,10] Finally, the PARSIFAL study provided no increased benefit for fulvestrant when compared with letrozole in combination with palbociclib in the first-line endocrine-sensitive, hormone receptor–positive/HER2-negative ABC population.[11]

Unfortunately, most patients on a CDK4/6i-based first-line therapy for hormone receptor–positive/HER2-negative ABC will progress, and there is no consensus on the optimal treatment beyond progression. In this setting, the median PFS reported for fulvestrant as a control arm from pivotal studies is in the range of 1.9-2.6 months.[12,13] The combination of fulvestrant with phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) inhibitors, such as everolimus,[14-16] alpelisib,[17,18] or capivasertib,[19] has provided consistent improvements, particularly for tumors harboring *PIK3CA/AKT1/PTEN* mutations. In the post-CDK4/6i scenario, elacestrant, the first of a new generation of selective estrogen downregulators (SERD), has shown significant activity on patients whose tumors harbor an estrogen receptor-1 (*ESR1*) gene mutation.[20]

Tumor samples from patients progressing on first-line regimens have shown that drivers of adaptive resistance were more frequently related to the endocrine agent than to CDK4/6i.[21,22] As a consequence, rechallenge of the CDK4/6 pathway inhibition beyond progression in combination with a second-line ET is being extensively explored.[22-26]

Here, we report the results of the PALMIRA trial, a phase II randomized study exploring palbociclib rechallenge with an alternative second-line ET versus second-line ET alone in patients with hormone receptor–positive/HER2-negative ABC who progressed on a first-line palbociclib-containing regimen.

METHODS

Study Design and Patients

PALMIRA trial is an international, randomized, open-label, phase II study (ClinicalTrial.gov identifier: NCT03809988; clinical study protocol available as Data Supplement) conducted across 41 sites in six countries.

Eligible participants were age 18 years or older with any menopausal status and locally confirmed hormone receptor–positive/HER2-negative, unresectable, locally advanced, not amenable to surgical resection or radiotherapy with curative intent, or metastatic breast cancer. Patients must have shown radiologically confirmed disease progression on first-line palbociclib plus ET-based treatment after having achieved a clinical benefit to this regimen (objective response or stable disease ≥24 weeks). In addition, patients relapsing on a palbociclib-based regimen in the adjuvant setting were suitable for the study if disease progression was confirmed after at least 12 months from CDKi-based treatment start but no more than 12 months after palbociclib treatment completion in this scenario. Last dose of palbociclib must have been administered no later than 8 weeks and not earlier than 7 days from study entry, with the exception of patients relapsing on a palbociclib-based regimen in the adjuvant setting. Key exclusion criteria were visceral crisis, previous

treatment with chemotherapy in the metastatic setting, the use of a CDK4/6i other than palbociclib, and previous resistance to fulvestrant and letrozole. Patients with active uncontrolled and symptomatic central nervous system metastases or leptomeningeal disease were excluded. Full eligibility criteria are described in the Data Supplement (Table S1, online only).

This study was performed in agreement with the guidelines of the International Conference on Harmonization and the ethical principles in the Declaration of Helsinki, and all applicable regulations. All patients provided written informed consent before participation in any study-related activities. Approvals from regulatory authorities and ethics committees were appropriately obtained.

Random Assignment and Masking

Patients were assigned in a 2:1 ratio to receive either palbociclib rechallenge plus ET or ET alone by a central randomization procedure using the electronic case-report-forms software (OpenClinica, Waltham, MA). Random assignment was stratified according to previous ET (fulvestrant *v* aromatase inhibitor) and the presence of visceral involvement (yes *v* no). All study participants and site teams were aware of treatment assignment.

Procedures

Study treatment was initiated at random assignment (day 0). Patients were treated with palbociclib at the same dose level received when completing the previous palbociclib-based regimen (125, 100, or 75 mg administered orally once daily in 4-week cycles [3 weeks of treatment followed by 1 week off]) in combination with second-line ET, either fulvestrant (500 mg once daily on days 1 and 15 during the first 28-day cycle, and once monthly thereafter, administered intramuscularly) or letrozole (2.5 mg once daily, administered orally; continuous treatment), or with second-line ET alone. Administration of second-line ET was chosen depending on the previous administered agent. Pre- or perimenopausal women also received a gonadotropin-releasing hormone agonist.

Treatment continued until disease progression, unacceptable toxicity, death, or patient withdrawal for any reason. Dosing interruptions and dose reduction were allowed for palbociclib as defined by prespecified protocol guidelines but were not applicable to fulvestrant and letrozole per label. Patients were permitted to discontinue palbociclib and continue with ET alone.

Tumor assessments were carried out by computed tomography or magnetic resonance imaging according to RECIST version 1.1 at baseline and every 8 weeks up to 12 months of study treatment start. Thereafter, disease assessment was performed every 12 weeks until disease progression, initiation of a new anticancer therapy, or withdrawal from the study, whichever came first. Bone scans were carried out at baseline and every 24 weeks until the end of the study for patients with bone lesions identified at baseline, unless clinically or biochemically suspected bone progression. Laboratory tests, vital signs, weight, and Eastern Cooperative Oncology Group (ECOG) performance status were assessed on day 1 of every cycle for the first six cycles and on day 1 every two cycles thereafter. A complete blood count was also performed on day 14 of the first two cycles.

Safety was evaluated with the same frequency in all patients who received at least one dose of study treatment by assessment of adverse events, clinical laboratory tests, physical examinations, and vital signs. Common Terminology Criteria for Adverse Events version 5.0 was used to grade toxicity at each cycle.

Outcomes

The primary end point was investigator-assessed PFS defined as the time from random assignment until objective tumor progression or death, whichever occurred first, according to RECIST version 1.1. Secondary end points included ORR (best overall response of complete/partial response in patients with/without measurable disease at baseline), duration of response (time from the first occurrence of a documented objective response to disease progression or death from any cause), time to response (time from the start of study treatment to the first objective tumor response [tumor shrinkage of ≥30%]), clinical benefit rate (CBR; best overall response of complete/partial response or stable disease for ≥24 weeks), OS (time from the first dose of study treatment until death from any cause), and safety. Exploratory end points included the analysis of potential molecular markers of sensitivity and/or resistance for the combination of palbociclib plus ET, according to, but not limited to, the results obtained from the BioPER trial (ClinicalTrials.gov identifier: NCT03184090).[22]

Statistical Methods

Efficacy end points were assessed in all patients randomly assigned to receive study treatment. Safety was assessed in all patients who received at least one dose of study treatment. Detailed statistical methodology is shown in the Data Supplement.

RESULTS

Patients and Treatment

From April 10, 2019, to October 26, 2022, 198 patients were randomly assigned (ratio 2:1) to receive palbociclib rechallenge plus letrozole or fulvestrant (n = 136) or single-agent letrozole or fulvestrant (n = 62). Of the randomly assigned patients, 195 (98.5%) patients received at least one dose of study treatment (135 [99.2%] in the palbociclib plus ET arm and 60 [96.8%] in the ET arm), whereas three (1.5%) patients did not start study treatment because of investigator

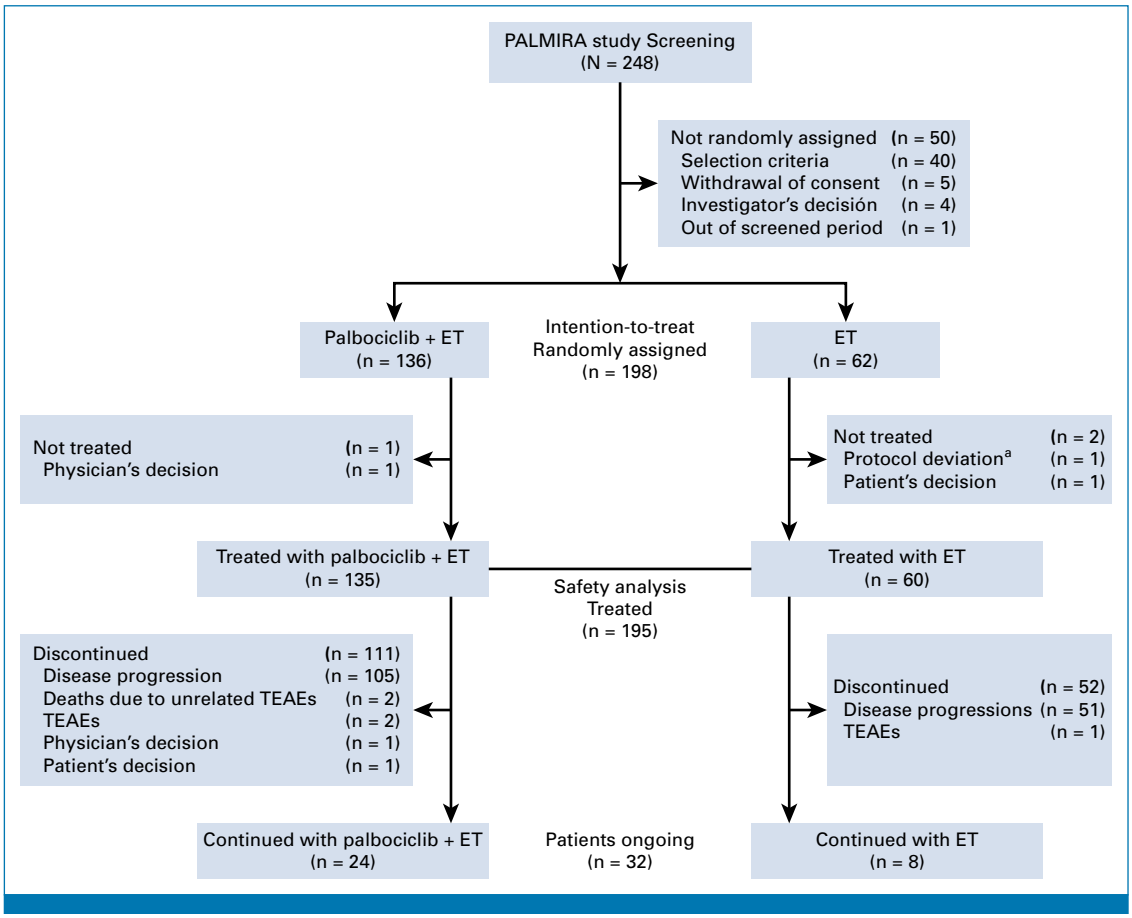

FIG 1. CONSORT diagram. Patient enrollment and disposition. [a]The patient was randomly assigned but did not meet selection criteria (history of bleeding diathesis with anticoagulation treatment). Consequently, the patient did not receive the study treatment. ET, endocrine therapy; TEAEs, treatment-emergent adverse events.

decision (n = 1), patient's decision (n = 1), and protocol violation (n = 1; Fig 1).

Baseline characteristics were balanced between study arms. The median age was 59 years (range, 33-85). Visceral disease and liver metastases were present in 121 (61.1%) and 77 (38.9%) of all patients, respectively. A total of 174 (87.9%) patients were postmenopausal, 121 (61.1%) had ECOG performance status 0, 178 (89.9%) had received previous treatment with an aromatase inhibitor–based regimen as first-line therapy for advanced disease, and 196 (99.0%) had previously been treated with palbociclib in the advanced scenario. Overall, 39.0% of patients in the palbociclib plus ET arm completed their previous treatment with palbociclib at a dose of 100 mg or less. Finally, 170 (85.9%) patients had received previous treatment with a first-line palbociclib-containing regimen for at least 12 months in the advanced setting. Table 1 shows the demographic and baseline characteristics for all patients.

The final analysis was conducted after the occurrence of 158 events of disease progression or death (107 [78.7%] in the palbociclib plus ET arm and 51 [82.3%] in the ET arm).

At this final analysis, with a median follow-up of 13.2 months (range, 0.0-41.1), 24 (17.6%) patients receiving palbociclib plus ET and eight (12.9%) patients receiving ET alone were continuing treatment (Fig 1).

Efficacy

At the data cutoff date for the primary efficacy analysis (February 2, 2023), the median investigator-assessed PFS was 4.9 months (95% CI, 3.6 to 6.1) in the palbociclib plus ET arm versus 3.6 months (95% CI, 2.5 to 4.2) in the ET arm (hazard ratio [HR], 0.84 [95% CI, 0.66 to 1.07]; two-sided $P = .149$; Fig 2 and Data Supplement, Table S2). For the preplanned events (April 7, 2022), the difference between arms showed an HR of 0.77 (95% CI, 0.59 to 1.02, $P = .068$; Data Supplement, Fig S1). In addition, landmark analysis for PFS was performed at 6 and 12 months. Accordingly, 6-month PFS rates were 42.1% (95% CI, 33.3 to 50.7) and 29.1% (95% CI, 18.1 to 40.9) for the palbociclib plus ET and ET arms, respectively. The difference rate between both arms in terms of 6-month PFS was 13.1% (95% CI, −1.6 to 27.7, $P = .086$). In contrast, 12-month PFS rates were 12.4% (95% CI, 6.8 to 19.8) and 12.3% (95% CI, 4.9 to 23.5), respectively

TABLE 1. Baseline Characteristics

Baseline Characteristic	Palbociclib + ET (n = 136)	ET (n = 62)	Overall (N = 198)
Age in years, median (min; max)	59 (33; 85)	61 (34; 83)	59 (33; 85)
Ethnicity, No. (%)			
Caucasian	126 (92.6)	58 (93.5)	184 (92.9)
Other	10 (7.4)	4 (6.5)	14 (7.1)
Menopausal status, No. (%)			
Premenopausal	18 (13.2)	6 (9.7)	24 (12.1)
Postmenopausal	118 (86.8)	56 (90.3)	174 (87.9)
ECOG performance status, No. (%)			
0	90 (66.2)	31 (50.0)	121 (61.1)
≥1[a]	46 (33.8)	31 (50.0)	77 (38.9)
Measurable disease at baseline, No. (%)			
No	42 (30.9)	18 (29.0)	60 (30.3)
Yes	94 (69.1)	44 (71.0)	138 (69.7)
De novo advanced breast cancer, No. (%)			
No	88 (64.7)	41 (66.1)	129 (65.2)
Yes	48 (35.3)	21 (33.9)	69 (34.8)
Visceral involvement, No. (%)			
No	52 (38.2)	25 (40.3)	77 (38.9)
Yes	84 (61.8)	37 (59.7)	121 (61.1)
Metastatic sites, No. (%)			
<3	92 (67.6)	38 (61.3)	130 (65.7)
≥3	44 (32.4)	24 (38.7)	68 (34.3)
Hormone receptor status, No. (%)			
ER-positive and PgR-positive	90 (66.2)	43 (69.4)	133 (67.2)
ER-positive and PgR-negative	46 (33.8)	19 (30.6)	66 (32.8)
Previous palbociclib-based regimen, No. (%)			
Adjuvant setting	1 (0.7)	1 (1.6)	2 (1.0)
Advanced disease	135 (99.3)	61 (98.4)	196 (99.0)
Palbociclib dose at last palbociclib line, mg, No. (%)			
125	83 (61.0)	33 (53.2)	116 (58.6)
100	45 (33.1)	27 (43.5)	72 (36.4)
75	8 (5.9)	2 (3.2)	10 (5.0)
Previous ET used in combination with first-line palbociclib, No. (%)			
Fulvestrant	16 (11.8)	4 (6.5)	20 (10.1)
Aromatase inhibitor	120 (88.2)	58 (93.5)	178 (89.9)
Best response to previous palbociclib-based regimen for advanced disease, No. (%)			
Complete response	8 (5.9)	5 (8.2)	13 (6.6)
Partial response	46 (34.1)	26 (42.6)	72 (36.7)
Stable disease ≥24 weeks	81 (60.0)	30 (49.2)	111 (56.6)
Duration of the previous palbociclib line of therapy in months, median (min; max)	20.6 (6.2; 64.6)	21.8 (6.3; 52.2)	21.0 (6.2; 64.6)
Duration of previous palbociclib line (<12; ≥12 months), No. (%)			
<12 months	18 (13.2)	10 (16.1)	28 (14.1)
≥12 months	118 (86.8)	52 (83.9)	170 (85.9)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ET, endocrine therapy.
[a]One patient in palbociclib + ET arm has ECOG 2.

(Data Supplement, Table S2). Although subgroup analyses of PFS according to stratification factors and other baseline characteristics showed no significant differences between treatment arms across all prespecified subgroups, they did suggest a potential benefit of palbociclib rechallenge in patients with visceral involvement, age <65 years, or those who had received ≥12 months of first-line palbociclib treatment. The median PFS was 5.5 months (95% CI, 3.6 to

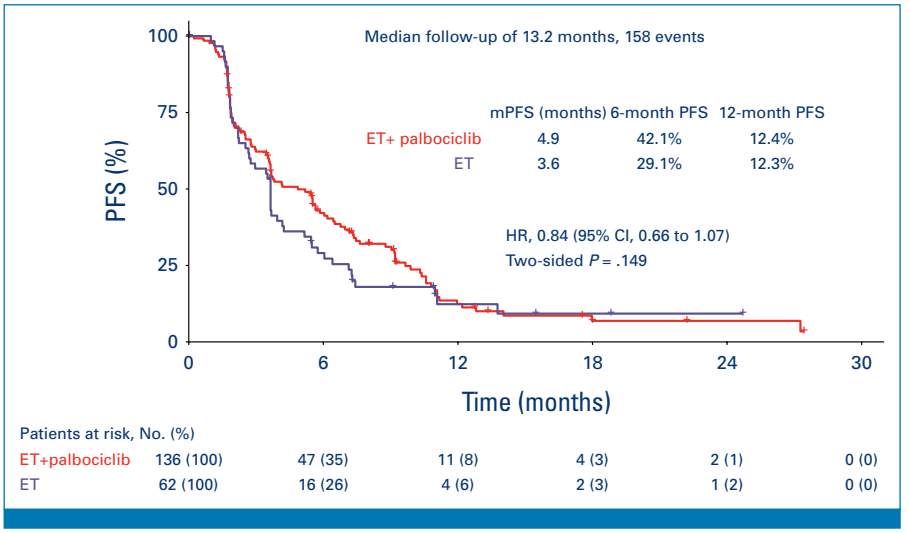

FIG 2. Kaplan-Meier curve for investigator-assessed progression-free survival at 158 events. ET, endocrine therapy, HR, hazard ratio; mPFS, median progression-free survival; PFS, progression-free survival.

6.4) in the palbociclib plus ET arm versus 3.6 months (95% CI, 2.5 to 5.2) in the ET arm for patients who received ≥12 months of first-line palbociclib-based treatment (HR, 0.83 [95% CI, 0.63 to 1.07]; Fig 3 and Data Supplement, Fig S2).

OS data were immature at data cutoff, with 70 events in total (35.3%) in both study arms. The median OS was 28.3 months (95% CI, 20.9 to 36.2) in the palbociclib plus ET arm versus 28.8 months (95% CI, 19.5 to 35.4) in the ET-alone arm (HR, 1.06 [95% CI, 0.75 to 1.51]; Data Supplement, Fig S3).

Locally determined ORR was 4.4% (95% CI, 1.6 to 9.4) in the palbociclib plus ET arm and 1.6% (95% CI, 0.0 to 8.7) in the ET alone arm, all being partial responses (Data Supplement, Table S3). In patients with measurable disease (n = 138; 69.7%), ORR was 6.4% (95% CI, 2.4 to 13.4) and 2.3% (95% CI, 0.1 to 12), respectively (Data Supplement, Table S3). CBR

Characteristic	ET + Palbociclib Events, No./No. (%)	(n = 136) Median PFS, Months (95% CI)	ET Events, No./No. (%)	(n = 62) Median PFS, Months (95% CI)	Adjusted HR (95% CI)	Interaction *P*
All patients	107 / 136 (78.7)	4.9 (3.6 to 6)	51 / 62 (82.3)	3.6 (2.5 to 4.2)	0.84 (0.66 to 1.07)	
Age						
<65 years	73 / 94 (77.7)	4.1 (3.5 to 5.8)	29 / 33 (87.9)	2.7 (1.9 to 3.9)	0.71 (0.52 to 0.97)	.239
≥65 years	34 / 42 (81)	5.5 (2.5 to 7.6)	22 / 29 (75.9)	3.6 (3.5 to 7.1)	0.95 (0.65 to 1.4)	
Endocrine therapy						
Fulvestrant	96 / 120 (80)	4.1 (3.5 to 5.8)	47 / 58 (81)	3.6 (2.7 to 4.2)	0.86 (0.67 to 1.11)	.313
Letrozole	11 / 16 (68.8)	6.7 (2.5 to 14)	4 / 4 (100)	3.1 (1.6 to NA)	0.53 (0.21 to 1.3)	
ECOG performance status						
0	70 / 90 (77.8)	4.9 (3.5 to 6.8)	25 / 31 (80.6)	3.6 (1.9 to 7.3)	0.8 (0.58 to 1.11)	.581
1-2	37 / 46 (80.4)	4.1 (2.8 to 5.7)	26 / 31 (83.9)	3.6 (2.5 to 5.5)	0.92 (0.64 to 1.32)	
Metastatic sites						
<3	65 / 92 (70.7)	5.7 (3.6 to 7.4)	30 / 38 (78.9)	3.7 (2.7 to 7.1)	0.91 (0.67 to 1.24)	.374
≥3	42 / 44 (95.5)	3.5 (2 to 5.5)	21 / 24 (87.5)	2.9 (1.8 to 4.2)	0.73 (0.5 to 1.07)	
Visceral involvement						
No	34 / 52 (65.4)	8.8 (4.2 to 11)	18 / 25 (72)	4.4 (2.8 to 11.1)	0.94 (0.62 to 1.42)	.239
Yes	73 / 84 (86.9)	3.6 (2.3 to 5.4)	33 / 37 (89.2)	2.8 (1.8 to 3.9)	0.79 (0.59 to 1.06)	
Duration of first-line palbociclib						
6 to <12 months	14 / 18 (77.8)	1.8 (1.7 to 12)	8 / 10 (80)	3.5 (1 to NA)	0.93 (0.5 to 1.73)	.734
≥12 months	93 / 118 (78.8)	5.5 (3.6 to 6.4)	43 / 52 (82.7)	3.6 (2.5 to 5.2)	0.83 (0.63 to 1.07)	

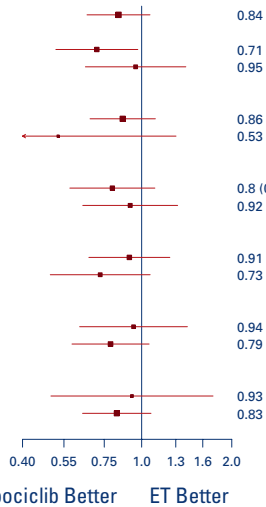

FIG 3. Forest plot of PFS according to stratification factors and baseline characteristics. ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HR, hazard ratio; NA, not applicable; PFS, progression-free survival.

was 41.9% (95% CI, 33.5 to 50.7) in the palbociclib plus ET arm and 27.4% (95% CI, 16.9 to 40.2) in the ET-alone arm (Data Supplement, Table S3). In addition, the difference between groups in terms of CBR estimated with odds ratio was 0.62 (95% CI, 0.38 to 0.98, $P = .044$).

Safety

Median relative dose intensity was 100.0% for ET in both arms and 95.6% (IQR, 86.8-99.6) for palbociclib in the palbociclib plus ET arm. Palbociclib dose was reduced and interrupted according to protocol in 14 (10.4%) and 54 (40.0%) patients, respectively. Overall permanent discontinuation of study treatment due to adverse events occurred in five (3.7%) patients in the palbociclib plus ET arm and in one (1.7%) patient in the ET-alone arm (Data Supplement, Table S4).

Treatment-emergent adverse events (TEAEs) of any grade occurred in 125 (92.6%) patients receiving palbociclib plus ET and in 52 (86.7%) patients receiving ET. Grade ≥3 TEAEs occurred in 64 (47.4%) patients receiving palbociclib plus ET and in six (10.0%) receiving exclusive ET. Except for neutropenia, most TEAEs were of grade 1 or 2. Only patients receiving palbociclib and ET developed grade 3 or 4 hematologic TEAEs, including neutropenia (38.5%), leukopenia (3.7%), anemia (3.0%), and thrombocytopenia (0.7%; Table 2).

Serious TEAEs from any cause occurred in 10 (7.4%) patients in the palbociclib plus ET arm and in two (3.3%) patients in the ET-alone arm (Data Supplement, Table S5). Two of these serious TEAEs were related to palbociclib (pneumonitis and transaminases increased). Two patients died due to unrelated toxicities in the palbociclib plus ET arm (pulmonary hypertension and thrombotic thrombocytopenic purpura). No treatment-related deaths were reported.

DISCUSSION

PALMIRA is the only randomized trial to specifically evaluate the activity of CDK4/6i palbociclib as rechallenge in combination with second-line ET in patients with hormone receptor–positive/HER2-negative ABC who had previously progressed on the same CDK4/6i. However, the study did not meet its primary objective as no significant improvement in PFS was observed for palbociclib as a rechallenge strategy in the second-line setting. The safety profile of study treatments was in line with previous studies and no unexpected safety signals were identified.

Our results are consistent with those reported in the PACE study, a randomized phase II study designed to determine the optimal subsequent line of therapy for patients with hormone receptor–positive/HER2-negative ABC that had progressed on previous treatment with CDK4/6i and an aromatase inhibitor. In the PACE study, a total of 220 patients were randomly assigned (1:2:1) to receive fulvestrant, fulvestrant plus palbociclib, or fulvestrant plus palbociclib and avelumab.[23,27] The study determined that combining palbociclib with fulvestrant after progression on previous CDK4/6i (90.0% palbociclib) did not prolong PFS compared with fulvestrant (4.6 *v* 4.8 months, HR, 1.11 [90% CI, 0.79 to 1.55]; two-sided $P = .62$). Taken together, the PALMIRA and PACE studies demonstrate that the strategy of maintaining the same CDK4/6i after progression, at least with palbociclib, is not an effective approach.

TABLE 2. Summary of TEAEs by Maximum Severity Affecting At Least 10% or Grade ≥4 (safety analysis)

	ET + Palbociclib (n = 135), No. (%)				ET (n = 60), No. (%)		
TEAE	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4
Any	125 (92.6)	54 (40.0)	8 (5.9)	2 (1.5)	52 (86.7)	6 (10.0)	0 (0)
Hematologic	81 (60)	47 (34.8)	6 (4.4)	1 (0.7)	8 (13.3)	0 (0)	0 (0)
Neutropenia	71 (52.6)	46 (34.1)	6 (4.4)	0 (0)	1 (1.7)	0 (0)	0 (0)
Anemia	25 (18.5)	4 (3.0)	0 (0)	0 (0)	5 (8.3)	0 (0)	0 (0)
Leukopenia	14 (10.4)	5 (3.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thrombotic thrombocytopenic purpura	1 (0.7)	0 (0)	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)
Nonhematologic	109 (80.7)	12 (8.9)	2 (1.5)	1 (0.7)	50 (83.3)	6 (10.0)	0 (0)
Fatigue	37 (27.4)	0 (0)	0 (0)	0 (0)	14 (23.3)	0 (0)	0 (0)
Arthralgia	23 (17.0)	2 (1.5)	0 (0)	0 (0)	7 (11.7)	0 (0)	0 (0)
Nausea	16 (11.9)	0 (0)	0 (0)	0 (0)	7 (11.7)	0 (0)	0 (0)
GGT increased	6 (4.4)	3 (2.2)	1 (0.7)	0 (0)	1 (1.7)	0 (0)	0 (0)
Colitis ischemic	1 (0.7)	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
Acidosis	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary hypertension	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)

NOTE. Two patients died due to unrelated toxicities (pulmonary hypertension plus acidosis and thrombotic thrombocytopenic purpura).
Abbreviations: ET, endocrine therapy; GGT, gamma-glutamyl transferase; TEAEs, treatment-emergent adverse events.

Conversely, the randomized double-blind phase II MAINTAIN trial explored the role of ribociclib versus placebo with fulvestrant or exemestane in patients progressing on a CDK4/6i that was mostly palbociclib (84.0%). The study included a slightly more pretreated population; 18% of patients had received more than one previous line of ET and 9% one pervious line of chemotherapy for advanced disease. The combination of ribociclib plus ET led to a statistically significant improvement in PFS compared with ET plus placebo (5.3 *v* 2.8 months, HR, 0.57 [95% CI, 0.39 to 0.95]; $P = .006$). Subgroup analysis suggested a similar benefit independently of the preceding CDK4/6i, but only 14 patients had received ribociclib as the previous line of treatment.[24] Following the findings from the MAINTAIN, the phase III postMONARCH trial provides additional insights into the potential benefit of the CDK4/6i rechallenge. This study investigated the efficacy of abemaciclib in combination with fulvestrant in patients with hormone receptor–positive/HER2-negative ABC who had previously progressed on a CDK4/6i and ET. Notably, 59% of patients had received previous treatment with palbociclib. The study demonstrated a significant improvement in PFS with the combination therapy compared with placebo (HR, 0.73 [95% CI, 0.57 to 0.95]; $P = .01$). Specifically, the median investigator-assessed PFS was 6.0 months (95% CI, 5.6 to 8.6) for the combination therapy versus 5.3 months (95% CI, 3.7 to 5.6) for fulvestrant alone. The 6-month PFS rates were 50% and 37%, respectively. This benefit seems to be mostly confined to patients previously treated with palbociclib.[28]

Interestingly, different real-world data studies have also suggested a continued benefit from the CDK4/6i rechallenge strategy. However, they must be interpreted with caution due to potential biases, including small sample size, patient selection, timing since previous CDK4/6i-containing regimen, and the use of a different CDK4/6i, such as abemaciclib or ribociclib after disease progression on previous palbociclib-based populations.[29-31]

The results from the above-mentioned studies raise the possibility for a noncomplete cross resistance in CDK4/6 inhibition. In addition, the ongoing randomized phase III EMBER-3 study is exploring abemaciclib in combination with imlunestrant (a next-generation SERD) as second-line therapy beyond recurrence or progression during or after aromatase inhibitor therapy, administered alone or with a CDK4/6i-based regimen.[26] Recent results indicate that the combination of abemaciclib with imlunestrant significantly improved PFS compared with imlunestrant, regardless of the *ESR1*-mutation status.[32]

The efficacy observed in PALMIRA and PACE studies in the control arm, mainly consisting of fulvestrant, was better than previous reports in other trials that included patients resistant to CDK4/6i therapy (median PFS approximately 2 months).[12,24,33] These results may be caused by differences in previous treatments and clinicopathologic characteristics. PALMIRA included a pure second-line patient population with no resistant criteria to at least one of the two endocrine options, fulvestrant or letrozole. As well, previous treatment with chemotherapy or other ET-based therapies was not allowed in the advanced setting. In the PACE trial, 77.0% of the patients received protocol therapy as second line and 16.0% had been treated with one previous line of chemotherapy for advanced disease. Therefore, although there are slight differences in the patient population between PALMIRA and PACE, both trials included a less pretreated patient population than other studies.[27,34,35]

Identifying clinical and molecular predictors of endocrine and CDK4/6i sensitivity is imperative for treatment decision in the clinic. Two biomarkers, *ESR1* and *PIK3CA*, are already available in the clinic, as both have shown to guide sensitivity to specific treatments after progression on a CDK4/6i-based regimen. Elacestrant as a single agent has provided a substantial gain in *ESR1*-mutated tumors progressing to at least a CDK4/6i-containing regimen.[12] Additionally, two studies conducted in patients with *PIK3CA*-mutated and endocrine-resistant ABC have shown a consistent PFS benefit with the addition of alpelisib, an alpha-specific PI3K inhibitor, to fulvestrant. The cohort of patients pretreated with a CDK4/6i achieved a similar benefit gain than non-pretreated patients. For this reason, the identification of predictors of response to second-line ET with CDK4/6i rechallenge therapy is critical to improve patient selection.[17,18]

In the BioPER study, potential biomarkers related to the efficacy of continuing palbociclib plus ET beyond progression on previous palbociclib-based regimen were explored. All 36 patients underwent a tumor biopsy before palbociclib rechallenge. The presence of baseline low retinoblastoma score, high cyclin E1 score, and *ESR1* mutations were all associated with a worse outcome, and a signature that included these biomarkers strongly predicted worse prognosis.[22]

The duration of the CDK4/6i regimen in the metastatic setting has been identified as a potential clinical marker. A subanalysis from PARSIFAL-Long identified that patients with a PFS ≥12 months during treatment with CDK4/6i had a much better OS than patients who progressed within a year of treatment, namely 81.5 and 24.0 months, respectively. Similarly, in the EMERALD study, a PFS ≥12 months on a CDK4/6i was strongly predictive for subsequent sensitivity to elacestrant among *ESR1*-mutated patients.[36,37]

Interestingly, in the PALMIRA study, up to 80% of patients presented a PFS ≥12 months on previous palbociclib, and we identified a higher difference in PFS in favor of rechallenge of palbociclib with ET.

In conclusion, palbociclib rechallenge did not significantly improve median PFS when combined with second-line ET in patients with hormone receptor–positive/HER2-negative ABC who had immediately progressed on previous palbociclib-based therapy. A planned biomarker analysis may help identify which patients are more likely to benefit from this therapeutic approach.

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DISCLAIMER

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REFERENCES

1. Cardoso F, Costa A, Senkus E, et al: 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). Ann Oncol 28:3111, 2017
2. Hortobagyi GN, Stemmer SM, Burris HA, et al: Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 375:1738-1748, 2016
3. Finn RS, Martin M, Rugo HS, et al: Palbociclib and letrozole in advanced breast cancer. N Engl J Med 375:1925-1936, 2016
4. Tripathy D, Im SA, Colleoni M, et al: Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): A randomised phase 3 trial. Lancet Oncol 19:904-915, 2018
5. Goetz MP, Toi M, Campone M, et al: MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 35:3638-3646, 2017
6. Cristofanilli M, Turner NC, Bondarenko I, et al: Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): Final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 17:425-439, 2016

7. Slamon DJ, Neven P, Chia S, et al: Phase III randomized study of ribociclib and fulvestrant in hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: MONALEESA-3. J Clin Oncol 36:2465-2472, 2018
8. Sledge GW, Toi M, Neven P, et al: MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2− advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 35:2875-2884, 2017
9. Sledge GW, Toi M, Neven P, et al: The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor–positive, ERBB2-negative breast cancer that progressed on endocrine therapy—MONARCH 2: A randomized clinical trial. JAMA Oncol 6:116-124, 2020
10. Slamon DJ, Neven P, Chia S, et al: Overall survival with ribociclib plus fulvestrant in advanced breast cancer. N Engl J Med 382:514-524, 2020
11. Llombart-Cussac A, Pérez-García JM, Bellet M, et al: Fulvestrant-palbociclib vs letrozole-palbociclib as initial therapy for endocrine-sensitive, hormone receptor–positive, ERBB2-negative advanced breast cancer: A randomized clinical trial. JAMA Oncol 7:1791-1799, 2021
12. Bidard FC, Kaklamani VG, Neven P, et al: Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the randomized phase III EMERALD trial. J Clin Oncol 40:3246-3256, 2022
13. Oliveira M, Rugo HS, Howell SJ, et al: Capivasertib and fulvestrant for patients (pts) with aromatase inhibitor (AI)-resistant HR+/HER2- advanced breast cancer (ABC): Subgroup analyses from the phase 3 CAPItello-291 trial. Ann Oncol 8:101223, 2023 (1supp1_4)
14. Bardia A, Hurvitz SA, DeMichele A, et al: Phase I/II trial of exemestane, ribociclib, and everolimus in women with HR+/HER2− advanced breast cancer after progression on CDK4/6 inhibitors (TRINITI-1). Clin Cancer Res 27:4177-4185, 2021
15. Baselga J, Campone M, Piccart M, et al: Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. N Engl J Med 366:520-529, 2012
16. Yardley DA, Noguchi S, Pritchard KI, et al: Everolimus plus exemestane in postmenopausal patients with HR+ breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther 30: 870-884, 2013
17. André F, Ciruelos E, Rubovszky G, et al: Alpelisib for *PIK3CA*-mutated, hormone receptor–positive advanced breast cancer. N Engl J Med 380:1929-1940, 2019
18. Rugo HS, Lerebours F, Ciruelos E, et al: Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): One cohort of a phase 2, multicentre, open-label, non-comparative study. Lancet Oncol 22:489-498, 2021
19. Turner NC, Oliveira M, Howell SJ, et al: Capivasertib in hormone receptor–positive advanced breast cancer. N Engl J Med 388:2058-2070, 2023
20. Bardia A, Aftimos P, Bihani T, et al: EMERALD: Phase III trial of elacestrant (RAD1901) vs endocrine therapy for previously treated ER+ advanced breast cancer. Future Oncol 15:3209-3218, 2019
21. Bidard FC, Hardy-Bessard AC, Dalenc F, et al: Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): A randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 23:1367-1377, 2022
22. Albanell J, Peréz-García JM, Gil-Gil M, et al: Palbociclib rechallenge for hormone receptor-positive/human epidermal growth factor receptor-negative advanced breast cancer: Findings from the phase II BioPER trial. Clin Cancer Res 29:67-80, 2023
23. Mayer EL, Ren Y, Wagle N, et al: Abstract GS3-06: GS3-06 palbociclib after CDK4/6i and endocrine therapy (PACE): A randomized phase II study of fulvestrant, palbociclib, and avelumab for endocrine pre-treated ER+/HER2− metastatic breast cancer. Cancer Res 83:GS3-06, 2023 (supp1 5)
24. Kalinsky K, Accordino MK, Chiuzan C, et al: Randomized phase II trial of endocrine therapy with or without ribociclib after progression on cyclin-dependent kinase 4/6 inhibition in hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer: MAINTAIN trial. J Clin Oncol 41:4004-4013, 2023
25. Kalinsky K, Layman RM, Kaufman PA, et al: postMONARCH: A phase 3 study of abemaciclib plus fulvestrant versus placebo plus fulvestrant in patients with HR+, HER2-, metastatic breast cancer following progression on a CDK4 & 6 inhibitor and endocrine therapy. J Clin Oncol 40, 2022 (suppl 16; abstr TPS1117)
26. Jhaveri K, Harbeck N, Aftimos P, et al: Abstract OT2-11-01: EMBER-3: A randomized phase 3 study of LY3484356, a novel, oral selective estrogen receptor degrader vs investigator's choice of endocrine therapy of either fulvestrant or exemestane, in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer previously treated with endocrine-based therapy. Cancer Res 82:OT2-11-01, 2022 (supp1 4)
27. Mayer EL, Ren Y, Wagle N, et al: Pace: A randomized phase II study of fulvestrant, palbociclib, and avelumab after progression on cyclin-dependent kinase 4/6 inhibitor and aromatase inhibitor for hormone receptor–positive/human epidermal growth factor receptor–negative metastatic breast cancer. J Clin Oncol 42:2050-2060, 2024
28. Kalinsky K, Bianchini G, Hamilton EP, et al: Abemaciclib plus fulvestrant vs fulvestrant alone for HR+, HER2- advanced breast cancer following progression on a prior CDK4/6 inhibitor plus endocrine therapy: Primary outcome of the phase 3 postMONARCH trial. JCO 42, 2024 (17 supp1; abstr LBA1001)
29. Wander SA, Han HS, Zangardi ML, et al: Clinical outcomes with abemaciclib after prior CDK4/6 inhibitor progression in breast cancer: A multicenter experience. J Natl Compr Cancer Netw 19:1-8, 2021
30. Martin JM, Handorf EA, Montero AJ, et al: Systemic therapies following progression on first-line CDK4/6-inhibitor treatment: Analysis of real-world data. Oncologist 27:441-446, 2022
31. Samuel Eziokwu A, Varella L, Lynn Kruse M, et al: Real-world outcomes of cyclin-dependent kinase inhibitors continued beyond first disease progression in hormone receptor-positive metastatic breast cancer. Clin Breast Cancer 21:205-209, 2021
32. Jhaveri KL, Neven P, Casalnuovo ML, et al: Imlunestrant with or without abemaciclib in advanced breast cancer. N Engl J Med 392:1189-1202, 2024
33. Lindeman GJ, Fernando TM, Bowen R, et al: VERONICA: Randomized phase II study of fulvestrant and venetoclax in ER-positive metastatic breast cancer post-CDK4/6 inhibitors—Efficacy, safety, and biomarker results. Clin Cancer Res 28:3256-3267, 2022
34. Llombart Cussac A, Medioni J, Colleoni MA, et al: Palbociclib rechallenge in hormone receptor (HR)[+]/HER2[-] advanced breast cancer (ABC). PALMIRA trial. Ann Oncol 30:v141, 2019
35. Mayer EL, Wander SA, Regan MM, et al: Palbociclib after CDK and endocrine therapy (PACE): A randomized phase II study of fulvestrant, palbociclib, and avelumab for endocrine pre-treated ER+/HER2- metastatic breast cancer. J Clin Oncol 36, 2018 (supp1 15; abstr TPS1104)
36. Bardia A, Cortés J, Bidard FC, et al: Elacestrant in ER+, HER2− metastatic breast cancer with *ESR1*-mutated tumors: Subgroup analyses from the phase III EMERALD trial by prior duration of endocrine therapy plus CDK4/6 inhibitor and in clinical subgroups. Clin Cancer Res 30:4299-4309, 2024
37. Llombart Cussac A, Pérez-García JM, Bellet M, et al: PARSIFAL-LONG: Extended follow-up of hormone receptor-positive/HER2-negative advanced breast cancer patients treated with fulvestrant and palbociclib vs. letrozole and palbociclib in the PARSIFAL study. Presented at the 2023 San Antonio Breast Cancer Symposium December 4-9, 2023 Abstract RF01-03.

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Second-Line Endocrine Therapy With or Without Palbociclib Rechallenge in Patients With Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: PALMIRA Trial

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