Treatment Patterns and Outcomes Associated With Palbociclib Plus Letrozole for Postmenopausal Women With HR$^+$/HER2$^-$ Advanced Breast Cancer Enrolled in an Expanded Access Program

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Abstract

A retrospective chart review of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer receiving palbociclib in combination with letrozole (as part of an expanded access program) in the United States suggested that most patients derived benefit from this treatment despite having received multiple prior treatment lines for metastatic disease.

Purpose: To evaluate treatment patterns and clinical outcomes of patients who received palbociclib in combination with letrozole in any line of therapy for treatment of hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer in an expanded access program (EAP) in the United States. **Patients and Methods:** A retrospective chart review study was conducted of patients previously enrolled in the palbociclib EAP. Complete data from time of initial diagnosis of metastatic breast cancer until date of chart abstraction were obtained. Clinical outcomes as assessed by site investigators included clinical benefit rate, progression-free survival, and overall survival. Survival was descriptively assessed using Kaplan-Meier methods. **Results:** Of 238 patients enrolled in the EAP, data from 126 patients were included. Median age was 62.5 years at EAP enrollment; 25% had de novo metastatic disease. Visceral disease was present in 71% of patients. The disease of most patients was heavily pretreated; nearly 60% of patients had received 3 or more prior lines for metastatic disease before initiating palbociclib + letrozole therapy. Most patients (87%) had received prior endocrine therapy, and 68% had received prior chemotherapy for metastatic disease. Patients with prior endocrine therapy for metastatic disease had a clinical benefit rate of 30%, while those with prior chemotherapy had a 26% clinical benefit rate. Patients receiving 2 or more prior lines had 6- and 12-month progression-free survival rates of 35% and 21%, respectively, and 12- and 24-month overall survival rates of 62% and 35%, respectively. **Conclusion:** Most patients derived benefit from palbociclib + letrozole treatment despite having received multiple prior treatment lines for metastatic disease.

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Introduction

Breast cancer was newly diagnosed in an estimated 252,710 persons in the United States in 2017 and remains one of the most commonly diagnosed types of cancer.[1] Most breast cancers in postmenopausal women are hormone sensitive and usually of estrogen receptor (ER)-positive phenotype.[2] The age-standardized

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incidence of breast cancer in the United States is estimated to be 92.9 per 100,000 persons.[3] Metastatic breast cancer (mBC) is incurable with current therapies and has an estimated 5-year survival rate of 27%.[1]

Recent advances in understanding molecular heterogeneity and irregular oncogenic pathways affecting cancer cell survival and growth have led to the development of new classes of targeted therapies that can provide benefit to certain subgroups of cancer patients. Approximately 70% of invasive breast cancers are hormone receptor (HR) positive (ie, ER^+ and/or progesterone receptor positive).[4] Treatment for postmenopausal women with HR^+ mBC usually begins with endocrine-based therapy. Before US Food and Drug Administration approval of palbociclib, a cyclin-dependent kinase (CDK) 4/6 inhibitor, the standard of care for postmenopausal women with locally advanced or metastatic HR^+, human epidermal growth factor receptor 2 (HER2)-negative breast cancer (in the absence of visceral crisis) typically included initial systemic therapy with at least one of the following endocrine treatments: (1) an aromatase inhibitor such as letrozole, anastrozole, or exemestane; (2) a selective ER modulator such as tamoxifen or toremifene; (3) a selective ER down-regulator such as fulvestrant; or (4) a progestin such as megestrol acetate. Some advanced or mBCs may have de novo resistance to endocrine-based treatment and therefore require chemotherapy as first-line treatment.[5-7] Regardless of initial therapy, patients with mBC eventually experience disease progression, representing an ongoing unmet need in this population.

On the basis of results of the PALOMA-1 trial, which evaluated outcomes in patients treated with palbociclib plus letrozole (P+L) versus letrozole alone, palbociclib received breakthrough designation for the treatment of postmenopausal women with $ER^+/HER2^-$ mBC as initial endocrine-based therapy.[8] In PALOMA-1, duration of median progression-free survival (PFS) was 20.2 months in the P+L arm versus 10.2 months in the letrozole-alone arm.[9] An expanded access program (EAP) was opened in the United States in September 2014 to provide access to palbociclib (in combination with letrozole) in advance of commercial availability. After Food and Drug Administration approval of palbociclib in February 2015, the EAP was closed, and patients were able to continue P+L treatment using commercial supply at the discretion of the treating physician. A total of 238 patients from 18 sites across the United States were enrolled in the EAP, and safety data were collected as part of the protocol. Safety findings from the original EAP study have been previously reported.[10]

In the present study, we retrospectively collected and analyzed long-term follow-up data on a subset of the EAP enrollees to understand treatment patterns and clinical outcomes. Outcome data on P+L (from the clinical studies) were previously limited to first-line treatment; the present study thus addresses this important data gap while also providing additional insight on the treatment history of patients enrolled in the EAP. To address this objective, we assessed the enrollees' long-term treatment patterns, as well as their P+L clinical outcomes including PFS, overall survival (OS), objective response rate, and clinical benefit rate (CBR).

Patients and Methods

Study Design

This study was a noninterventional retrospective medical record review conducted in a subset of enrollees in the palbociclib EAP. The retrospective analysis was approved by the local institutional review boards of individual sites with a waiver of consent. All data were collected via a customized electronic data collection form. The collected data spanned the period from the patient's initial diagnosis of breast cancer through the end of available follow-up (on or before April 30, 2016) or death, whichever occurred first. The study was composed of the following 3 distinct observation periods:

1. Period before enrollment in the EAP (before September 2014): beginning with the patient's initial diagnosis of breast cancer through the study index date (defined as enrollment date into the EAP).
2. Period during treatment with P+L as part of the EAP (from September 2014 through February 2015): beginning with the patients' enrollment in the EAP (index date) through the patients' disenrollment from the EAP.
3. Period after the EAP (from March 2015 through April 2016): beginning with the patient's disenrollment from the EAP through the end of follow-up or death, whichever occurred first. For some patients, the post-EAP period was composed of time periods on multiple therapies, including therapies used after discontinuation of P+L, as follows: a period while the patient continued on P+L using the commercial supply of palbociclib; and a period after discontinuation of P+L.

Patient Selection

Medical records of patients with $HR^+/HER2^-$ mBC from sites that participated in the EAP were eligible for abstraction. Medical record abstraction was open to all EAP sites and included any sites that were available and willing to participate in the present follow-on study; in this regard, no a priori selection was conducted among the original EAP sites. The EAP used inclusion criteria similar to those used in the PALOMA-1/2 studies, with the exception that patients were allowed to have received any number of prior systemic therapies (except for CDK inhibitors) for advanced or mBC. Basic inclusion criteria consisted of women aged 18 years or older, postmenopausal, with proven diagnosis of advanced $HR^+/HER2^-$ (per local laboratory criteria) adenocarcinoma of the breast (locoregionally recurrent or metastatic disease). Detailed inclusion and exclusion criteria for the EAP are available at ClinicalTrials.gov (NCT02142868).

Study Measures

Patient Characteristics. Patient characteristics were abstracted directly from the medical record, including age at EAP enrollment, ethnic origin, insurance type, and vital status (alive or dead at the time of record abstraction). Background clinical characteristics noted at the time of initial breast cancer diagnosis included disease

stage, tumor grade, ER status, and progesterone receptor status. Additional patient characteristics were noted at the time of EAP enrollment, including number and sites of metastases, Eastern Cooperative Oncology Group performance status, chronic comorbidities (based on the Charlson comorbidity index[11]), and types of cancer-directed treatment received for advanced or metastatic disease before EAP enrollment.

Treatment Patterns. Treatment pattern data that were collected focused on the period from EAP enrollment through last available follow-up, and for some patients included a period after discontinuation of P+L therapy, when available. Specific variables collected included total duration of P+L treatment, including reasons for final P+L discontinuation if the patient was no longer receiving therapy at last follow-up, and prevalence and timing of P+L dosing changes. Among patients who discontinued P+L treatment before last available follow-up, information was collected on any additional systemic therapies initiated, including the regimens prescribed and duration of therapy.

Clinical Outcomes. Several clinical outcomes associated with P+L treatment were recorded. Tumor response and progression were evaluated on the basis of physician assessments carried out according to local practice. Formal response criteria typically used in prospective trials, such as Response Evaluation Criteria in Solid Tumors (RECIST), were not used. Response measurements included objective response rate, defined as the proportion of patients with either complete response or partial response, and CBR, defined as the proportion of patients with complete response, partial response, or stable disease for at least 24 weeks. PFS was calculated as time (months) from P+L initiation at EAP enrollment to first clinician-documented progression, start of a new therapy line (if patients discontinued palbociclib due to disease progression as the reason for discontinuation), or death due to any cause, whichever occurred first. If a patient died or initiated a new therapy line on a date more than 24 weeks after the final palbociclib dose, then the patient was censored at that date (last palbociclib dose plus 24 weeks) and was not counted as having a progression event. OS was calculated as time (months) from P+L initiation at EAP enrollment to the earliest of death or end of follow-up. For OS measurement, patients were censored if they were still alive at the end of the follow-up period.

Statistical Analyses

All analyses were descriptive and exploratory in nature, and were conducted by SAS 9.4 statistical software (SAS Institute, Cary, NC). Clinical response and survival outcomes were stratified by various levels and types of exposure to prior treatments for advanced or metastatic disease before initiation of P+L. No formal statistical tests comparing outcomes by prior treatment exposure were conducted. Results are presented as frequencies, proportions, means, and other summary measures of categorical distributions as appropriate. All event time measures, including PFS and OS, were estimated using the Kaplan-Meier method.

Results

Patient Characteristics

A total of 126 patients (52.9% of the original EAP population) were included in the study. Of the original 18 EAP study sites, 6 participated in this study: 3 cancer centers, 2 outpatient clinics, and 1 academic teaching hospital (Supplemental Table 1 in the online version). Mean (standard deviation [SD]) past-year mBC caseload per site was 225.0 (183.7) patients. Data on various demographic and other background characteristics for patients included in the study sample are presented in Table 1. Among these patients, mean (SD) age at EAP enrollment was 62.5 (12.2) years, with more than 90% of patients aged at least 45 years. Mean (SD) duration of available follow-up from initial breast cancer diagnosis was 160.5 (101.6) months; mean (SD) follow-up duration was 56.5 (37.5) months from mBC diagnosis and 14.2 (8.0) months from EAP enrollment. A total of 59 patients (46.8%) had died at the time of last available follow-up.

More than 90% of patients had an Eastern Cooperative Oncology Group status of 0 or 1 at EAP enrollment (Supplemental Figure 1 in the online version). The most common comorbidities present at EAP enrollment were hypertension (27.8%) and diabetes (5.6%), while 54.8% had none of the comorbidities examined (Supplemental Figure 1 in the online version). The most common sites of distant metastasis at EAP enrollment were bone (77.8%), liver (46.0%), lymph nodes (43.7%), and lung (25.4%) (Supplemental Figure 2 in the online version). A substantially higher proportion of patients had visceral metastases (72.2%) than had nonvisceral metastases (27.8%). Approximately 55% of patients had both bone metastases and visceral disease.

More than 90% of patients received some form of cancer-directed treatment (systemic treatment and/or other therapy, such as radiation) for metastatic disease before EAP enrollment. The most common treatment modality for metastatic disease before EAP enrollment was endocrine therapy (with or without chemotherapy), with only 2.4% of patients receiving chemotherapy alone (Table 1). Overall, 109 patients (86.5%) received prior endocrine therapy and 85 patients (67.5%) received prior chemotherapy. Most patients had 3 or more lines of systemic treatment (58.7%) for metastatic disease before EAP enrollment. In the total sample, 112 patients (88.9%) received at least one line of systemic therapy before EAP enrollment, 94 (74.6%) received at least 2 prior lines of therapy, and 74 (58.7%) received at least 3 prior lines of therapy (Table 1).

Among patients receiving at least one line of treatment for metastatic disease before EAP enrollment (n = 112), endocrine monotherapies (52.7% combined), endocrine therapies in combination with chemotherapy (17.9%), and chemotherapy alone (single agent or combination chemotherapies) (17.0%) were the most common regimens observed for first-line treatment (Supplemental Table 2 in the online version). Median first-line pre-EAP treatment duration was 10.6 months across all regimens combined (n = 112). Endocrine-based treatment (either alone or in combination with other agents) was also the predominant treatment selection in second- and third-line pre-EAP therapy, but among patients receiving a fourth line of pre-EAP treatment, chemotherapy-based regimens were most common.

Table 1 Patient Characteristics

Characteristic	Value
Total patients	126 (100.0%)
Age at EAP Enrollment (Y)	
Mean (SD)	62.5 (12.2)
Median	62.5
Min, max	37, 89
Age Distribution	
36-45 y	11 (8.7%)
46-55 y	29 (23.0%)
56-65 y	29 (23.0%)
≥65 y	57 (45.2%)
Ethnic Origin	
White	105 (83.3%)
Black or African American	11 (8.7%)
Asian	4 (3.2%)
Hispanic or Latino	1 (0.8%)
Unknown	5 (4.0%)
Primary Insurance Plan	
Medicaid	1 (0.8%)
Medicare	33 (26.2%)
Commercial	44 (34.9%)
Unknown	48 (38.1%)
Duration of Follow-up (Months)[a]	
From initial BC diagnosis (among those with early-stage diagnosis[b]) (n = 94)	
Mean (SD)	160.5 (101.6)
Median	144.5
Min, max	23.5, 465.7
From mBC diagnosis (n = 126)	
Mean (SD)	56.5 (37.5)
Median	50.9
Min, max	2.5, 235.1
From EAP enrollment (n = 126)	
Mean (SD)	14.2 (8.0)
Median	15.0
Min, max	0.9, 27.0
Time (Mos) From Initial BC Diagnosis to First Diagnosis of or Progression to Metastatic Disease (Among Those With Early-Stage Diagnosis[b]) (N = 94)	
Mean (SD)	103.3 (86.0)
Median	81.8
Min, max	1.0, 407.2
Vital Status at Last Available Medical Record/Follow-up	
Alive	48 (38.1%)
Deceased	59 (46.8%)
Unknown	19 (15.1%)
Type of Cancer-Directed Treatment Received for Advanced or Metastatic Disease Before EAP Enrollment	
Chemotherapy only	3 (2.4%)
Endocrine therapy only	27 (21.4%)
Both chemotherapy and endocrine therapy	82 (65.1%)
No treatment	11 (8.7%)
Radiotherapy	1 (0.8%)
Unknown	2 (1.6%)
No. of Systemic Therapy Lines Received For Metastatic Disease Before EAP Enrollment	
0	14 (11.1%)
1	18 (14.3%)
2	20 (15.9%)
3 or more	74 (58.7%)

Abbreviations: BC = breast cancer; EAP = expanded access program; mBC = metastatic breast cancer; SD = standard deviation.
[a]Follow-up duration calculated as number of months between date of interest (initial breast cancer diagnosis—ie, study index date) and last available medical record or record in EAP.
[b]Local, regional, and unknown stage at initial breast cancer diagnosis.

Treatment Patterns

Mean time to P+L initiation after EAP enrollment was less than a week (Supplemental Table 3 in the online version). For all patients, the initial palbociclib dose was 125 mg; the initial letrozole dose was 2.5 mg for all but 2 patients (for these 2 patients, the initial dose was 1.3 mg). Among the 126 patients reviewed here, 100 patients had discontinued palbociclib at the time of chart abstraction, with a majority (84.0%) of these discontinuations due to disease progression; 2% of discontinuations were due to toxicities/side effects, 5% were due to patient decision, 1% were due to completion of planned treatment with no further anticipated benefit, 5% were due to death and 3% were due to other reasons. Among these 100 patients, 76 initiated a new treatment regimen after discontinuing P+L, and the remainder of patients either survived to follow-up end with no other treatments initiated or died before another treatment could be initiated. Among patients with no evidence of palbociclib discontinuation (n = 26), 12 (46.2%) were still receiving treatment at last follow-up. More than one third of all patients (34%) had at least one dose reduction episode, with neutropenia (83.7%) and fatigue (11.6%) being the most commonly cited reasons for dose reductions. Kaplan-Meier estimated median time to first dose reduction was 9.1 months. Almost half (47.6%) of all patients in the study had more than one treatment interruption episode, with neutropenia (75.0%) and leukopenia (11.7%) cited as the most common reasons for treatment interruption; median duration of treatment interruption was 7 days.

As noted previously, among the 100 patients who discontinued P+L therapy, 76 received additional systemic therapy after last P+L dose (Table 2). Across all further lines of therapy in the post-P+L setting, chemotherapy regimens (single agents or combination chemotherapies) were the predominant treatment selection. Across all regimens observed, median duration of the first additional treatment regimen after P+L was 3.3 months; duration of therapy steadily decreased with each subsequent regimen after P+L completion/discontinuation.

Clinical Outcomes

The CBR for all P+L recipients, defined as having a best response of complete response, partial response, or stable disease for

Table 2 Additional Treatment Regimens After P+L Completion/Discontinuation

First Additional Therapy After P+L (76, 100%)			Second Additional Therapy After P+L (46, 100%)			Third Additional Therapy After P+L (21, 100%)			Fourth Additional Therapy After P+L 8 (10%)		
Chemotherapy (single agent or combination)	52	68.4%	Chemotherapy (single agent or combination)	35	76.1%	Chemotherapy (single agent or combination)	19	90.5%	Chemotherapy (single agent or combination)	6	75.0%
Endocrine + chemotherapy	16	21.1%	Endocrine + chemotherapy	9	19.6%	Endocrine + chemotherapy	1	4.8%	Endocrine + chemotherapy	2	25.0%
Endocrine therapy			Endocrine therapy			Endocrine therapy					
Combination[a]	2	2.6%	Tamoxifen	1	2.2%	Fulvestrant	1	4.8%	—		
Exemestane	2	2.6%	Fulvestrant	1	1.2%	—			—		
Tamoxifen	2	2.6%	—			—			—		
Fulvestrant	1	1.3%	—			—			—		
Letrozole	1	1.3%	—			—			—		
Median treatment duration (mos), all regimens	3.3		Median treatment duration (mos), all regimens	3.0		Median treatment duration (mos), all regimens	2.4		Median treatment duration (mos), all regimens	1.9	

Includes only patients who discontinued P+L therapy and received treatments after P+L (n = 100). Line of treatment varies for each patient depending on last treatment line received.
Abbreviation: P+L = palbociclib + letrozole.
[a]Combination regimen including two or more endocrine-based therapies (without chemotherapy).

Table 3 Best Clinical Response to Palbociclib + Letrozole Therapy, by Type of Prior (Pre-EAP) Systemic Therapy for Metastatic Disease

Response	All Patients (N = 126)	Prior (Pre-EAP) Endocrine Therapy Exposure		Prior (Pre-EAP) Chemotherapy Exposure	
		Yes (N = 109)	No (N = 17)	Yes (N = 85)	No (N = 41)
CR	2 (1.6%)	0	2 (11.8%)	0	2 (4.9%)
PR	5 (4.0%)	2 (1.8%)	3 (17.6%)	1 (1.2%)	4 (9.8%)
Stable disease ≥ 24 weeks	35 (27.8%)	31 (28.4%)	4 (23.5%)	21 (24.7%)	14 (34.1%)
Stable disease < 24 weeks	27 (21.4%)	22 (20.2%)	5 (29.4%)	16 (18.8%)	11 (26.8%)
No response; progression of disease	45 (35.7%)	43 (39.4%)	2 (11.8%)	37 (43.5%)	8 (19.5%)
Unknown	12 (9.5%)	11 (10.1%)	1 (5.9%)	10 (11.8%)	2 (4.9%)
Objective response (CR + PR)	7 (5.6%)	2 (1.8%)	5 (29.4%)	1 (1.2%)	6 (14.6%)
Clinical benefit rate (CR + PR + stable disease ≥ 24 weeks)	42 (33.3%)	33 (30.3%)	9 (52.9%)	22 (25.9%)	20 (48.8%)

Clinical response was based on physician assessment per local practice and not per formal criteria such as RECIST.
Abbreviations: CR = complete response; EAP = expanded access program; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

at least 24 weeks, was 33.3% (Table 3). The CBR was higher in patients without prior treatment for metastatic disease regardless of type of therapy. However, patients pretreated with endocrine therapy and/or chemotherapy represented the majority of the study sample (n = 106 and 85, respectively), and the results indicated that many of these patients still benefited from P+L therapy. For example, nearly one third (30.3%) of those pretreated with endocrine therapy experienced clinical benefit. Similarly, in patients receiving prior chemotherapy, who represented more than two thirds of the study sample, more than one quarter benefited from P+L treatment with an estimated CBR of 25.9%. As expected, response rates to P+L treatment decreased as the number of prior therapy lines increased (regardless of therapy type). The CBR was 57.1% for patients with no prior therapy lines, compared to 26.6% for patients with at least 2 prior lines of treatment (Table 4).

During P+L treatment, 98 patients (77.8%) had a progression event and 28 (22.2%) were censored without a progression event. Kaplan-Meier median (95% confidence interval [CI]) PFS after P+L initiation was 4.5 (3.7-6.2) months (Table 5). Median (95% CI) PFS after P+L initiation was almost twice in patients without prior endocrine therapy versus with prior endocrine therapy for metastatic disease in any pre-EAP metastatic treatment line. Similarly, median (95% CI) PFS was almost twice in patients without prior chemotherapy versus with prior chemotherapy exposure in any pre-EAP treatment line for metastatic disease. Among all patients, 46.8% (n = 59) died during the available follow-up period. Using Kaplan-Meier estimation, the median (95% CI) OS from the start of P+L treatment was 21.1 (14.8-not estimable) months; survival rates at 12 and 24 months were 66.2% and 43.5%, respectively. Median OS from P+L initiation did not vary greatly by type of prior treatment received for metastatic disease before EAP enrollment. As noted for clinical response rates, PFS and OS duration decreased with increasing number of prior lines of treatment (Table 6). PFS and OS durations of at least 12 months were reached for a substantial proportion of patients (20.7% and 61.7%, respectively) with at least 2 prior lines of systemic therapy.

Discussion

This study was a retrospective evaluation of medical records of 126 postmenopausal women with $HR^+/HER2^-$ advanced breast cancer using P+L therapy as part of an EAP in the United States. The objectives of the study were to assess treatment patterns and clinical outcomes associated with P+L provided to these EAP enrollees. Because of the observational nature of this study and the limited control of potential confounding, the results presented here are descriptive rather than suggestive of causal relationships and may not be directly comparable to outcomes reported from randomized clinical trials.

Table 4 Best Clinical Response to Palbociclib + Letrozole Therapy, by Number of Prior (Pre-EAP) Systemic Treatment Lines Received for Advanced/Metastatic Disease

Response	No Prior Lines (N = 14)	1 Prior Line (N = 18)	2 or More Prior Lines (N = 94)
CR	2 (14.3%)	0	0
PR	3 (21.4%)	1 (5.6%)	1 (1.1%)
Stable disease ≥ 24 weeks	3 (21.4%)	8 (44.4%)	24 (25.5%)
Stable disease < 24 weeks	4 (28.6%)	4 (22.2%)	19 (20.2%)
No response; progression of disease	1 (7.1%)	4 (22.2%)	40 (42.6%)
Unknown	1 (7.1%)	1 (5.6%)	10 (10.6%)
Objective response (CR + PR)	5 (35.7%)	1 (5.6%)	1 (1.1%)
Clinical benefit rate (CR + PR + stable disease ≥ 24 weeks)	8 (57.1%)	9 (50.0%)	25 (26.6%)

Abbreviations: CR = complete response; EAP = expanded access program; PR = partial response.

Table 5 Survival Outcomes of Palbociclib + Letrozole Therapy, by Type of Prior (Pre-EAP) Systemic Treatment Received for Metastatic Disease

Characteristic	All Patients (N = 126)	Prior (Pre-EAP) Endocrine Therapy Exposure		Prior (Pre-EAP) Chemotherapy Exposure	
		Yes (N = 109)	No (N = 17)	Yes (N = 85)	No (N = 41)
PFS (Mos)					
Patients with progression event	98 (77.8%)	87 (79.8%)	11 (64.7%)	69 (82.2%)	29 (70.7%)
Median (95% CI)	4.5 (3.7-6.2)	4.4 (3.5-5.5)	8.6 (3.5-NE)	3.9 (2.5-5.1)	7.0 (4.2-14.7)
PFS Rates (From K-M Life Table)					
3 mos	65.0%	62.3%	82.4%	57.5%	80.5%
6 mos	42.1%	38.4%	64.7%	35.5%	55.5%
9 mos	30.8%	28.2%	47.1%	26.0%	40.4%
12 mos	27.0%	23.7%	47.1%	19.8%	40.4%
18 mos	20.9%	18.9%	32.3%	14.8%	32.1%
24 mos	12.3%	7.0%	32.3%	—	24.1%
30 mos	—	—	—	—	—
Crude PFS Rates Among Patients With Available Follow-up Through Each Interval					
3 mos	64.3%	61.5%	82.4%	56.5%	80.5%
6 mos	39.7%	35.8%	64.7%	32.9%	53.7%
9 mos	27.0%	23.9%	47.1%	21.2%	39.0%
12 mos	21.4%	18.3%	41.2%	14.1%	36.6%
18 mos	13.5%	12.8%	17.6%	8.2%	24.4%
24 mos	1.6%	0.9%	5.9%	—	4.9%
30 mos	—	—	—	—	—
Overall Survival (Mos)					
Patients with death event	59 (46.8%)	53 (48.6%)	6 (35.3%)	45 (52.9%)	14 (34.1%)
Median time to death among those who died	7.0	7.0	6.3	7.7	6.9
Median (95% CI)	21.1 (14.8-NE)	19.8 (13.9-NE)	— (7.0-NE)	14.9 (12.1-23.5)	— (19.8-NE)
Survival Rates (From K-M Life Table)					
12 mos	66.2%	65.4%	70.6%	62.8%	72.5%
24 mos	43.5%	39.8%	61.8%	31.8%	63.1%
36 mos	—	—	—	—	—
48 mos	—	—	—	—	—

Abbreviations: CI = confidence interval; EAP = expanded access program; K-M = Kaplan-Meier; NE = not estimable; PFS = progression-free survival.

There are limited published data from routine clinical settings on treatment patterns and outcomes in patients treated with P+L for $HR^+/HER2^-$ advanced breast cancer. Evidence from MONARCH 1, which evaluated abemaciclib monotherapy in women with refractory $HR^+/HER2^-$ mBC whose disease had progressed on or after prior endocrine therapy and had one or two chemotherapy regimens for metastatic disease, indicates that CDK4/6 inhibitors may represent a major advance in therapy for refractory $HR^+/HER2^-$ mBC who are pretreated and have poor prognosis.[12] The findings of other previous interventional studies, particularly the PALOMA-1-3 studies,[9,13,14] also help put the results of our study into context. These trials have demonstrated clinical benefit of palbociclib compared to endocrine therapy alone for patients with $HR^+/HER2^-$ mBC in combination with an aromatase inhibitor for first-line endocrine therapy and in combination with fulvestrant in patients who had progressed on or after prior endocrine therapy. Although the patient population characteristics in the present study are generally consistent with those in the PALOMA trials, patients in our study were more heavily pretreated before starting P+L treatment. The patients in the current study were somewhat older, and a greater proportion had visceral metastases and had received chemotherapy for metastatic disease before treatment with P+L. The current EAP study provides observations on the real-world clinical outcomes of patients receiving P+L, particularly in later treatment lines, adding to the body of evidence derived from phase 3 trial populations, thus representing a major strength of this study.

Patients in the EAP still benefited from P+L treatment after having received multiple prior lines of therapy, as evidenced by a 33% CBR and 12- and 24-month survival rates of 66% and 44%, respectively. For patients with prior endocrine exposure for advanced/metastatic disease, 12- and 24-month PFS rates were 23.7% and 7.0%, respectively; 12- and 24-month response rates for patients with no prior endocrine exposure were 47.1% and 32.3%, respectively. Median OS was 19.8 months in patients with prior

Table 6 Survival Outcomes of Palbociclib + Letrozole Therapy, by Number of Prior (Pre-EAP) Systemic Treatment Lines Received for Advanced/Metastatic Disease

Characteristic	No Prior Lines (N = 14)	1 Prior Line (N = 18)	2 or More Prior Lines (N = 94)
PFS (Mos)			
Patients with progression event	8 (57.1%)	15 (83.3%)	75 (79.8%)
Median (95% CI)	13.3 (3.5-NE)	6.3 (4.2-12.6)	3.9 (2.6-5.1)
PFS Rates (From K-M Life Table)			
3 mos	85.7%	83.3%	58.4%
6 mos	71.4%	55.6%	34.8%
9 mos	57.1%	33.3%	26.3%
12 mos	57.1%	33.3%	20.7%
18 mos	39.2%	22.2%	17.7%
24 mos	39.2%	16.7%	—
30 mos	—	—	—
Crude PFS Rates Among Patients With Available Follow-up Through Each Interval			
3 mos	85.7%	83.3%	57.4%
6 mos	71.4%	55.6%	31.9%
9 mos	57.1%	33.3%	21.3%
12 mos	50.0%	33.3%	14.9%
18 mos	21.4%	22.2%	10.6%
24 mos	7.1%	5.6%	—
30 mos	—	—	—
OS (Mos)			
Patients with death event	4 (28.6%)	6 (33.3%)	49 (52.1%)
Median time to death among those who died	6.3	14.5	6.9
Median (95% CI) (from K-M estimation)	(7.0-NE)	(19.8-NE)	15.3 (12.1-23.5)
Survival Rates (From K-M Life Table)			
12 mos	71.4%	83.3%	61.7%
24 mos	0.7143	64.5%	34.6%
36 mos	—	—	—
48 mos	—	—	—

Abbreviations: CI = confidence interval; EAP = expanded access program; K-M = Kaplan-Meier; NE = not estimable; OS = overall survival; PFS = progression-free survival.

endocrine therapy and 14.9 months in patients with prior chemotherapy. These findings further highlight the benefit of treatment with palbociclib combination therapy in $HR^+/HER2^-$ mBC, even in heavily pretreated patients.

Results reported here are subject to several limitations inherent to most retrospective medical record review studies. First, not all patients who participated in the EAP were included as not all elected to participate in this follow-up study. Second, data were entered directly into the electronic data collection form by the treating physicians or delegated clinical research staff based on medical records available at the time of data entry; therefore, the data are potentially subject to inadvertent entry or keying errors. Clinical responses were based on clinician assessment and although published response criteria[15] were provided as guidance in the electronic data collection form, the clinicians were not required to retrospectively apply a specific set of response criteria. Third, assessments of PFS occurred as part of routine clinical practice and not at predetermined time points. It is possible that the participating clinicians assessed PFS at more or less frequent intervals than would otherwise be required in a clinical trial, and progression events may have been identified somewhat earlier or later than they would have been if the patients had been in a clinical trial. For these reasons, findings regarding the endpoints of clinical response and survival, particularly PFS, may not be directly comparable to those observed in clinical trials such as PALOMA-2. Finally, because of the retrospective nature of the study, it was not possible to collect patient-reported data on quality-of-life measures that may have provided useful additional context to the reported findings on clinical outcomes. Prospective studies in this population that include a quality-of-life component should be considered.

Despite these limitations, this study captures detailed clinical, treatment, and outcome data for postmenopausal women with $HR^+/HER2^-$ advanced breast cancer treated with P+L after varying degrees of prior treatment exposure in real-world settings in the United States.

Conclusion

Patients eligible for the current study, by design of the EAP, may have received multiple prior therapy lines for metastatic disease. Studying this population provides unique insight into the real-world clinical outcomes of patients receiving P+L treatment who are older, have more visceral metastases, and are generally more difficult to treat. In our study, patients with fewer prior treatments for advanced or metastatic disease generally obtained better outcomes. Despite having received several prior lines of therapy, patients enrolled in the EAP still benefited from receiving P+L therapy. These findings further highlight the importance and potential benefit of treatment with palbociclib combination therapy in HR^+/$HER2^-$ advanced or mBC.

Clinical Practice Points

- Based on results of the PALOMA-1 trial, palbociclib received breakthrough designation for the treatment of postmenopausal women with ER^+/$HER2^-$ mBC as initial endocrine-based therapy.
- Outcomes data on palbociclib (from the clinical studies) were previously limited to first-line treatment; the present study thus addresses this important data gap while also providing additional insight on the treatment history of patients enrolled in the EAP.
- Patients in the EAP still benefited from P+L treatment after having received multiple prior lines of therapy, as evidenced by a 33% CBR and 12- and 24-month survival rates of 66% and 44%, respectively.
- Our study provides observations on the real-world clinical outcomes of patients receiving P+L, particularly in later treatment lines, adding to the body of evidence derived from phase 3 trial populations, thus representing a major strength of this study.
- Overall, our findings further highlight the benefit of treatment with palbociclib combination therapy in HR^+/$HER2^-$ mBC, even in heavily pretreated patients.

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Disclosure

This study was performed under a research contract between RTI Health Solutions and Pfizer Inc. K.L.D. and S.P.N. are salaried employees of RTI Health Solutions. L.M., M.C., and D.M. are salaried employees of Pfizer Inc. A.B. receives consulting fees from Pfizer, Roche, Lilly, Novartis, Merck, Puma, Eisai, and Sandoz. V.S. has research funding from AbbVie, MedImmune, Novartis, Pfizer, and Puma.

Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2019.04.005.

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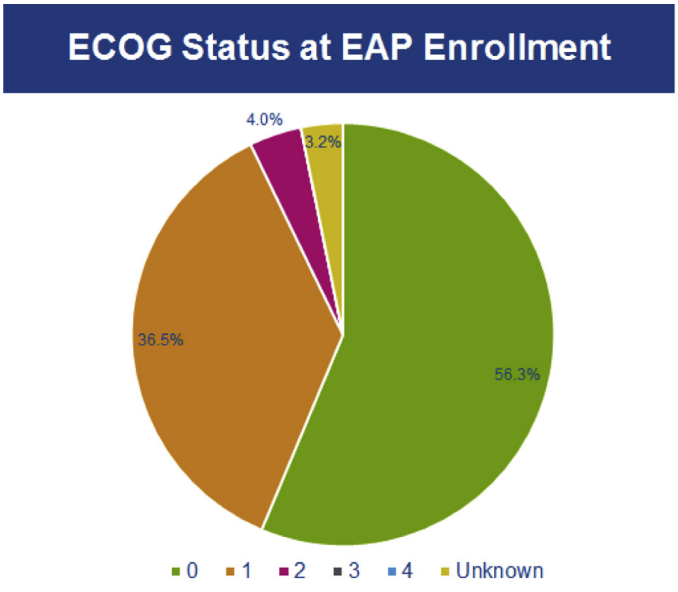
Supplemental Data

Supplemental Figure 1 ECOG Status and Comorbidities at EAP Enrollment. ECOG Status and Most Frequently Occurring Comorbidities in Patients at EAP Enrollment

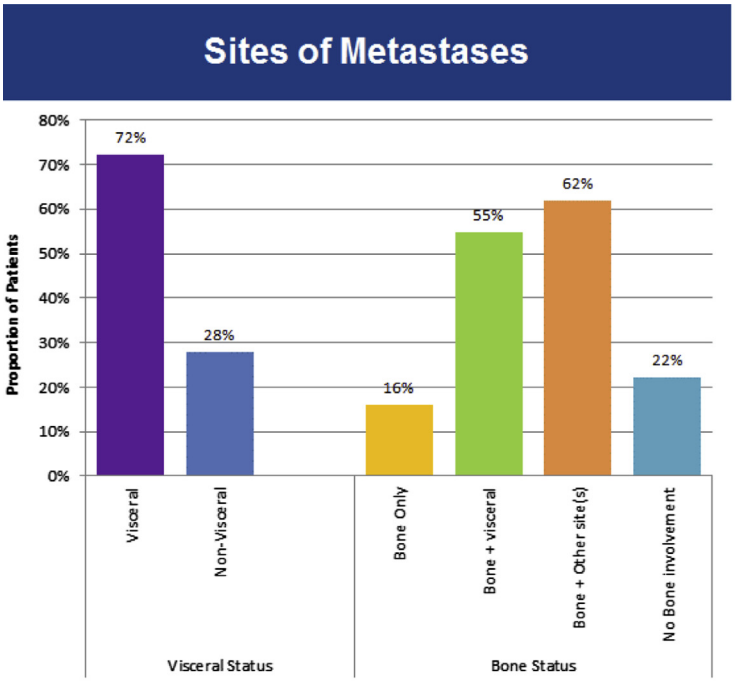


Most Frequently Occurring Comorbidities

Comorbidity	N	%
Hypertension	35	27.8%
Diabetes	7	5.6%
History of pulmonary embolism	4	3.2%
Congestive heart failure	2	1.6%
History of myelosuppression	2	1.6%
Mild liver disease	2	1.6%
Moderate/severe kidney disease	1	0.8%
Other	21	16.7%

Abbreviations: EAP = expanded access program; ECOG = Eastern Cooperative Oncology Group.

Supplemental Figure 2 Sites of Metastases at EAP Enrollment. Shown are Overall Sites of Metastases (eg, Visceral, Bone) and Most Frequent Specific Sites of Metastases in Patients at EAP Enrollment



Most Frequently Occurring Sites

Site	N	%
Bone	98	77.8%
Liver	58	46.0%
Lymph nodes	55	43.7%
Lung	32	25.4%
Pleura	23	18.3%
Skin/soft tissue	12	9.5%
Brain	8	6.3%
Peritoneal	6	4.8%
Adrenal	2	1.6%
Chest Wall	2	1.6%
Mediastinum	2	1.6%
Spleen	2	1.6%

Abbreviation: EAP = expanded access program.

Supplemental Table 1 Site Characteristics

Characteristic	Value
Total sites	6 (100.0%)
Facility Type	
Academic teaching hospital	1 (16.7%)
Nonteaching hospital	0
Cancer center	3 (50.0%)
Outpatient clinic	2 (33.3%)
Metastatic Breast Cancer Caseload (No. of Patients) in Past Year (N = 5)	
Mean (standard deviation)	225.0 (183.7)
Median	200
Min, max	50, 500
Geographic Region	
Northeast	3 (50.0%)
Midwest	1 (16.7%)
South	1 (16.7%)
West	0
Unknown	1 (16.7%)

Site characteristics of 6 expanded access program study sites that participated in this study (3 cancer centers, 2 outpatient clinics, and 1 academic teaching hospital).

Supplemental Table 2 Treatment Regimens for Advanced/Metastatic Disease Before EAP Enrollment

First-Line Therapy (Pre-EAP) (112, 100%)			Second-Line Therapy (Pre-EAP) (94, 100%)			Third-Line Therapy (Pre-EAP) (74, 100%)			Fourth-Line Therapy (Pre-EAP) (47, 100%)		
Anastrazole	*21*	*18.8%*	*Fulvestrant*	*30*	*31.9%*	***Endocrine + chemotherapy***	***25***	***33.8%***	**Chemotherapy (single agent or combination)**	**25**	**53.2%**
Endocrine + chemotherapy	***20***	***17.9%***	***Endocrine + chemotherapy***	***20***	***21.3%***	*Chemotherapy (single agent or combination)*	*18*	*24.3%*	***Endocrine + chemotherapy***	***12***	***25.5%***
Chemotherapy (single agent or combination)	*19*	*17.0%*	*Chemotherapy (single agent or combination)*	*17*	*18.1%*	*Fulvestrant*	*10*	*13.5%*	*Fulvestrant*	*5*	*10.6%*
Letrozole	*16*	*14.3%*	*Letrozole*	*7*	*7.5%*	*Endocrine combination therapy*[a]	*7*	*9.5%*	*Exemestane*	*2*	*4.3%*
Endocrine combination therapy[a]	*14*	*12.5%*	*Endocrine combination therapy*[a]	*7*	*7.5%*	*Anastrazole*	*4*	*5.4%*	*Letrozole*	*1*	*2.1%*
Tamoxifen	*10*	*9%*	*Exemestane*	*5*	*5.3%*	*Letrozole*	*4*	*5.4%*	*Tamoxifen*	*1*	*2.1%*
Exemestane	*6*	*5.4%*	*Anastrozole*	*4*	*4.3%*	*Exemestane*	*3*	*4.1%*	*Endocrine combination therapy*[a]	*1*	*2.1%*
Fulvestrant	*5*	*4.5%*	*Tamoxifen*	*3*	*3.2%*	*Tamoxifen*	*3*	*4.1%*			
Gosereline	*1*	*0.8%*	*Megestrol*	*1*	*1.1%*						
Median treatment duration (mos), all regimens	10.6		Median treatment duration (mos), all regimens	6.6		Median treatment duration (mos), all regimens	5.6		Median treatment duration (mos), all regimens	7.1	

Abbreviation: EAP = expanded access program.
Values in bold represent chemotherapy.
Values in italic represent endocrine therapy.
Values in bold italic represent endocrine + chemotherapy.
[a]Combination regimen including 2 or more endocrine-based therapies (without chemotherapy).

Supplemental Table 3 Palbociclib + Letrozole Treatment Patterns

Characteristic or Pattern	Value
Total patients	126 (100.0%)
Time (Wk) to P+L Initiation After EAP Enrollment	
Mean (SD)	0.9 (0.9)
Median	0.6
Min, max	0.1, 6.9
Primary Reason for Final Discontinuation of P+L Treatment (Among Those Who Discontinued) (N = 100)	
Toxicities/adverse effects	2 (2.0%)
Patient decision	5 (5.0%)
Disease progression	84 (84.0%)
Completion of planned treatment, with no further benefit anticipated	1 (1.0%)
Death	5 (5.0%)
Other	3 (3.0%)
Follow-up Disposition of Patients Without P+L Discontinuation (N = 26)	
Still receiving treatment at last follow-up	12 (46.2%)
Lost to follow-up	14 (53.8%)
Follow-up Disposition of Patients Who Discontinued P+L (N = 100)	
New treatment/line of therapy initiated	76 (76.0%)
Died (before initiation of new treatment)	18 (18.0%)
Survived to follow-up end with no new treatment	6 (6.0%)
Dose reduction or treatment delay/interruption required during course of P+L therapy	70 (55.6%)
Had ≥ 1 dose reduction	43 (34.1%)
No. of dose reductions, mean (SD)	1.2 (0.4)
Reason Reported for Dose Reduction (N = 43)	43 (100.0%)
Adverse event	43 (100.0%)
Neutropenia	36 (83.7%)
Leukopenia	2 (4.7%)
Fatigue	5 (11.6%)
Had ≥ 1 treatment/cycle delay/interruption	60 (47.6%)
No. of delays/interruptions, mean (SD)	1.7 (0.8)
Median duration (d) of delay/interruption	7
Reason Reported for Treatment/Cycle Delay/ Interruption (N = 60)	60 (100.0%)
Adverse event	58 (96.7%)
Neutropenia	45 (75.0%)
Leukopenia	7 (11.7%)
Fatigue	3 (5.0%)
Receipt of palliative surgery	1 (1.7%)
Patients with first P+L dose reduction	43 (34.1%)
Time (Mos) to First P+L Dose Reduction[a]	
Mean (SD)	3.2 (3.8)
Kaplan-Meier Mean (SD)	8.5 (0.7)
Median (95% CI)	9.1 (6.1-13.4)
Proportion With Dose Reduction (From K-M Life Table)	
3 months after initiation	30.6%
6 months after initiation	37.0%
12 months after initiation	62.7%
18 months after initiation	80.1%

Total treatment duration defined as number of months between therapy initiation date and date of final discontinuation of regimen.
Abbreviations: CI = confidence interval; K-M = Kaplan-Meier; P+L = palbociclib + letrozole; SD = standard deviation.
[a]Estimates based on K-M analysis, except where noted for crude mean, which is reported only among patients with event.