NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study Information

Title	Retrospective Assessment of Treatment Patterns and Outcomes Associated with Palbociclib in Combination With Letrozole in Postmenopausal Women With HR+/HER2– Advanced Breast Cancer
Protocol number	A5481064
Version identifier of the final study report	1.0
Date	16 October 2018
EU Post Authorization Study (PAS) register number	EUPAS13869
Active substance	Palbociclib (L01XE33)
Medicinal product	IBRANCE (Palbociclib)
Research question and objectives	The aim of this study is to describe the patient and clinical characteristics, treatment patterns, and clinical outcomes of patients who received palbociclib plus letrozole for the treatment of hormone receptor–positive/human epidermal growth factor receptor 2–negative metastatic breast cancer as part of an expanded access program (EAP). More specifically, data from a medical record review were used to address the following objectives: ▪ Describe the demographic and clinical characteristics of patients. ▪ Evaluate treatment patterns, including safety of treatment with palbociclib plus letrozole (duration of therapy, cycle delays or dose interruptions, dose

	reductions and discontinuation of palbociclib) including reasons for these treatment events to the extent documented in the charts, ▪ Receipt of supportive care medications while receiving palbociclib plus letrozole, and additional therapies received for metastatic breast cancer before and after palbociclib plus letrozole. ▪ Assess palbociclib plus letrozole outcomes, including progression-free survival, overall survival, and objective response rate, and ▪ Assess healthcare resource utilization including hospitalizations and reasons for hospitalization to the extent documented in the charts
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACS	American Cancer Society
CBR	clinical benefit rate
CI	confidence interval
EAP	expanded access program
ECOG	Eastern Cooperative Oncology Group
DCF	data collection form
eDCF	electronic data collection form
ER	estrogen receptor
HER	human epidermal growth factor receptor
HR	hormone receptor
IRB	institutional review board
mBC	metastatic breast cancer
NE	not estimable
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PgR	progesterone receptor
RECIST	Response Evaluation Criteria In Solid Tumors
SD	standard deviation

2. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
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Matthew Cotter, PhD, MSc	Senior Medical Director, Global Medical Affairs Co-Study Lead	Pfizer
Lynn Mc Roy, MD	Senior Medical Director Advisor (Medical)	Pfizer
Keith Davis, MA	Senior Director, Health Economics Study Supervisor	RTI Health Solutions

3. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
Saurabh Nagar RTI Health Solutions	Data Analysis
Valerie Derrien A+A Research	DCF implementation Data Collection

4. MILESTONES

Milestone	Planned date	Actual date	Comments
Dates of institutional review board (IRB) approvals of protocol. The IRBs consulted for this study and approval dates for the protocol and any amendments is provided in Appendix 3.1.	June 2016	First IRB approval: December 2015 Last IRB approval: April 2016	
Start of data collection	June 2016	August 2016	
End of data collection	July 2016	November 2017	
Registration in the EU PAS register	June 2016	June 2016	
Final report of study results.	October 2016	October 2018	

5. RATIONALE AND BACKGROUND

Breast cancer was newly diagnosed in an estimated 252,710 persons in the United States (US) 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-positive phenotype.[2] The age-standardized incidence of breast cancer in the US 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–positive (HR+) (i.e., estrogen receptor–positive [ER+] and/or progesterone receptor–positive [PgR+]).[4] Treatment for postmenopausal women with HR+ mBC usually begins with endocrine-based therapy. Prior to US Food and Drug Administration (FDA) approval of palbociclib, a CDK4/6 inhibitor, the standard of care for postmenopausal women with locally advanced or metastatic hormone receptor–positive, human epidermal growth factor receptor 2–negative (ER+/HER2–) 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 metastatic breast cancers may have de novo resistance to endocrine-based treatment and therefore require chemotherapy as first-line treatment.[5,6,7] Regardless of initial therapy, patients with mBC eventually experience disease progression, representing an ongoing unmet need in this population.

Based on 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 US in September 2014 to provide access to palbociclib (in combination with letrozole) in advance of commercial availability. After FDA 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 US were enrolled in the EAP, and safety data were collected as part of the protocol. 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. Outcomes data on P+L (from the clinical studies) were previously limited to first-line treatment, thus the present study addresses this important data gap while also providing additional insight on the treatment history of patients enrolled in the EAP.

This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and was conducted voluntarily by Pfizer.

6. RESEARCH QUESTION AND OBJECTIVES

The aim of this study is to assess the characteristics, treatment patterns, and clinical outcomes of patients who initially received palbociclib as part of an EAP for the treatment of HR+/HER2− metastatic breast cancer. In addition to providing details of patient treatment while in the original EAP study, the study described herein included information on the EAP enrollees before and after their participation in the EAP. The current study will provide Pfizer with an opportunity to collect supplemental information on the use of P+L as well as patterns of use of other therapies received before and after the EAP. Data from a medical record review were used to address the following objectives:

- Describe the patient demographic and clinical characteristics of patients.
- Evaluate patterns of treatment with P+L (including overall treatment patterns, dose reductions, delays and discontinuation in treatment) and the reasons for these treatment events to the extent documented in patients' charts
- Receipt of supportive care medications while receiving P+L, and prior and subsequent treatments.
- Assess outcomes associated with palbociclib, including PFS, overall survival, and objective response rate,
- Assess rates of resource utilization including hospitalization (and the reasons for hospitalizations to the extent documented in patients' charts) in a subgroup of patients who had not received any prior treatment for metastatic breast cancer prior to P+L.

7. AMENDMENTS AND UPDATES

None.

8. RESEARCH METHODS

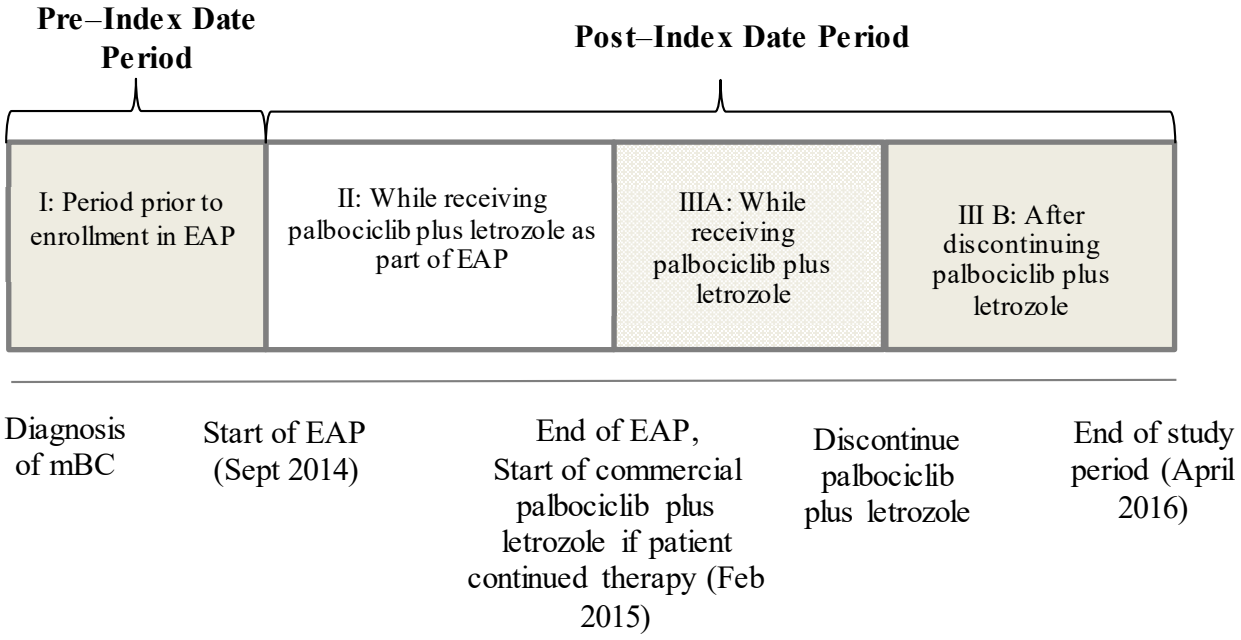
This study was a noninterventional retrospective medical record review conducted in a subset of enrollees in the palbociclib EAP. A customized Data Collection Form (DCF) was developed to capture demographic, clinical, and treatment data on each patient. The research methods are summarized below and presented in detail in the study protocol (Appendix 2).

8.1. Study design and setting

All data were collected via a customized electronic data collection form (eDCF). 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 three distinct observation periods (Figure 1):

- Period prior to 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);
- 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;
- Period following 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.
  - A period after discontinuation of P+L.

Figure 1. Study Period



8.2. Subjects

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 employed 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 metastatic breast cancer. 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).

8.3. Variables

All relevant study variables were gathered using a web-based DCF. Many analysis variables were directly derived from the raw DCF responses, while others required additional calculation based on combinations of the raw variables.

8.3.1. Patient Characteristics

Patient characteristics were abstracted directly from the medical record, including age at EAP enrollment, ethnic origin, insurance type, and vital status (alive/deceased 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 PgR status. Additional patient characteristics were noted at the time of EAP enrollment, including number and sites of metastases, Eastern Cooperative Oncology Group (ECOG) performance status, chronic comorbidities (based on the Charlson comorbidity index[10]), and types of cancer-directed treatment received for advanced or metastatic disease prior to EAP enrollment.

8.3.2. Treatment Patterns

Treatment pattern data that were collected include the period from diagnosis of mBC until enrollment in the palbociclib EAP, the period from patients' enrollment in the palbociclib EAP through last available follow-up and for some patients, a period following discontinuation of P+L therapy, when available. Specific variables collected included, but were not limited to, treatments received prior to EAP enrollment, total duration of P+L treatment, reasons for final P+L discontinuation if the patient was no longer on 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.

8.3.3. Supportive Care and Resource Utilization

Supportive care and hospitalization data were collected during P+L treatment. Variables included use of anti-infection medications, blood products, and pain medications, as well as number of inpatient visits, type of hospital ward, and reason of hospitalization.

8.3.4. Clinical Outcomes

Several clinical outcomes associated with P+L treatment were recorded. Tumor response and progression were evaluated based on physician assessments carried out per local practice. Formal response criteria typically used in prospective trials, such as Response Evaluation Criteria In Solid Tumors (RECIST), were not employed. Response measurements included ORR, 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. Progression-free survival 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 “progression” as the reason for discontinuation), or death due to any cause, whichever occurred first. If a patient died or started a new therapy line on a date more than 24 weeks after the final palbociclib dose, the patient was censored at that date (last palbociclib dose plus 24 weeks) and was not counted as having a progression event. Overall survival 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.

A detailed listing of all variables is presented in the SAP (Appendix 4).

8.4. Data sources and measurement

All data for this study were gathered from patients' existing medical records. No new data were collected for this study. The eDCF that was used for abstracting medical records is presented in Appendix 5.

8.5. Bias

This study was subject to potential selection bias inherent in most retrospective medical record reviews in that patients' assignment to the observed treatments was not randomized, having been previously determined during the course of routine clinical practice. Because this was a study documenting the natural history of HR+/HER2− mBC patients treated with P+L, formal testing of *a priori* hypotheses regarding comparative effectiveness or safety of P+L versus alternative treatments was not conducted. Therefore, based on the descriptive, exploratory nature of the analysis, no formal adjustments for bias (via matching, adjudication, or co-variate adjusted regressions, etc.) were made. Furthermore, the patients selected for study inclusion represented a convenience sample in that the records were obtained from EAP sites who were willing to participate in the study. The extent to which site self-selection influenced the study results is unknown. Both the sampling procedures and the patient eligibility criteria may further limit the generalizability of this study.

8.6. Study Size

Of the 238 patients across the 18 sites that were enrolled in the original EAP, six sites agreed to participate in this study and abstracted medical record data for 126 patients. Participation by original EAP sites in this follow-up study was optional, and some sites declined to participated due to resource constraints.

8.7. Data transformation

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), are documented in the statistical analysis plan (SAP), which is dated, filed and maintained by the sponsor (Appendix 4).

8.8. Statistical methods

An overview of the main statistical methods is presented below. For detailed description of the methods, please refer to the SAP in Appendix 4.

Based on the descriptive, exploratory nature of the study, all study measures were summarized descriptively through the tabular and graphical display of mean values, medians, ranges, and standard deviations of continuous variables of interest and frequency distributions for categorical variables. Missing and unknown categories for each variable were also presented. Percentages were calculated excluding missing values. Time-to-event outcomes (i.e., time to treatment start, time to dose reduction, treatment duration, PFS, OS) were described using the Kaplan-Meier method. In addition to reporting median event times for these measures, time-dependent event rates (e.g., proportion of patients without event at various time points from a starting point of

interest) were also be reported based on lifetables derived from the Kaplan-Meier analyses. All analyses were conducted using SAS (version 9.3 or higher) statistical software.

This study employed a convenience sample; thus, results may not be generalizable to the entire population with the disease.

8.8.1. Missing values

There was no imputation of missing values.

8.8.2. Sensitivity analyses

None.

8.8.3. Amendments to the statistical analysis plan

None.

8.9. Quality control

8.9.1. Documentation of SAS programming

To ensure smooth transitions of analytic methods and work among programmers, reviewers, and other project personnel, documentation of the following information was created for each SAS program:

- Project name
- Program name
- Program purpose
- Program author
- Date the program was completed
- Descriptions of subsequent changes and/or enhancements, with name of programmer and date for each.

This information was incorporated into each program in the form of a header. In addition to documenting this information in a general program header, each program included detailed comments throughout to describe the purpose and method of specific programming statements.

8.9.2. Validation of SAS programs

In this section, we describe a variety of programming validation methods, including log review, review of data listings, and independent programming, which were used to ensure that the SAS programs functioned as intended.

8.9.3. Log review

Programmers reviewed all SAS log files. This procedure is a widely accepted, basic level of program validation. The following common issues were assessed as part of a log review:

- No errors should appear in a log file.
- If warning messages or messages related to uninitialized variables are permitted in the log file, the programmer documented why they are permitted.
- The programmer accounted for the number of observations reported at each executed data step, especially when the number of observations increased or decreased.
- The log file contained all lines of the program as it was saved at the time of execution, and it contained only those lines of code.

8.9.4. Review of data listings and tables of summary statistics

Because an error-free log file does not necessarily demonstrate that a SAS program has functioned as intended, programmers produced, when needed, cell frequencies, means, and other summary statistics on specific data items to demonstrate that the program results were valid. Where appropriate, we also had a separate analyst review these listings independent of the programmer.

8.9.5. Other aspects of quality control

The following data checks were performed for all data collected in the DCF:

- Check for illogical or unusual data (e.g., treatment starting prior to diagnosis).
- Check for speeders (i.e., physicians who seem to skim through the DCF by falling below a certain tolerance time interval of an estimated average duration needed for completing the form).
- Check for responders with a typical unrealistic response pattern, such as always checking the same value in a numerical scale or responding in an erratic, implausible manner to certain questions.
- Check for an extremely high percentage of "Do not know" or "Data not available" responses.
- Check for an extremely high percentage of answering filter questions in a way so as to avoid having to answer subsequent questions in more detail.

In addition to the procedures noted above, the study followed standard operating procedures (SOPs) of the RTI-HS Office of Quality Assurance (OQA), which is an independent unit that reports to the Vice President of RTI-HS and provides training on applicable regulations and guidelines, implements and maintains a series of SOPs, and provides quality assurance monitoring for compliance with regulatory requirements.

8.10. Protection of human subjects

Subject information and consent

Not Applicable.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The final protocol, was reviewed and approved by an IRB(s) and/or IEC(s) for each site participating in the study.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

9. RESULTS

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. Mean (standard deviation [SD]) past-year mBC caseload per site was 225.0 (183.7) patients.

9.1. Patient Characteristics

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 ECOG status of 0 or 1 at EAP enrollment. 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. 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%). 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.

Table 1. Patient Characteristics

Total patients, n (%)	**126**	**100.0%**
Age at EAP enrollment, years		
Mean (SD)	62.5	12.2

Median	62.5	
Min, Max	37	89
Age distribution, n (%):		
36-45 years	11	8.7%
46-55 years	29	23.0%
56-65 years	29	23.0%
≥ 65 years	57	45.2%
Ethnic origin, n (%)		
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, n (%)		
Medicaid	1	0.8%
Medicare	33	26.2%
Commercial	44	34.9%
Unknown	48	38.1%
Duration (months) of follow-up[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 (months) 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, n (%)		
Alive	48	38.1%
Deceased	59	46.8%
Unknown	19	15.1%

[a] Follow-up duration calculated as number of months between date of interest (initial breast cancer diagnosis, i.e., study index date) and last available medical record or record in the EAP.

[b] Local, regional, and unknown stage at initial breast cancer diagnosis.

9.2. Treatment Patterns

9.2.1. Pre -EAP Enrollment

More than 90% of patients received some form of cancer-directed systemic treatment and/or other therapy, such as radiation, for metastatic disease before EAP enrollment (Table 2). 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. Most patients had three 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 two prior lines of therapy, and 74 (58.7%) received at least three prior lines of therapy.

Table 2. Pre-EAP Treatment Patterns

Total patients, n (%)	**126**	**100.0%**
Type of cancer-directed treatment received for advanced or metastatic disease prior to EAP enrollment, n (%)		
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%
Number of systemic therapy lines received for metastatic disease before EAP enrollment, n (%)		
0	14	11.1%
1	18	14.3%
2	20	15.9%
3 or more	74	58.7%

9.2.2. Post EAP Enrollment

Mean time to P+L initiation after EAP enrollment was less than a week (Table 3). For all patients, the initial palbociclib dose was 125 mg; the initial letrozole dose was 2.5 mg for all but two patients (for these two 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; 10.0% were due to patient decision or death. 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 on 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.

Table 3. Palbociclib + Letrozole Treatment Patterns

Total patients, n (%)	**126**	**100.0%**
Time (weeks) 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), n (%)		
Toxicities / side 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), n (%)		
Still on 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), n (%)		
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, n (%)	70	55.6%
Had ≥1 dose reduction, n (%)	43	34.1%
Mean (SD) number of dose reductions	1.2	0.4
Reason(s) reported for dose reductions (N = 43), n (%)	43	100.0%
Adverse event, n (%)	43	100.0%
Neutropenia	36	83.7%
Leukopenia	2	4.7%
Fatigue	5	11.6%
Had ≥1 treatment/cycle delay/interruption, n (%)	60	47.6%
Mean (SD) number of delays/interruptions	1.7	0.8
Median (days) duration of delays/interruptions	7	
Reason(s) reported for treatment/cycle delays/interruptions (n = 60), n (%)	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, n (%)	43	34.1%
Time (months) to first P+L dose reduction		
Mean (SD)	3.2 (3.8)	
Mean (SD), Kaplan-Meier	8.5 (0.7)	
Median (95% CI), Kaplan-Meier	9.1 (6.1-13.4)	
Proportion with dose reduction at (from K-M lifetable)		
3 months after initiation	30.6%	
6 months after initiation	37.0%	
12 months after initiation	62.7%	
18 months after initiation	80.1%	

Among the 100 patients who discontinued P+L therapy, 76 received additional systemic therapy after last P+L dose (Table 3). 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 (Table 4).

Table 4. Additional Treatment Regimens After Palbociclib + Letrozole Completion/Discontinuation[a]

First Additional Therapy After P+L			Second Additional Therapy After P+L			Third Additional Therapy After P+L			Fourth Additional Therapy After P+L		
	N	%		N	%		N	%		N	%
	76	100%		46	100%		21	100%		8	100%
Chemotherapy (single agent or combo)	52	68.4%	Chemotherapy (single agent or combo)	35	76.1%	Chemotherapy (single agent or combo)	19	90.5%	Chemotherapy (single agent or combo)	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[b]	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 in months (all regimens)	3.3	Median treatment duration in months (all regimens)	3.0	Median treatment duration in months (all regimens)	2.4	Median treatment duration in months (all regimens)	1.9

[a] Table includes only patients who discontinued P+L therapy and received treatments after P+L (N = 100). Line of treatment varies for each patient depending upon the last treatment line received.

[b] Combination regimen including two or more endocrine-based therapies (without chemotherapy).

9.3. Supportive Care

Data for supportive care treatments received during P+L are presented in Table 5. Most common treatments were for pain control (53.2%), antiemetics (20.6%), and antibiotics (14.3%).

Table 5. Supportive Treatments Received During Palbociclib + Letrozole Treatment

Total Patients, n (%)	**126**	**100.0**
Supportive Therapy(ies) Received During P+L Treatment, n (%)		
Antibiotics	18	14.3%
Antiemetics	26	20.6%
Antifungals	1	0.8%
Antivirals	3	2.4%
Hematopoietic growth factor	8	6.3%
WBC growth factors	5	4.0%
Erythropoiesis stimulating agents	3	2.4%
Other	0	0.0%
Pain control	67	53.2%
Transfusions	9	7.1%
Red blood cell transfusion	8	6.3%
Platelet transfusion	1	0.8%
Other	0	0.0%
Unknown	7	5.6%

9.4. Resource Utilization

Results on hospitalization utilization are presented in Table 6. Approximately 15% of patients had at least one hospitalization during P+L treatment with a mean length of stay of 11 days. The most common reasons for hospitalization were management of toxicities (63.2%) and disease progression (26.3%).

Table 6. Hospitalizations During Palbociclib + Letrozole Treatment

Total Patients, n (%)	**126**	**100.0%**

Had ≥1 Hospitalization During Palbociclib+Letrozole Treatment, n (%)	**19**	**15.1%**
Number of hospitalizations, among patients with ≥1 hospitalization		
Mean (SD)	1.3	0.6
Median	1	
Min, Max	1	3
Length of stay (days) per hospitalization, among patients with ≥1 hospitalization (n = 19)		
Mean (SD)	10.8	7.7
Median	9	
Min, Max	1	24
Total days hospitalized, among patients with ≥1 hospitalization (n = 19)		
Mean (SD)	13.6	10.8
Median	9	
Min, Max	1	36
Hospital Ward(s) Utilized, Among Patients with ≥1 Hospitalization (n = 19), n (%)		
General/Medical ward	6	31.6%
Oncology ward	2	10.5%
Intensive care unit	1	5.3%
Other	4	21.1%
Unknown	8	42.1%
Reported Reason(s) for Hospitalization, Among Patients with ≥1 Hospitalization (n = 19), n (%)		
Treatment-related procedures	0	0.0%
Management of toxicities/side-effects related to treatment or procedures	12	63.2%
Neutropenia	1	5.3%
Leukopenia	0	0.0%
Fatigue	1	5.3%
Other	11	57.9%
Disease progression or complications	5	26.3%
Palliative care	1	5.3%
Reason unrelated to metastatic breast cancer	3	15.8%
Unknown	0	0.0%

9.5. Clinical Outcomes

Data on best clinical response and survival outcomes of P+L treatment are presented in Tables 7 through 10. The CBR for all P+L recipients, defined as having a best response of complete response, partial response, or stable disease for at least 24 weeks, was 33.3% (Table 7). The CBR

was higher in patients without prior treatment for metastatic disease regardless of type of therapy: 53% versus 30% for patients without versus with prior endocrine therapy, and 49% versus 26% for patients without versus with prior chemotherapy. 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 with 26.6% for patients with at least two prior lines of treatment (Table 8).

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 9). 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-NE) months; survival rates at 12 and 24 months were 66.2% and 43.5%, respectively. As noted for clinical response rates, PFS duration decreased with increasing number of prior lines of treatment (Table 10). Progression-free survival 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 two prior lines of systemic therapy.

Table 7. Best Clinical Response[a] to Palbociclib + Letrozole Therapy, by Type of Prior (Pre-EAP) Systemic Therapy for Metastatic Disease

		Prior (Pre-EAP) Endocrine Therapy Exposure		Prior (Pre-EAP) Chemotherapy Exposure	
	All Patients (n = 126)	Had Prior Endocrine Therapy Exposure (n = 109)	No Prior Endocrine Therapy Exposure (n = 17)	Had Prior Chemotherapy Exposure (n = 85)	No Prior Chemotherapy Exposure (n = 41)
Complete response	2 (1.6%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	2 (4.9%)
Partial response	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%)*

[a] Clinical response was based on physician assessment per local practice and not per formal criteria such as RECIST.

Table 8. Best Clinical Response to Palbociclib + Letrozole Therapy, by Number of Prior (Pre-EAP) Systemic Treatment Lines Received for Advanced/Metastatic Disease

	No Prior Lines (n = 14)	1 Prior Line (n = 18)	2 or More Prior Lines (n = 94)
Complete response	2 (14.3%)	0 (0.0%)	0 (0.0%)
Partial response	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%)

Table 9. Survival Outcomes of Palbociclib + Letrozole Therapy, by Type of Prior (Pre-EAP Systemic Treatment Received for Metastatic Disease)

	All Patients (n = 126)	Prior (Pre-EAP) Endocrine Therapy Exposure		Prior (Pre-EAP) Chemotherapy Exposure	
		Had Prior Endocrine Exposure (n = 109)	No Prior Endocrine Exposure (n = 17)	Had Prior Chemotherapy Exposure (n = 85)	No Prior Chemotherapy Exposure (n = 41)
Progression-free survival, months					
Patients with progression event, n (%)	98 (77.8%)	87 (79.8%)	11 (64.7%)	69 (82.2%)	29 (70.7%)
Median PFS (95% CI)	4.5 (3.7-6.2)	4.4 (3.5-5.5)	8.6 (3.5-.)	3.9 (2.5-5.1)	7.0 (4.2-14.7)
PFS rates (from K-M life table)					
3-month PFS rate	65.0%	62.3%	82.4%	57.5%	80.5%
6-month PFS rate	42.1%	38.4%	64.7%	35.5%	55.5%
9-month PFS rate	30.8%	28.2%	47.1%	26.0%	40.4%
12-month PFS rate	27.0%	23.7%	47.1%	19.8%	40.4%
18-month PFS rate	20.9%	18.9%	32.3%	14.8%	32.1%
24-month PFS rate	12.3%	7.0%	32.3%	.	24.1%
Crude PFS rates among patients with available follow-up through each interval					
3-month PFS rate	64.3%	61.5%	82.4%	56.5%	80.5%

	All Patients (n = 126)	Prior (Pre-EAP) Endocrine Therapy Exposure		Prior (Pre-EAP) Chemotherapy Exposure	
		Had Prior Endocrine Exposure (n = 109)	No Prior Endocrine Exposure (n = 17)	Had Prior Chemotherapy Exposure (n = 85)	No Prior Chemotherapy Exposure (n = 41)
6-month PFS rate	39.7%	35.8%	64.7%	32.9%	53.7%
9-month PFS rate	27.0%	23.9%	47.1%	21.2%	39.0%
12-month PFS rate	21.4%	18.3%	41.2%	14.1%	36.6%
18-month PFS rate	13.5%	12.8%	17.6%	8.2%	24.4%
24-month PFS rate	1.6%	0.9%	5.9%	.	4.9%
Overall survival					
Patients with death event, n (%)	59 (46.8%)	53 (48.6%)	6 (35.3%)	45 (52.9%)	14 (34.1%)
Median time to death, among those who died (months)	7.0	7.0	6.3	7.7	6.9
Median overall survival (95% CI), months	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-month survival rate	66.2%	65.4%	70.6%	62.8%	72.5%
24-month survival rate	43.5%	39.8%	61.8%	31.8%	63.1%

Table 10. Survival Outcomes of Palbociclib + Letrozole Therapy, by Number of Prior (Pre-EAP) Systemic Treatment Lines Received for Advanced/Metastatic Disease

	No Prior Lines (n = 14)	1 Prior Line (n = 18)	2 or More Prior Lines (n = 94)
Progression-free survival, months			
n (%) of patients with progression event	8 (57.1%)	15 (83.3%)	75 (79.8%)
Median PFS (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-month PFS rate	85.7%	83.3%	58.4%
6-month PFS rate	71.4%	55.6%	34.8%
9-month PFS rate	57.1%	33.3%	26.3%
12-month PFS rate	57.1%	33.3%	20.7%
18-month PFS rate	39.2%	22.2%	17.7%
24-month PFS rate	39.2%	16.7%	NE
Crude PFS rates among patients with available follow-up through each interval			
3-month PFS rate	85.7%	83.3%	57.4%
6-month PFS rate	71.4%	55.6%	31.9%
9-month PFS rate	57.1%	33.3%	21.3%
12-month PFS rate	50.0%	33.3%	14.9%
18-month PFS rate	21.4%	22.2%	10.6%
24-month PFS rate	7.1%	5.6%	NE
Overall survival			
Patients with death event, n (%)	4 (28.6%)	6 (33.3%)	49 (52.1%)
Median time to death, among those who died, months	6.3	14.5	6.9
Median overall survival (95% CI), from K-M estimation, months	NE (7.0-NE)	NE (19.8-NE)	15.3 (12.1-23.5)
Survival rates (from K-M life table)			
12-month survival rate	71.4%	83.3%	61.7%
24-month survival rate	71.4%	64.5%	34.6%

NE = not estimable

9.6. Adverse events / adverse reactions

Based on the retrospective nature of this study, no safety-related objectives have been pre-specified. However, the study protocol required human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions, and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer was obligated to report adverse events (AE) with explicit attribution of causality to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution of causality

is not necessarily inferred or solely based on a temporal relationship between drug administration and an AE, but must be based on a definitive statement of causality by a health care provider linking drug administration to the AE.

The requirements for reporting safety events on the Noninterventional Study (NIS) Adverse Event Monitoring (AEM) Report Form to Pfizer Safety were as follows:

- All serious and nonserious AEs with explicit attribution to any Pfizer drug that appears in the reviewed information must be recorded on the DCF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.
- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to or associated with use of a Pfizer product, the data captured in the medical record constituted all clinical information known regarding these AEs. No follow-up on related AEs were conducted.

10. DISCUSSION

10.1. Key results

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 US. 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.

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 who 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.[11] The findings of other previous interventional studies, particularly the PALOMA 1-3 studies,[9,12,13] also help put the results of our study into context. These trials have demonstrated clinical benefit of palbociclib compared with 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 this 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 endocrine therapy and 14.9 months in patients with prior chemotherapy.

10.2. Limitations

Results reported here are subject to several limitations inherent to most retrospective medical record review studies. First, participation by original EAP sites in this follow-up study was optional, and some sites declined to participated due to resource constraints. Therefore, not all patients who participated in the EAP were included in the follow-up study. Second, data were entered directly into the eDCF 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 as per local procedures, and so the clinicians were not required to retrospectively apply a specific set of response criteria. Finally, 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.

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 US.

10.3. Interpretation

Findings from this study highlight the benefit of treatment with palbociclib combination therapy in HR+/HER2– mBC, even in heavily pretreated patients

11. OTHER INFORMATION

Not Applicable

12. CONCLUSIONS

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.

13. REFERENCES

1. American Cancer Society. Breast cancer facts & figures 2017–2018. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf. Accessed July 19, 2018.

2. Brodie AM. Aromatase inhibitors in the treatment of breast cancer. *J Steroid Biochem Mol Biol*. 1994;49:281-287.

3. World Cancer Research Fund. Breast cancer statistics [data for 2012]. 2015. Available at: https://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/breast-cancer-statistics. Accessed July 19, 2018.

4. Vici P, Pizzuti L, Natoli C, et al. Triple positive breast cancer: a distinct subtype? *Cancer Treat Rev*. 2015;41:69-76. https://doi.org/10.1016/j.ctrv.2014.12.005.

5. National Comprehensive Cancer Network (NCCN) 2017 NCCN Guidelines for Metastatic Breast Cancer. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed July 19, 2018.

6. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Ann Oncol*. 2014;25:1871-1888. https://doi.org/10.1093/annonc/mdu385.

7. Reinert T, Barrios CH. Optimal management of hormone receptor positive metastatic breast cancer in 2016. *Ther Adv Med Oncol*. 2015;7:304-320. https://doi.org/10.1177/1758834015608993.

8. Beaver JA, Amiri-Kordestani L, Charlab R, et al. FDA approval: palbociclib for the treatment of postmenopausal patients with estrogen receptor–positive, HER2-negative metastatic breast cancer. *Clin Cancer Res*. 2015;21:4760-4766. https://doi.org/10.1158/1078-0432.CCR-15-1185.

9. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol*. 2015;16:25-35. https://doi.org/10.1016/S1470-2045(14)71159-3.

10. Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol*. 2008;61:1234-1240. https://doi.org/10.1016/j.jclinepi.2008.01.006.

11. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2− metastatic breast cancer. *Clin Cancer Res*. 2017;23:5218-5224. https://doi.org/10.1158/1078-0432.CCR-17-0754.

12. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375:1925-1936. https://doi.org/10.1056/NEJMoa1607303.

13. 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*. 2016;17:425-439. https://doi.org/10.1016/S1470-2045(15)00613-0.

14. LIST OF SOURCE TABLES AND FIGURES

Not Applicable