NON-INTERVENTIONAL (NI) STUDY REPORT

Study Information

Title	Descriptive Analyses of Clinical Characteristics and Treatment Patterns of Breast Cancer Patients Initiating Palbociclib (Ibrance®) Treatment in the US Community Oncology Setting
Protocol number	A5481067
Version identifier of the final study report	V1
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EU Post Authorization Study (PAS) register number	EUPAS16710
Active substance	Palbociclib
Medicinal product	Ibrance
Research question and objectives	Palbociclib (Ibrance®) was approved in the United States (US) in February 2015. This study describes the characteristics of patients prescribed palbociclib in terms of demographic and clinical characteristics, real-world treatment patterns, dosing, and neutropenia-related outcomes among female patients with breast cancer following US approval.
Author	Jonathan Kish, PhD, MPH Director, Health Economics and Outcomes Research 2515 McKinney Avenue Suite 1600, Dallas, TX 75201 313.570.8220 mobile E: jonathan.kish@cardinalhealth.com

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	Pfizer Limited Ramsgate Road, Sandwich, Kent CT130NJ United Kingdom
MAH contact person	Melea Ward, PhD, PharmD 4222 Emperor Blvd, Suite 335 Durham, North Carolina 27703 USA Email: melea.ward@pfizer.com

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

Annex 1. List of stand-alone documents

APPENDIX 1. SIGNATURES

APPENDIX 2. PROTOCOL

APPENDIX 3. INVESTIGATORS AND CORRESPONDING INDEPENDENT ETHICS COMMITTEES (IECs) OR INSTITUTIONAL REVIEW BOARDS (IRBs)

Not applicable

APPENDIX 4. STATISTICAL ANALYSIS PLAN

1. ABSTRACT (STAND-ALONE DOCUMENT)

Title: Descriptive Analyses of Clinical Characteristics and Treatment Patterns of Breast Cancer Patients Initiating Palbociclib (Ibrance®) Treatment in the US Community Oncology Setting

Date of Abstract: 28 February 2017

Name and affiliation of the main author:

Jonathan Kish, PhD, MPH

Director, Health Economics and Outcomes Research

2515 McKinney Avenue Suite 1600, Dallas, TX 75201

313.570.8220 mobile

E: jonathan.kish@cardinalhealth.com

Keywords: palbociclib, breast cancer, neutropenia, real-world data

Rationale and background: The arrival of new classes of therapy on the treatment landscape warrant evaluation of real-world data regarding patient characteristics and treatment patterns to aid in the understanding of use in broad clinical practice. Pfizer is interested in gathering real-world data describing the population of patients prescribed palbociclib, concomitantly with letrozole or fulvestrant, in the community oncology setting. The purpose of this study was to assess the settings in which palbociclib was prescribed (i.e. clinical/demographic characteristics of patients, line of therapy), occurrence of neutropenia and how providers monitored and managed these events. The results of this research provide insights into these patterns during the first year of palbociclib adoption into clinical practice among community oncologists across the US.

Research question and objectives: The goals of this research were to evaluate the real-world treatment dosing patterns, line of therapy in the treatment sequence and occurrence of neutropenia (assessed through CBC laboratory test results) for female breast cancer patients prescribed palbociclib following drug approval (01 February 2015). Real-world data from patients' electronic medical records (EMR) were utilized to achieve the following research objectives:

1. Characterize the demographic and clinical characteristics of patients at the initiation of treatment with palbociclib.

2. Describe palbociclib utilization by line of therapy (LOT).

3. Assess the frequency and timing of palbociclib dose reduction.

4. Quantify the frequency of complete blood count (CBC) monitoring during treatment with palbociclib

5. Assess the incidence (by grade) and timing of neutropenia events through calculation of absolute neutrophil count (ANC) during treatment with palbociclib.

6. Describe utilization of chemotherapy and endocrine therapy prior to and following treatment with palbociclib and the use of supportive pharmacological agents concomitant with palbociclib treatment.

Study design: This was a retrospective observational study of female patients diagnosed with breast cancer and newly initiating treatment with palbociclib.

Setting: Community oncology practices treating female metastatic breast cancer patients in the United States (US).

Subjects and study size, including dropouts: All female metastatic breast cancer patients initiating therapy with palbociclib between 01 February 2015 and 31 January 2016. Patients were required to have received palbociclib concomitantly with either letrozole or fulvestrant. Patients were grouped into 6 cohorts based on the month of initiation of palbociclib (February through March 2015, April through May 2015, June through July 2015, August through September 2015, October through November 2015, and December 2015 through January 2016).

Variables and data sources: Data including demographics, clinical characteristics (ECOG-PS, stage, ER/HER2 status), laboratory assessments (complete blood counts, white blood cell counts, neutrophil percentages), treatments (oral and IV, breast cancer directed or supportive care agents) and vital status were captured for female patients receiving treatment with palbociclib from structured data fields within the EMR data system. No review of unstructured clinical progress notes was performed. No linkage to administrative claims for prescription data was available and initiation/receipt of therapies was based on treatment orders recorded in the EMR. Timing of events in terms of palbociclib cycle was approximated by using the days from palbociclib initiation where one cycle was equal to 28 days.

Results: 965 women with metastatic breast cancer were identified who had at least one treatment order for palbociclib during the study period. Of the 965 identified patients, 612 (63.4%) were treated with palbociclib concomitantly with letrozole, 151 (15.6%) concomitantly with fulvestrant, and the remaining 202 (20.9%) did not meet selection criteria. Results highlighted below are for the palbociclib + letrozole cohort only.

Mean (±SD) follow-up for palbociclib + letrozole patients was 6.4±3.9 months. The proportion of patients initiating treatment with palbociclib + letrozole in first-line was from 35.9%-42.4% of all new palbociclib + letrozole treatment starts while the proportion of new starts in fourth-line or greater declined from 40.6% (Feb/Mar 2015) to 24.3% (Dec 2015/Jan 2016). At the end of follow-up, 78.8% (n=482) were on any treatment as of last follow-up (with 296 of those receiving palbociclib + letrozole as last recorded line of therapy), 9.5% (n=58) were lost to follow-up, and 11.8% were deceased (n = 21 with last treatment received palbociclib + letrozole and n = 51 with last recorded line another therapy).

Of patients with a known palbociclib starting dose (n=417), 88.0% (n=367) initiated therapy at 125 mg, 11.0% (n=46) at 100 mg, and 1.0% (n=4) at 75 mg. Dose reductions were observed in 20.1% (n=84) of patients with a known starting dose. Mean days to first dose

reduction was 48 (SD=31, median =39); 69.0% (58/84) occurred within the first two cycles (within 56 days of palbociclib initiation).

CBC laboratory data were available for 351 patients (57.4%). Of the 351 patients with CBC data available, 74.6% (n=262) had a laboratory value consistent with neutropenia (of any grade). Among patients with neutropenia, the highest grade was: grade 1 = 12.8%; grade 2 = 20.5%; grade 3 = 35.3%; and grade 4 = 6.0%.

Discussion: The entry of a novel drug such as palbociclib in the marketplace may present unique challenges for inexperienced providers who were not participants in the clinical trial development program for the agent. While randomized controlled trials (RCTs) remain the gold standard for demonstrating efficacy and safety, real-world data is important to demonstrate differences in utilization and outcomes across heterogeneous patients. In this US community oncology EMR database, patients initiating palbociclib + letrozole were a more heterogeneous patient population in terms of older, had lower performance status scores at initiation, and had more prior exposure to chemotherapy than patients in the registration trials. Over time, we noted increased initiation of palbociclib + letrozole therapy earlier in the treatment sequence. These findings suggest that early use after drug approval of palbociclib in heavily pre-treated patients has decreased over the time of observation. Next, our results demonstrated that on average two CBC tests are conducted during the first cycle of palbociclib treatment suggesting good provider compliance with monitoring guidelines in the USPI. In regard to the occurrence of neutropenia, 47.3% and 8.0% of patients in this study had laboratory findings consistent with grade 3 and grade 4 neutropenia, respectively during the treatment with palbociclib + letrozole. While results from this research cannot be directly compared to RCTs given the heterogeneity of the patient populations these findings are consistent with the 56.1% and 10.4% observed rates of grade 3 and grade 4 neutropenia, respectively, found in the PALOMA-2 trial. Further long-term follow-up of patients would allow for more direct subgroup comparisons to patients with similar disease and treatment characteristics in the RCTs to confirm these findings.

Names and affiliations of principal investigators:

Jonathan Kish, PhD, MPH

Director, Health Economics and Outcomes Research

2515 McKinney Avenue Suite 1600, Dallas, TX 75201

E: jonathan.kish@cardinalhealth.com

Bruce Feinberg, DO

Chief Medical Office, Cardinal Health

2515 McKinney Avenue Suite 1600, Dallas, TX 75201

E: bruce.feinberg@cardinalhealth.com

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
CBC	Complete blood count
CDK	Cyclin-dependent kinase
DNA	Deoxyribonucleic acid
ECOG	Eastern cooperative oncology group
EMR	Electronic medical records
ER	Estrogen receptor
FDA	Food and Drug Administration
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HR	Hormone receptor
IRB	Institutional Review Board
IV	Intravenous
LOT	Line of therapy
MBC	Metastatic breast cancer
NCCN	National Comprehensive Cancer Network
PASS	Post-Authorization Safety Study
PFS	Progression-free survival
US	United States
WBC	White blood cell

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Melea Ward, PhD, PharmD, BCPS	Director, Global Outcomes and Evidence, Oncology	Pfizer Inc.	4222 Emperor Blvd Suite 335 Durham, NC 27703
Jonathan Kish, PhD, MPH	Director, Health Economics and Outcomes Research	Cardinal Health	2515 McKinney Avenue Suite 1600, Dallas, TX 75201
Bruce Feinberg, DO	Chief Medical Officer	Cardinal Health	2515 McKinney Avenue Suite 1600, Dallas, TX 75201

4. OTHER RESPONSIBLE PARTIES

Not applicable

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Project kick-off	27 October 2015	27 October 2015	
Study protocol approval	20 November 2015	03 December 2015	
Statistical analysis plan approval	4 December 2015	21 December 2015	
Date of Institutional Review Board (IRB) approval of protocol	25 December 2015	15 December 2015	
First report using data from the first data cut: (01 February 2015 through 30 September 2015)	22 January 2016	25 March 2016	
Interim report using data from the second data cut: (01 February 2015 through 31 January 2016)	01 April 2016	08 April 2016	
Final report using data from the third data cut: (01 February 2015 through 31 March 2016)	03 June 2016	30 June 2016	
Final report of full study results	01 July 2016	28 February 2017	

6. RATIONALE AND BACKGROUND

Pharmaceutical innovation within the past two decades has resulted in unprecedented new drug development. Novel therapies that target the cell cycle and immunotherapies that activate the immune system have resulted in a rapid expansion in the arsenal of systemic cancer therapies to treat metastatic disease and many are being reviewed by the U.S. Food and Drug Administration (FDA) under breakthrough therapy designation with accelerated approval cycles. The arrival of new classes of therapy on the treatment landscape warrant evaluation of real world data regarding patient characteristics and treatment patterns to aid in the understanding use in broad clinical practice.

In 2016, it is estimated that breast cancer accounted for just under 30% of all new cancers diagnosed in women in the United States and was the leading cause of cancer-related deaths among women aged 20-59 years.[1] Annually approximately 6% of new breast cancer cases are de novo metastatic disease however it has been estimated that as much as 30% of early stage recurs at a distant site. [2,3] Survival from breast cancer is highly dependent upon the stage at diagnosis; the 5-year relative survival rate for women with local or regional disease at diagnosis is 98.8% and 85.2%, respectively, compared to 26.3% for those diagnosed with distant disease.[2] Treatment selection for metastatic breast cancer (MBC) is based on biomarkers including hormone-receptor and Human Epidermal Growth Factor Receptor 2 status, and individual patient and clinical characteristics that may include tumor burden, timing of disease recurrence and the type of prior adjuvant therapies. MBC remains incurable and presents a significant unmet medical need.[4] Novel agents for the treatment of MBC including tyrosine kinase inhibitors (TKIs), PARP inhibitors, and more recently immunotherapy and cyclin-dependent kinase (CDK) 4/6 inhibitors, hold promise for improving outcomes in MBC patients.

One such novel agent is palbociclib, an oral CDK 4/6 inhibitor, which prevents deoxyribonucleic acid (DNA) replication by preventing progression from the G1 to the S phase of the cell division cycle thereby preventing tumor cell proliferation. Palbociclib in combination with the aromatase inhibitor letrozole was granted accelerated approval by the FDA as initial endocrine based therapy in postmenopausal women with estrogen receptor (ER)-positive/HER2-negative MBC in February 2015 based on the results of the phase II PALOMA-1 trial.[5] Palbociclib in combination with fulvestrant was approved one year later (February 2016) in pre or post-menopausal women with disease progression following endocrine therapy based on results from the PALOMA-3 trial.[6] Recently the phase III RCT, PALOMA-2, confirmed the findings in PALOMA-1, demonstrating a median progression-free survival (PFS) in the palbociclib plus letrozole arm of 24.8 months compared to 14.5 months in the placebo plus letrozole arm (hazard ratio [HR] = 0.58; P = <0.001).[7,*] The safety results from all three trials were consistent, with no new safety signals identified in the phase III studies. Palbociclib is indicated[8] for the treatment of HR+, HER2- advanced or metastatic breast cancer in combination with:

- Letrozole as initial endocrine based therapy in postmenopausal women, or

[*] Results of PALOMA-2 have been reported to the U.S. FDA.

- Fulvestrant in women with disease progression under accelerated approval based on progression-free survival (PFS)

Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Real -world treatment patterns, patient characteristics and safety outcomes for novel treatments are important to practitioners who may be prescribing a new agent with little or no practical experience. The purpose of this study was to assess the settings in which a newly approved cancer therapy was being initiated (e.g., clinical/demographic characteristics of patients, line of therapy) and examine the real-world estimates of the frequency, grade and timing of neutropenia (and other AEs) and how providers monitored and managed these events (e.g., dose modifications). The results of this research provide insights into these patterns during the first year of adoption of a drug with novel mechanism of action into clinical practice among community oncologists across the US.

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

7. RESEARCH QUESTION AND OBJECTIVES

The goals of this research were to evaluate the real-world treatment dosing patterns, line of therapy in the treatment sequence, and occurrence of neutropenia for female breast cancer patients prescribed treatment with palbociclib following drug approval (01 February 2015). Real-world data from patients' electronic medical records (EMR) were utilized to achieve the following research objectives:

1. Characterize the demographic and clinical characteristics of patients at the initiation of treatment with palbociclib.

2. Describe palbociclib utilization by line of therapy (LOT).

3. Assess the frequency and timing of palbociclib dose reduction.

4. Quantify the frequency of complete blood count (CBC) monitoring during treatment with palbociclib

5. Assess the incidence (by grade) and timing of neutropenia events through calculation of absolute neutrophil count (ANC) during treatment with palbociclib.

6. Describe utilization of chemotherapy and endocrine therapy prior to and following treatment with palbociclib and the use of supportive pharmacological agents concomitant with palbociclib treatment.

8. AMENDMENTS AND UPDATES

None

9. RESEARCH METHODS

The approved study protocol, detailing the study methods, analysis and outcomes of interest is included in Appendix 2.

9.1. Study design

This was a retrospective observational study of female patients diagnosed with metastatic breast cancer treated in US community oncology practices prescribed palbociclib during the 12-month period following initial drug approval.

9.2. Setting

Female metastatic breast cancer patients prescribed treatment with palbociclib between 01 February 2015 and 31 January 2016 (index period) were selected from the EMR database. The index date for the analysis was the date of first prescription for palbociclib. EMR data were extracted for each patient from the first date of diagnosis for breast cancer (as available) through 31 March 2016. Patients meeting all of the following criteria were selected for analysis.

9.3. Subjects

To fulfil the study objectives, patients were selected from the EMR dataset if there was an entry for “palbociclib” or “Ibrance” in any of the structured treatment description data fields contained within the EMR. Patient records were extracted at three time points during the course of the study. The initial patient selection included those patients with a treatment order entry for palbociclib anytime between 01 February 2015 and 30 September 2015. Subsequently, the dataset was refreshed to include additional follow-up and new patients prescribed palbociclib through 31 January 2016. A final dataset update included additional follow-up time (but no new patient selection) through 31 March 31 2016.

9.3.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Received at least one prescription for palbociclib during the index period.

2. Diagnosed with breast cancer (ICD-9 CM: 174.x; ICD-10 CM: C50.01X, C50.11X, C50.21X, C50.31X, C50.41X, C50.51X, C50.61X, C50.81X, C50.91X) anytime prior to or on the date of first prescription for palbociclib.

3. Female sex.

4. At least 18 years of age at date of breast cancer diagnosis.

9.3.2. Exclusion criteria

Patients meeting any of the following criteria were excluded from the study:

1. Diagnosis or treatment of a second primary malignancy anytime during the study period.

2. Receiving a prescription for palbociclib prior to the index period.

3. Treatment record indicating participation in any palbociclib clinical trial after 01 February 2015.

9.4. Variables

The list of variables and their operational definitions obtained from the EMR for this research are included in Table 1. The following data were abstracted from the structured fields of the EMR: demographics, tumor/disease characteristics (e.g. stage, sites of metastases), drug regimens received (endocrine therapy, chemotherapy, targeted agents), dates of initiation of regimens, dose of palbociclib (dose at initiation, reduction, and timing of dose modifications), supportive care agents received during palbociclib treatment, laboratory testing results from CBC (white blood cell count and neutrophil percentage), and AEs/neutropenia (AE via diagnosis codes; neutropenia via lab values). EMR data is not linked to a prescription dispensing record or pharmacy claims and is reliant on staff to enter records into treatment orders. Appendix 4 refers to the study SAP which is included in this document.

Table 1. Demographic, Clinical and Treatment-related Variables Collected/Calculated from the EMR Database.

Variable	Description	Collection Point	Operational
Demographic and Clinical Variables			
Age	Continuous and categorical (at palbociclib initiation) • ≤64 • 65-74 • ≥75	• At advanced/ metastatic BC diagnosis • At palbociclib treatment initiation	Structured data field
Body Mass Index (BMI)	Continuous	• At palbociclib treatment initiation	Structured data field
Stage	• 0 • 0, ductal carcinoma in situ • I • IA • IB • IIA • IIB • IIIA • IIIB • IIIC • IV • Unknown	• At diagnosis • At palbociclib treatment initiation	Structured data field
Vital status	• Known deceased	• Anytime during the study period	Matched by EMR vendor to Social Security Index Death Master File
TNM Stage	• T: T1 - T4 including prefix and suffix • N: N1 - N4 including prefix and suffix	• At palbociclib treatment initiation • At palbociclib treatment	Combined from each of T, N and M structured date fields

Variable	Description	Collection Point	Operational
	• M: M0 - M1 including prefix and suffix • Unknown	discontinuation†	
ECOG Performance Status	• 0/1 • 2 • ≥3	• At palbociclib treatment initiation	Structured data field
ER Receptor Status	• Positive • Negative • Unknown	• Most recent evaluation nearest to palbociclib treatment initiation	Structured data field
PR Receptor Status	• Positive • Negative • Unknown	• Most recent evaluation nearest to palbociclib treatment initiation	Structured data field
HER2 Receptor Status	• Positive • Negative • Unknown	• Most recent evaluation nearest to palbociclib treatment initiation	Structured data field
Date of diagnosis of metastatic BC	Date, includes all patients with any distant metastasis	• At first occurrence	AJCC stage IIIA-C or stage IV; ICD-9/10-CM code for metastatic disease; M1 stage at any time; If no indication from AJCC, TNM, or ICD-9/10 diagnoses codes, the assumed metastatic date was the date of the first palbociclib treatment order
Menopausal status	• Postmenopausal • Unknown	• At advanced/ metastatic breast cancer diagnosis	Unstructured keyword search of progress notes (see Appendix 4)
Location of Metastatic Disease	• Bone • Brain • Liver • Lung • Lymph • Other	• At palbociclib treatment initiation	ICD-9 diagnosis codes (see Appendix 4)
Histology	• invasive ductal carcinoma • invasive lobular carcinoma	• At advanced/ metastatic breast cancer diagnosis	ICD-9 diagnosis codes (see Appendix 4)
Palbociclib Utilization Variables			
Palbociclib treatment initiation date	Date, first prescription order for palbociclib	• First prescription order (index date)	Structured data field
Line of therapy at initiation of palbociclib	• 1st • 2nd • 3rd • 4th or above	• At palbociclib treatment initiation	Based on the type and timing of the receipt of oral of IV drugs
Combination partner	• Letrozole • Fulvestrant	• ±30 days of first palbociclib order	Structured data field

Variable	Description	Collection Point	Operational
	• Other	(index date)	
Palbociclib dose	• 125 mg • 100 mg • 75 mg • Unknown	• At each prescription order	Structured data field
Other Treatments Received Variables			
Use of chemotherapy	Identify occurrence of treatment with any chemotherapy drugs listed in Appendix 4	• see Endpoints for description of time intervals	Structured data field
Use of endocrine therapy	Identify occurrence of treatment with any endocrine therapies listed in Appendix 4	• see Endpoints for description of time intervals	Structured data field
Use of supportive care medications	Identify occurrence of treatment with any supportive care medications listed in Appendix 4	• see Endpoints for description of time intervals	Structured data field
Laboratory Tests Variables			
CBC lab tests	Data flag/ Date of test collected for each WBC count test and % neutrophil test	• Closest date prior to palbociclib treatment initiation • Any instance during palbociclib treatment	Structured data field
WBC quantity	Numeric, cells/mm^3 of blood	• Date of tests and results anytime during study period	Structured data field
WBC neutrophil percentage	Numeric, reported as % (segments + bands) of the WBC	• Date of tests and results anytime during study period	Structured data field
AE Variables			
Absolute Neutrophil Count Grade	• Grade 0 : Normal • Grade 1 : 1500-2000 • Grade 2 : 1000-1499 • Grade 3 : 500-999 • Grade 4 : <500	• Anytime during follow-up when both WBC quantity and neutrophil % present on same day	Calculated based on conversion†† of WBC count and neutrophil %
AE diagnosis	Date of diagnosis collected for each event including on palbociclib treatment	• Each occurrence during treatment with palbociclib	Events based on ICD-9 diagnosis codes (see Appendix 4)

† Treatment discontinuation date based on no further treatment order or censored at end of study follow-up. All refills may not be entered into the structured field in the EMR for treatment orders.
†† Conversion: divide neutrophil % by 100, multiply value by WBC quantity (neutrophil value in K/µl), and multiply by 1000 to convert to mm^3

9.5. Data sources and measurement

EMR data were sourced from Navigating Cancer, a third party-vendor of patient EMR data aggregated across community oncology practices. The Navigating Cancer database contains EMR data, in both structured and unstructured fields (patient/clinical progress notes), from over 975 oncology and hematology providers across more than 50 locations in 25 states. Records of patients receiving care in these facilities date back to the year 2007, and as such the database contains over 2 million individual cancer patients. Data are aggregated from seven EMR systems and include the outpatient-practice encounter history of the patients under care including diagnosis type (ICD-9/10 CM), disease profile (e.g., American Joint

Committee on Cancer stage, tumor-node-metastasis stage, anatomic sites of involvement, etc.), biomarkers (e.g., ER, PR, HER2/NEU, etc.), standard laboratory records (e.g., blood chemistry, lipid, renal function tests/panels, etc.) and vital status (through Social Security Death Master File matching and practice input). Both structured data fields and unstructured data are available for research purposes with single-keyword natural language processing available to search the unstructured data elements. No manual review of clinical progress notes was planned or conducted as a part of this research. Keyword searching was conducted to identify select data points as detailed in Table 1.

Both intravenous and oral antineoplastic agent treatment orders were captured (drug name, treatment date/ cycle number, and prescription date) from structured data elements in the treatment profile from the EMR. For oral agents, refill orders may not be captured as records are not linked to the practices dispensing pharmacy claim file (if present) nor to a payer-based administrative claims database. Providers (and staff) are assumed to enter a record for each oral agent prescribed at each point when a new prescription would be needed. EMR data is not linked to a prescription dispensing record or pharmacy claims and is reliant on staff to enter records into treatment orders. Additional information on the dose, days of supply and schedule for oral agents is provided in a free-text course description field along with each treatment order.

All patients in the dataset were assigned a unique patient ID key allowing linkage across each of the three data extracts. All data are de-identified to protect Personal Health Information in accordance with the Health Insurance Portability and Accountability Act. Manual human review of clinical progress notes was not conducted during the course of this study however keyword searching of progress notes was conducted by Navigating Cancer staff and results provided for the purposes of these analyses. All data used in the study are as they were entered into the EMR system; no manual review or quality assessment of the structured or unstructured data fields was conducted.

9.6. Bias

When evaluating treatment patterns for a newly approved treatment for advanced/metastatic cancer, the most cause for concern is that treatment decisions can be influenced by severity of disease, frailty and other prognostic factors (confounding by indication). [4] Initially, a bolus of patients who have no further therapeutic options may be treated with the novel agent inflating the number of those who receive treatment in later lines of therapy. This phenomenon was observed in this analysis where the proportion of fourth-line or greater usage was highest in the first months following approval and lowest nearly one-year post approval. Although we attempted to reduce selection bias by using a new user design of patients initiating therapy with palbociclib + letrozole, the results from this study should be interpreted with caution due to the potential of unmeasured confounding. Additionally, there may have been inadequate length of follow-up depending on during which two-month interval following the approval of palbociclib patients initiated treatment. The length of follow-up necessary to assess outcomes associated with specific exposures requires a period of follow-up that takes the natural history of the outcomes. For this study, the length of follow-up may not be adequate for certain outcomes such as post-palbociclib treatment patterns.

9.7. Study Size

Study analyses were descriptive in nature and thus no formal power calculations were conducted. No subgroup comparisons were planned and thus no estimates of precision were conducted. All patients with an entry for “palbociclib” or “Ibrance” in any of the structured treatment order description data fields contained within the EMR were initially selected for study inclusion.

9.8. Data transformation

Analyses were reported for each successive two-month interval following the approval of palbociclib in the US on 01 February 2015 leading to the formation of six period-specific analysis cohorts (e.g., cohort 1 = index date anytime between 01 February 2015 and 31 March 2015; cohort 2 = index date anytime between 01 April 2015 and 30 May 2015; through cohort 6 = index date anytime between 01 December 2015 and 31 January 2016). Cumulative results are presented for the total patient sample in the dataset after each incident cohort analysis (e.g., summary results for cohort 1-2, 1-3, 1-4, 1-5 and complete sample including cohorts 1-6). Analyses were performed on all incident and cumulative cohorts.

For the analytical cohorts, line of therapy (LOT) was assigned by evaluating the type and timing of the receipt of oral and IV drugs. LOT was assigned from the date of initiation of drug therapy following the date of metastatic diagnosis. Patients for whom a confirmed date of a metastatic diagnosis could not be retrieved from the structured data were assumed to be metastatic on the date at which they began treatment with palbociclib.

LOT assignment, and hence utilization of chemotherapy drugs in combination, was done by grouping chemotherapy drugs into treatment regimens given the dates of the treatment orders fall within 30 days of each other, and the drugs were representative of known treatment plans. The addition of new agents that occur beyond 30 days trigger drug combination reassignment, and the LOT was increased except in the case of a known sequential therapy, which were accounted for by distinct grouping rules, and for drugs used in the maintenance setting. The removal of an agent (i.e. no record of a treatment order for a component of the original combination) did not constitute the end of a regimen if the removal was temporary in that the patient resumed the same combination treatment regimen within 60 days of the start of the LOT.

Several exceptions were made to the general LOT assignment methodology to accommodate the potential for missing oral prescription refill data. First, a patient with a treatment order for palbociclib and a treatment order for letrozole (occurring within 30 days to be considered combination; same logic applied for fulvestrant) who was previously treated with letrozole (or fulvestrant in the case of that combination) was considered to be receiving the combination as LOT 1 (not LOT 2 as would be indicated using only a strict 30-day gap rule). Next, patients who had received palbociclib + letrozole and for whom no subsequent letrozole order was found but who did have a subsequent palbociclib treatment order were considered to still be on the numerical LOT of the initial palbociclib treatment (i.e. the LOT was not advanced to indicate “palbociclib monotherapy”).

9.9. Statistical methods

9.9.1. Main summary measures

Objective 1 - Characterize the demographic and clinical characteristics of patients at the initiation of treatment with palbociclib.

- Age
- Body Mass Index
- Menopause status
- Histology
- Stage recorded in EMR
- ECOG-PS at initiation of palbociclib
- ER, PR and HER2 status (positive/negative/unknown)
- Sites of metastatic disease
- Status at last follow-up (alive/deceases, on treatment, lost to follow-up [no treatment or medical encounters within 90 days of data end])

Objective 2 – Describe palbociclib utilization by line of therapy (LOT)

- Proportion of use in each of first-, second-, third-, ≥ fourth- line therapy
- Proportion of patients with prior endocrine therapy
- Proportion of patients with prior chemotherapy
- Time to initiation of palbociclib from metastatic diagnosis

Objective 3 – Assess the frequency and timing of palbociclib dose reduction.

- Frequency of any dose reduction
- Frequency of reduction from 125 mg to 100 mg
- Frequency of reduction from 125 mg to 75 mg
- Frequency of reduction from 100 mg to 75 mg
- Time to first dose reduction
- Frequency of escalation from starting dose higher dose

The starting dose order for palbociclib was collected from the course description field of the treatment order form in the EMR. A dose reduction was defined as any prescribed palbociclib treatment at a lower dose than that of the index palbociclib order. The time to first dose reduction was calculated from the date of the index palbociclib treatment to the date of the prescription for the lower dosage form (either 125 mg to 100 mg, 125 mg to 75 mg, or 100 mg to 75 mg).

Objective 4 – Quantify the frequency of complete blood count (CBC) monitoring during treatment with palbociclib

- Proportion of patients with CBC results available prior to first palbociclib order
- Mean (median) number of tests over duration of palbociclib treatment

- Mean (median) number of tests by cycle of palbociclib therapy (with cycle approximated by length of time since initiation of palbociclib)

Objective 5 - Assess the incidence (by grade) and timing of neutropenia events through calculation of absolute neutrophil count (ANC) during treatment with palbociclib.

- Any neutropenia event by grade (see Table 1 for grade operational definitions) during palbociclib treatment
- Highest grade neutropenia event by time since initiation of palbociclib
- Frequency of neutropenia (based on CBC test results) within 56, 112, 168 days palbociclib treatment initiation (as a proxy for number of cycles completed)

The date and results of each WBC count and % neutrophil laboratory test were collected from the structured data elements of the EMR. Within these results, a conversion between the WBC count and % neutrophil was performed for analysis of neutropenia (see *Table 1* footnote). Only patients with at least one CBC test value were included in any analysis related to neutropenia.

Objective 6 – Utilization of other chemotherapy, endocrine therapy, and supportive care

- By line of therapy (first or second or greater) and length of follow-up (< 6 months and ≥ 6 months
- As endocrine monotherapy or combination therapy
- As chemotherapy
- Supportive care agents by name of agent

9.9.2. Main statistical methods

The statistical analysis plan is included for reference in Appendix 4. Descriptive statistics were reported for continuous variables (e.g., age) using means, medians and standard deviations. Categorical variables (e.g., histology, stage) were reported using frequencies and proportions. No univariate comparisons across subgroups of categorical or continuous variables were assessed in this study. No other inferential statistical analyses, such as multivariable models, were used in the course of analysis.

9.9.3. Missing values

Frequencies of missing observations by variable are reported in the study. In case of missing observations, the calculation of percentages dependent upon a known value was restricted to the total number of observations with a known value.

9.9.4. Sensitivity analyses

None

9.9.5. Amendments to the statistical analysis plan

Definition modifications:

The following statement indicated in the SAP was modified to only include data from the laboratory evaluations. Furthermore, only patients with at least 1 recorded CBC laboratory test result were assessed for the occurrence of neutropenia

"The date of diagnosis of neutropenia is the first occurrence of any of the following: 1) an ICD-9 based diagnosis of neutropenia; 2) a calculation (based on previously described algorithm of WBC count and % neutrophil) resulting in an absolute neutrophil count <1000; or 3) the presence of the keyword neutropenia (and other derivatives – see Appendix 1) in a clinical progress note" would be used to mark a neutropenia diagnosis.

The following elements listed in the statistical analysis plan (Appendix 4) **were revised** for the final analysis:

- LOT was only assessed as LOT 1, LOT 2, LOT 3 and LOT 4+. Given that few patients had progressed to LOT 5 or greater, LOT5+ use was not reported in this final analysis.
- Frequency of palbociclib treatment discontinuation: Final results present the proportion of patients who switched to another therapy, were lost to follow-up (no record of medical/pharmacy claim with 90 days of study period end) or were deceased at the end of follow-up. Given the inconsistency in reporting of prescription refills for palbociclib and its combination agents (letrozole or fulvestrant) it was not possible to reliably calculate a date of treatment discontinuation and thus the proportion of patients discontinuing palbociclib treatment could not be determined. Only the number of patients considered to have switched to a new therapeutic regimen (based on LOT assignment rules) or those with a known date of death could be considered as discontinuations.
- Frequency of CBC laboratory evaluations during first palbociclib cycle (i.e., within 30 days of palbociclib initiation): Modified to be within 28 days given palbociclib cycle definition.
- Frequency of CBC laboratory evaluations during second palbociclib cycle (i.e., >30 and ≤60 days following palbociclib initiation): Modified to be within 28 and 56 days given palbociclib cycle definition.
- Proportion receiving any and/or each recorded chemotherapy, endocrine and supportive care drugs for advanced/metastatic breast cancer during the following timeframes (anytime prior to palbociclib treatment initiation, within 6 months following palbociclib treatment initiation): Revised to examine switching patterns pre and post palbociclib treatment due to lack of prescription refill information and reliability in accurately assessing treatment discontinuation date as a result.
- Proportion receiving any and/or each recorded endocrine therapy at start of (±14 days) palbociclib treatment initiation: Accounted for in LOT assignment and treatment regimen grouping based on the receipt of other drugs within 30 days of the start of palbociclib and/or modified LOT rules to account for lack of refill for endocrine therapies started prior to palbociclib treatment.
- Proportion receiving any and/or each recorded supportive care medications during the following timeframes (anytime during palbociclib treatment, at start of (±14 days)

first palbociclib prescription, at start of (±14 days) second palbociclib prescription: Revised to examine receipt of supportive care agents during palbociclib treatment.
- Proportion receiving any and/or each recorded chemotherapy or endocrine therapy as their first therapy subsequent to palbociclib treatment discontinuation: LOT assignment and treatment regimen grouping based on the receipt of other drugs within 30 days of the start of palbociclib and/or modified LOT rules to account for lack of refill for endocrine therapies started prior to palbociclib treatment.

The following elements listed in the statistical analysis plan were **not assessed** for the final analysis due to data limitations uncovered in the course of conducting the analysis:

- Duration of treatment: due to the inconsistency in reporting of prescription refills for palbociclib and its combination agents (letrozole or fulvestrant), calculations of duration of treatment were deemed unreliable and removed from the final analysis
- Time to second dose reduction
- Proportion of palbociclib treatment discontinuations due to any and/or specific AEs (based on ICD-9/10 diagnosis codes)
- Time between lower dose and resumption of higher dose: removed from analysis due to short follow-up time and few data points
- Time to palbociclib treatment discontinuation: Given the inconsistency in reporting of prescription refills for palbociclib and its combination agents (letrozole or fulvestrant), it was not possible to reliably calculate a date of treatment discontinuation and thus the proportion of patients discontinuing palbociclib treatment could not be fully assessed.
- Average time of treatment interruption/delay: Given the inconsistency in reporting of prescription refills for palbociclib and its combination agents (letrozole or fulvestrant), it was not possible to reliably calculate start and stop dates for prescription fills and estimates of the interval of treatment interruption/delay were deemed unreliable.
- Mean number of neutropenia events before and during palbociclib treatment by LOT: Given the variable pre-palbociclib treatment interval and the duration of treatment with palbociclib the mean number of neutropenia events was not considered a reliable measure.
- Proportion of palbociclib dose reductions due to an AE or neutropenia: rationale for dose reduction could not be inferred as no access to patient progress notes was available.

The following elements not listed in the statistical analysis plan were **included** for the final analysis:

- Highest grade of neutropenia diagnosis during palbociclib treatment
- Dose reductions during first 2 cycles (56 days), 4 cycles (112 days) and 6 cycles (168 days) of palbociclib treatment. Cycle number approximated by time since initiation as described.

9.10. Quality control

Data were provided as anonymized patient-level analytical files. To ensure quality control of the data, a set of quality control (QC) measures upon retrieval of the data and throughout the study process were conducted to ensure validity. Specifically, three levels of QC were performed:

9.10.1. Variables

Checks on coding for specific diseases and subtypes of diseases including specific biomarker and mutations were conducted using ICD-9 codes and structured data inputs using both current and retrospective retired codes. Completion rates for specified inclusion and exclusion fields were checked to determine if additional algorithms need to be developed to identify patients. LOT determination was conducted with both automated and manual clinical review to determine appropriate drug lines, and combinations of therapy and drug regimens are compared to the NCCN guidelines' treatment regimen library.

9.10.2. Analysis

Rules were developed to ensure that the appropriate outcomes variables were calculated from the available data. Derived variables rules and missing data imputation rules were created and recorded in the statistical analysis plan. A check for duplicates was conducted and rules for removing duplicate data were created in addition to rules for dealing with multiple data points for a specific variable. Drug administration dates and verified min and max dates for drug administration were compared to ensure temporal consistency.

9.10.3. Validation

The goal was to determine reliability and consistency of data sources between updates to the database over time. Consistency checks were conducted upon final database creation for both internal and external consistency by validating the measured variables, treatment patterns and outcomes for patients contained within subsequent datasets. A patient ID key was maintained by both the analysis team and the data vendor to ensure identification of matched patients between the dataset updates.

9.11. Protection of human subjects

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

This research utilized secondary data from a fully anonymized dataset. A central IRB reviewed the study protocol and deemed the study exempt from full review. A waiver of informed consent was obtained for 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.

10. RESULTS

10.1. Participants

Overall, 965 female adults who had a treatment order including palbociclib anytime from 01 February 2015 to 31 January 2016 were selected from the EMR database. Table 2 shows the study attrition table and analytical cohort formation. Of the initial 965, 763 (79.1%) were retained for analysis. The 202 patients removed from analysis were excluded sequentially due to the following reasons: (1) no breast cancer diagnosis = 13; (2) received palbociclib as part of a clinical trial or a palbociclib prescription prior to 01 February 2015 = 21; (3) no record of combination/concomitant treatment with letrozole or fulvestrant = 168. The final cohort consisted of 763 patients of which 80.2% (n=612) were treated with palbociclib + letrozole and 19.8% (n=151) who were treated with palbociclib + fulvestrant.

Table 2. Study attrition table and analytical cohort sample size.

Inclusion Criteria	N	Cumulative
Received at least one prescription for palbociclib during the index period	965	965
Exclusion Criteria		
No confirmed diagnosis of breast cancer (ICD-9/10 diagnosis codes)	13	952
Prescribed palbociclib prior to 01 February 2015 or as part of a clinical trial	21	931
No record of combination/concomitant treatment with letrozole or fulvestrant within 30 days of palbociclib order date	168	763
Analytical Cohorts		
Palbociclib in combination/concomitant with either letrozole or fulvestrant	-	763
Palbociclib in combination with letrozole	-	612
Palbociclib in combination with fulvestrant	-	151

Results summarized within Section 10 describe only patients prescribed palbociclib + letrozole (N=612) as during the study enrollment period the only approved concomitant therapy approved for use with palbociclib was letrozole. Use of palbociclib + fulvestrant was considered off-label use during the reporting period. All detailed source tables of the results for this cohort are presented in Section 15 – Source Tables and Figures for Palbociclib + Letrozole Analysis. Additional source tables providing the results of analysis for the 151 patients who received letrozole + fulvestrant are included in Section 16.

10.2. Descriptive data

10.2.1. Demographic and Clinical Characteristics

Full descriptive results of the demographic and clinical characteristics of patients are presented in Table 15.1. Patients treated with palbociclib + letrozole were categorized into bi-monthly groups based on the month of palbociclib treatment initiation. Of all identified patients treated with palbociclib + letrozole 10.5% initiated therapy in February/March 2015, 17.6% in April/May 2015, 20.4% in June/July 2015, 17.6% in August/September 2015, 15.0% in October/November 2015, and 18.8% in December 2015/January 2016.

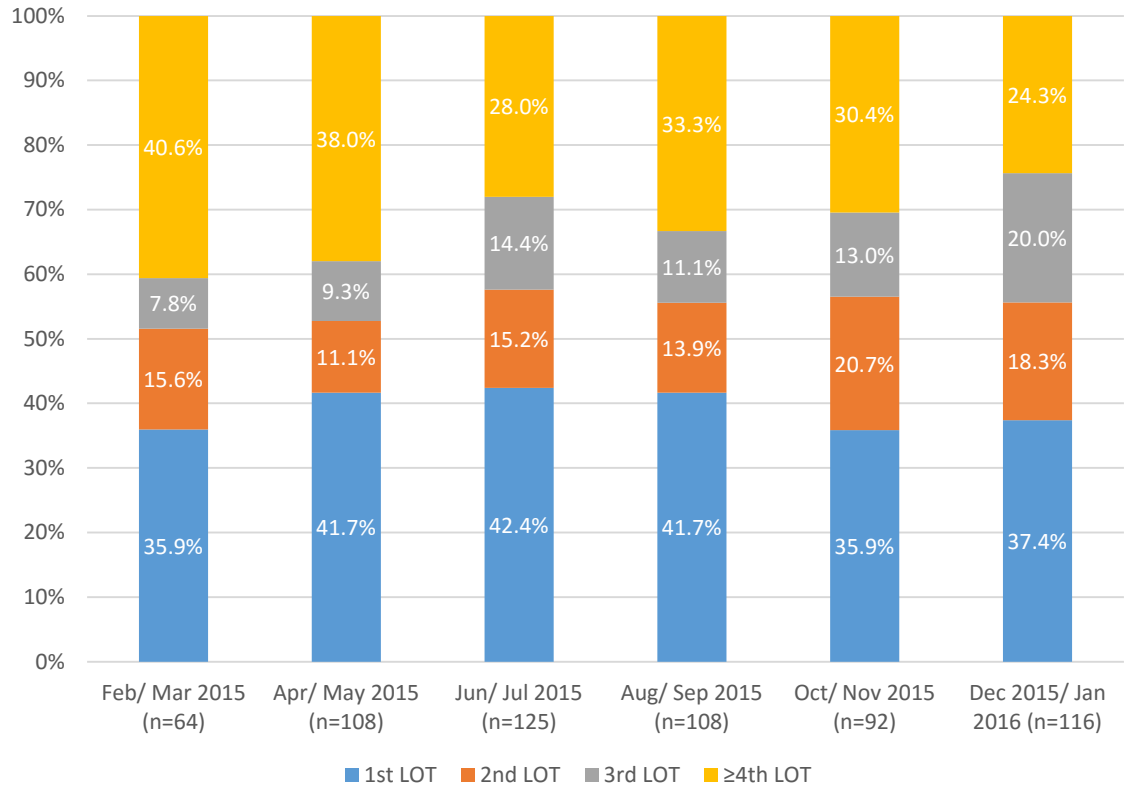
Overall, the mean age at advanced breast cancer diagnosis was 61 years (SD=12) while the mean age at initiation of palbociclib was 64 years (SD=12). In this cohort, 49.7% (n=304) were <65 years of age at initiation of palbociclib treatment and 50.3% were ≥65 years of age. A large proportion, 72% of women had unknown menopause status (n = 443) and unknown tumor histological subtype (unknown = 68%; n=415). The average weight at initiation of palbociclib was 165 pounds (SD=37) with the average BMI of 28.2 (SD = 7.6). Restaging of patients is not typically recorded in the EMR; therefore, the distribution of AJCC stages recorded in the EMR for patients was: ≤ IIB = 25.2%, IIIA = 7.2%, IIIB = 1.6%, IIIC = 4.4%, IV = 45.4%, unknown = 16.2%. More than two-thirds (69.9%) of patients had a confirmed ER+/ HER2- tumor while the ER and HER2 status could not be confirmed for the remainder due to lack of reporting in the EMR. Additionally, 82.5% were confirmed ER+ and 76.0% were confirmed HER2-. Site of metastatic disease was not available in the EMR structured data for the majority of patients. The number of patients for whom a location of metastases was indicated (based on ICD-9/10 diagnosis codes) included: bone = 24 patients, liver = 7 patients, lung = 3 patients, lymph = 1 patient and skin = 1 patient.

10.2.2. Line of Therapy at Initiation of Palbociclib + Letrozole Initiation

Overall, 39.5% female breast cancer patients initiated palbociclib + letrozole as a first-line treatment while 15.7%, 13.1% and 31.7% received their initial palbociclib + letrozole treatment in second-, third- and fourth-line or greater, respectively (Table 15.2). The proportion of patients initiating palbociclib + letrozole by month of initiation and LOT is shown in Figure 1 (and Table 15.2). Overall, palbociclib + letrozole use as first-line treatment ranged from 37.4%-40.6%, second-line 11.1%-20.7%, third-line 7.8%-20.0% and fourth-line or greater from 24.3%-40.6%. As illustrated in the figure, the proportion of patients initiating at fourth-line and greater declined from 40.6% to 24.3% during the first year following palbociclib approval while the proportion of patients initiating at first-line remained stable, starting at 35.9% in February/March 2015 and ending at 37.4% in December 2015/January 2016.

Treatments received and included in the EMR prior to the initiation of palbociclib + letrozole were examined. The number of patients who received any prior endocrine or chemotherapy was smaller for those with palbociclib use as first-line treatment (46.3% and 15.3%, respectively), compared to those with second- (75.0% and 43.8%), third-(87.5% and 70.0%) or fourth-line treatment (95.9% and 87.1%).

Figure 1. Proportion of patients initiating palbociclib + letrozole as first-, second-, third-, and fourth-line or higher treatment by month of initiation.



Key: LOT – line of therapy.

10.2.3. Patient Disposition

Table 15.3 shows the disposition of patients at the end of the study period in terms of the length of follow-up, proportion receiving treatment, proportion deceased, and proportion lost to follow-up. Data were analyzed by the treatment initiation line (first-line vs second-line or higher) and stratified by the length of follow-up period (< 6 months versus ≥ 6 months). The mean length of follow-up (months) was 6.4 (SD = 3.9) with 51.3% of patients having ≥ 6 month of follow-up. The proportion of patients with a follow-up of ≥ 6 months was approximately even at 55.8% among those who initiated in first-line compared to 51.6% of those who initiated palbociclib + letrozole in second-line or higher. At the end of the study period, 78.8% (n = 482) were on treatment, 11.8% (n = 72) were deceased and 9.5% (n = 58) were lost to follow-up where a patient was considered lost to follow-up if there was no record of a medical encounter or treatment order within 90 days of the end of the study period. Of the 482 patients on treatment, 61.4% (n=296) had palbociclib + letrozole as their last recorded LOT. Among patients with ≥ 6 months of follow-up, the proportion of patients on palbociclib + letrozole treatment was 61.5% for first-line and 40.2% among those who received palbociclib + letrozole in second-line or higher. Of the 72 deceased patients, 29.2% (n=21) had received no additional chemotherapy treatment after palbociclib + letrozole while 71.8% (n=51) had received a subsequent LOT prior to death. The majority of the 72 deaths, 68.1% (n=49) occurred among patients receiving palbociclib + letrozole in second-line or higher at treatment initiation and who had < 6 months of follow-up. Of those 49 deaths,

63.3% (n = 31) occurred after a patient had received a line of therapy following palbociclib + letrozole treatment with the remainder, 37.7% (n=18) not having received a LOT following palbociclib + letrozole treatment. Of the 18 deaths among patients with palbociclib + letrozole as their last line of therapy, 13 (72.2%) occurred among patients initiating palbociclib in third-line or higher (data not shown).

10.2.4. Treatments Received Prior to Palbociclib + Letrozole Initiation

Treatments received prior to initiating treatment with palbociclib + letrozole are shown in Table 15.4. Only treatments considered as the LOT prior to the palbociclib initiation LOT were assessed. Treatments are presented individually by drug/combination and aggregated into the following categories: endocrine monotherapy, combination endocrine with chemotherapy or targeted therapy, or chemotherapy (categories were not considered mutually exclusive, combination of endocrine and chemotherapy were counted in both combination and chemotherapy subgroups). Overall, 68.5% (n=419/612) of patients had a record of at least one therapy prior to initiation of palbociclib + letrozole. Restricting to only patients with a LOT prior (n=419), 43.9% (n=184/419) received endocrine monotherapy, 16.0% (n=67/419) received endocrine therapy in combination with either chemotherapy or targeted therapy, and 49.4% (n=207/419) received prior chemotherapy. Of the 242 patients who initiated palbociclib + letrozole as first-line treatment for metastatic disease, a minimum of 20.2% (n=49/242) received prior therapy in the adjuvant setting (all therapies received prior to first-line initiation may not have been available in the dataset – see Section 11.2 – Limitations – for further discussion).

Endocrine therapy in the LOT prior to initiation of palbociclib + letrozole was observed in 65.6% (n=63) of patients initiating palbociclib + letrozole in second-line (n=96), 71.3% (n=57) of third-line (n=80) and 51.5% (n=100) of fourth-line or higher (n=194). Of 251 patients with endocrine therapy in the LOT prior to the initiation of palbociclib + letrozole, 73.3% received monotherapy with the most common regimens (observed among ≥ 5 patients) being: anastrozole = 21.9% (n=55), tamoxifen = 20.7% (n=52), fulvestrant = 19.9% (n=50), exemestane = 7.2% (n=18), and letrozole = 3.2% (n=8). Of the 67 patients who received a combination of endocrine with another endocrine, chemotherapy or targeted therapy, the most common regimens (observed among ≥ 5 patients) were: everolimus + exemestane = 29.9% (n=20), anastrozole + fulvestrant = 11.9% (n=8), and exemestane + fulvestrant = 7.5% (n=5).

Chemotherapy in the LOT prior to initiation of palbociclib + letrozole was observed in 40.6% (n=39) of patients initiating palbociclib + letrozole in second-line, 33.8% (n=27) of third-line and 63.4% (n=123) of fourth-line or higher. Of the 207 patients with chemotherapy prior to initiation of palbociclib + letrozole, the most common agents received were: capecitabine = 5.9% (n=36), paclitaxel = 3.6% (n=22), and everolimus + exemestane = 3.3% n=20), eribulin mesylate = 7.7% (n=16), paclitaxel (protein-bound) = 7.2% (n=15), everolimus = 5.3% (n=11), cyclophosphamide = 4.8% (n=10), doxorubicin = 2.9% (n=6), docetaxel = 2.4% (n=5), cyclophosphamide + docetaxel = 2.4% (n=5), and ixabepilone = 2.4% (n=5).

10.2.5. Treatments Received Following Palbociclib + Letrozole Initiation

Treatments received in the LOT following palbociclib + letrozole are shown in Table 15.5, overall, and by LOT at initiation (first- versus second-line or higher), stratified by length of follow-up (< 6 months compared to ≥ 6 months). Of 612 patients receiving treatment with palbociclib + letrozole, 38.6% (n=236) received treatment with a new regimen following their palbociclib + letrozole LOT. The next most common regimens included: 56.8% (n=134) received a regimen containing any endocrine therapy and 64.8% (n=153) initiated treatment with a regimen containing a chemotherapy agent (not all agents shown including targeted monotherapy). The most common endocrine monotherapies were fulvestrant (n = 39) and letrozole (n = 20), the most common combination endocrine post-therapies were fulvestrant + palbociclib (n = 10) and everolimus + exemestane (n = 6). The most common chemotherapies were capecitabine (n = 24) and paclitaxel protein-bound (n = 10).

10.2.6. Palbociclib Dosing

The palbociclib + letrozole patterns of dose initiations and reductions are shown in Table 15.6, categorized by the number of cycles of palbociclib received by the patient over the course of their follow-up (using the number of days from initiation of palbociclib + letrozole as proxy with each 28 day interval considered 1 cycle). Overall, 85.6%, 72.7% and 54.9%, of palbociclib + letrozole patients had completed ≤2, ≤4, and ≤6 cycles of palbociclib treatment. The proportion of the 612 palbociclib + letrozole patients with a known starting dose recorded in the treatment order course description field of the EMR was 68.1% (n = 417). Patients who had received fewer cycles of palbociclib were more frequently without a known starting dose (30.0% of those who had completed ≤ 2 cycles compared to 19.9% of patients who had completed ≤ 6 cycles).

Of the 417 with a known starting dose, 88.0% (n = 367) initiated palbociclib at 125 mg, 11.0% at 100 mg and 1.0% at 75 mg. Dose reductions were observed in 20.1% (n=84) patients with known starting dose. All dose reductions (n=84 among patients with ≤ 6 cycles) occurred within 168 days of palbociclib treatment initiation (approximately first 6 cycles assuming 28 days per cycle) while 69.0% (58/84) occurred within the first two cycles. Of those patients who did reduce the initial dose, 77.4% (n = 65) were from 125 mg – 100 mg. The average number of days to the first dose reduction was 48 (SD = 31). The median days to first dose reduction was 39 (data not shown). Of note, 5 patients had a record of a dose increase of which 3 dose increases occurred among patients initiating at either 75 mg or 100 mg and 2 dose increases occurred among patients who were initially dosed at 125 mg, dose reduced, and then subsequently increased.

10.2.7. Supportive Care Treatment

Table 15.7 comprehensively lists all supportive care agents received during palbociclib + letrozole treatment which were recorded in the treatment orders of the EMR database. Overall, 64.1% (n=392) of palbociclib + letrozole patients received at least 1 supportive care agent while receiving treatment with palbociclib. Among patients receiving palbociclib + letrozole as first-line treatment, 69.6% (n=94) of those with ≥ 6 months of follow-up received a supportive care agent compared to 64.5% (n=69) of those with < 6 months of follow-up. For those patients who received palbociclib + letrozole in ≥ second-line, 66.5% (n=119) with

≥ 6 months of follow-up received a supportive care agent compared to 57.6% (n=110) of those with < 6 months of follow-up.

The most common supportive care treatments received were: bone preserving agents (41.7%, n=255) and antiemetics (28.1%, n=172). Of note, oxycodone was received by 5.6% of patients receiving palbociclib + letrozole as second-line or higher therapy for those with more than 6 months of follow-up. The rank order, in terms of the frequency of use among patients initiating palbociclib in first-line or ≥ second-line remained the same as for the rank order when examining the most common drugs (≥5%) across all LOTs.

10.3. Outcome data

Not applicable

10.4. Main results

Not applicable

10.5. Other analyses

None

10.6. Adverse events / adverse reactions

As described, this study employed a retrospective cohort study design and utilized an EMR database to assess outcomes of interest for patients receiving palbociclib for the treatment of metastatic breast cancer. No chart review was planned for this study and therefore it was not possible to evaluate if the patient was actively on-treatment (e.g. not during a drug holiday) when an AE occurred. Therefore, a determination of causality in regards to the relation between palbociclib treatment and any AEs experienced while receiving palbociclib treatment (or other therapies and the experience of AEs), including neutropenia, could not be made. Also, not all AEs may be documented by ICD-9/10 diagnosis codes in the EMR database.

10.6.1. Adverse Events (Excluding Neutropenia)

AEs were evaluated based on ICD-9/10 diagnosis codes occurring post initiation of treatment with palbociclib + letrozole. The list of AEs for consideration mirrored the AE profile in the package insert for palbociclib. The list of AEs considered is included in the SAP (see Appendix 4). Table 15.8 shows the rates of diagnoses of AEs (excluding neutropenia – see section 10.6.2) according to the number of cycles of palbociclib + letrozole received (using days post palbociclib initiation as a proxy for number of cycles). As an active treatment interval for palbociclib + letrozole could not be defined due to the lack of a record for the prescription fill (i.e., no administrative claims linkage) the occurrence of an AE was evaluated based on the time from the initiation of palbociclib + letrozole treatment assuming the patient was on therapy until treatment regimen switch, lost to follow-up or death. The rate of diagnosis of any AE (based on ICD-9/10 codes) was 28.0% (n=112/400) for patients who had received at least 6 cycles (168 days) of treatment and including patients who were diagnosed with the event but may not have completed 6 cycles of treatment (i.e. patient diagnosed with AE during cycle 2 counted in numerator and denominator for 6 cycle calculation). The five most common AEs diagnosed included: fatigue = 8.3% (n=33), nausea

= 8.3% (n=33), leukopenia = 4.8% (n=19), pain = 4.5% (n=18), and thrombocytopenia = 4.0% (n=16). By the 4th and 2nd cycle, respectively, among those who received treatment for at least those interval or who were diagnosed with anytime within the interval, the rate of diagnosis of any AE was lower at 19.3% (n=89/460, by 4th cycle) and 11.1% (n=58/522), respectively.

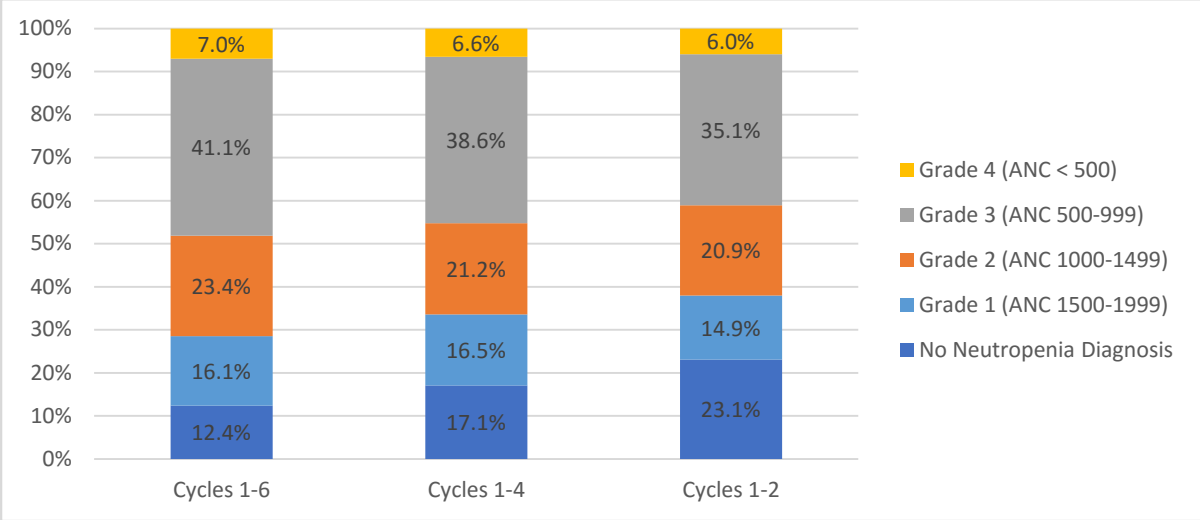
10.6.2. Adverse Events (Neutropenia)

Neutropenia was assessed based on available laboratory data; the diagnosis of neutropenia was not confirmed by the patients treating physician. Only patients with at least one valid CBC test result available in structured data fields of the EMR were considered for the neutropenia analysis. Table 15.9 presents the CBC testing and neutropenia rates overall and by cycles of palbociclib therapy completed.

Overall, 55.1% (n=337) of patients had at least one EMR documented CBC both in the period prior to palbociclib + letrozole initiation and during palbociclib + letrozole treatment (data not shown). During the palbociclib + letrozole treatment interval, 57.4% of patients (n=351) had a record of at least one CBC test (Table 15.9). Regardless of cycles completed, the mean number of CBC tests among all patients was 6.0 (SD=5.7). Mean number of CBC tests during the first cycle (28 days of treatment) was 2.0 (SD = 1.1). During the first two cycles (56 days) of treatment the mean number of tests was 3.3 (SD=2.2), during the first 4 cycles (112 days) the mean number of tests was 4.7 (SD=3.6), and over the first 6 cycles (168 days) the mean number of tests was 5.3 (SD=4.5).

Among the 351 patients with a least one CBC laboratory test during palbociclib + letrozole treatment, 74.6% (n=262) had a first laboratory test indicative of neutropenia at a mean 28.4 days (SD = 19.6) following treatment initiation. Median days to first neutropenia occurrence was 26. The highest grade of neutropenia (consistent with observed lab values) anytime during the palbociclib + letrozole treatment by time since initiation of palbociclib (number of cycles) is shown in Figure 2. Overall, the proportion of patients with lab values consistent with grade 3 and grade 4 neutropenia by the 2nd cycle was 35.1% and 6.0%, respectively. By the 4th cycle, the rate of lab values consistent with grade 3 and 4 neutropenia increased to 38.6% and 6.6%. Finally, by the 6th cycle the rate of lab values consistent with grade 3 and 4 neutropenia was 41.1% and 7.0%, respectively. By the 6th cycle, 12.4% of patients did not have lab values consistent with neutropenia (of those patients with at least one CBC laboratory test available during that time period) and 123/124 of lab values consistent with grade 3 and 21/21 lab values consisted with grade 4 neutropenia had occurred. The rate of any grade of neutropenia during treatment with palbociclib + letrozole was not significantly different (p-value=0.24) among patients without pre-palbociclib + letrozole neutropenia testing compared with those patients with a pre-palbociclib + letrozole neutropenia testing (data not shown).

Figure 2. Highest grade of neutropenia (based on laboratory results) (%) by number of cycles completed† among patients receiving treatment with palbociclib + letrozole.



† Cycles approximated by time since initiation of palbociclib: cycles 1-2 = 1-56 days; cycles 1-4=1-112 days; cycles 1-6=1-168 days.
Key: ANC – absolute neutrophil count; LOT – line of therapy.

11. DISCUSSION

11.1. Key results

In summary, this research was able to identify female metastatic breast cancer patients receiving treatment with palbociclib, assess the line of therapy at which patients initiated treatment, and describe the real-world frequency, severity, and timing of neutropenia events. We observed that the proportion of patients initiating treatment with palbociclib + letrozole in first-line remained consistent, varying from 35.9%-42.4% of all new palbociclib + letrozole treatment starts over the 12 months post US approval. The results also indicated a trend over time (since approval) of increased initiation of palbociclib + letrozole in third-line with a corresponding decrease in the proportion of patients initiating treatment in fourth-line or higher. Fourth-line use was highest, at 40.6% of patients initiating treatment, in the two month interval immediately post-approval (February/March 2015) and lowest, at 24.3%, nearly one-year later (December 2015/January 2016). At the end of the study period, after patients were followed for a mean of 6.4 months, 78.8% (n = 482) were considered still to be receiving treatment (of which 61.4% were receiving palbociclib+ letrozole), 11.8% (n = 72) were deceased and 9.5% (n = 58) were lost to follow-up. Of deceased patients, 29.2% had palbociclib + letrozole as their last line of therapy while 71.8% had received another treatment regimen following palbociclib + letrozole before their death.

Of patients with a known palbociclib starting dose (n=417), 88.0% (n=367) initiated therapy at 125 mg, 11.0% (n=46) at 100 mg, and 1.0% (n=4) at 75 mg. Dose reductions were observed in 20.1% (n=84) of patients with a known starting dose. Mean days to first dose

reduction was 48 (SD=31); 69.0% (58/84) occurred within the first two cycles (defined as within 56 days of palbociclib + letrozole treatment initiation) and 100% (84/84) occurred within the first 6 cycles (168 days) of palbociclib + letrozole treatment initiation.

Of the 612 patients included in this research, CBC tests and results after initiation for palbociclib + letrozole were available for 57.4% of patients. On average, patients had 2.0 (SD=1.1) CBC tests by the end of the first cycle, 3.3 CBC tests (SD=2.2) by the end of first 2 cycles of treatment and 5.3 tests (SD = 4.5) by the end of the first 6 cycles. Of the 351 patients with CBC data available, 74.6% (n=262) had a laboratory value consistent with neutropenia (of any grade) over the course of follow-up. The highest grade of neutropenia (based on laboratory data) events among 351 patient with at least one CBC: no neutropenia event = 25.4%; grade 1 = 12.8%; grade 2 = 20.5%; grade 3 = 35.3%; and grade 4 = 6.0% regardless of length of follow-up. The mean time to the first neutropenic event was 28.4 days (median=26) and the proportion of patients with laboratory data consistent with grade 3 or grade 4 neutropenia increased from 35.1% and 6.0% by the completion of the first two cycles to 41.1% and 7.0% by the completion of the first 6 cycles of therapy, respectively, when restricting to patients with the event occurring in that interval or having been on treated during the interval.

11.2. Limitations

The main limitations of this research include a lack of complete care history since the breast cancer diagnosis and the lack of prescriptions claims to validate the use of palbociclib and other drugs (including dose, quantity) used in the course of treatment and the dates of those uses. Additionally, no chart review was planned or conducted to access patient data within clinical progress notes to verify items such as menopausal status, capture of additional AEs, and pathology reports or laboratory findings interpretation not available through the structured data fields. Finally, use of palbociclib + letrozole outside of the labeled indication (as initial endocrine based therapy) limits the applicability of the findings although a better reflection of how care is received in the real-world setting. These limitations are not unique to this dataset per se but are a reflection of the diverse EMR systems captured in the database and the extent to which providers, nurses and practioners in general complete fields, and the degree to which data, such as prescription orders and fills or laboratory results are passively updated within the patient's record.

More specifically, the complete treatment history of the patient may not have been captured. Care received prior to treatment at a practice contributing data to the aggregated EMR database is not included in structured data fields. Therefore, palbociclib + letrozole LOT at initiation may have been misclassified should patients have received treatment prior to or outside of the practices contributing data to the EMR database. This misclassification is thought to be limited due to the fact that the mean time from the metastatic diagnosis to palbociclib treatment initiation overall was 36 months; 11 months for patients receiving first-line palbociclib + letrozole and 67 months for those receiving palbociclib + letrozole in fourth-line or greater. Additionally, the proportion of patients who received prior therapy (68.5%) was appreciably higher than estimates from the clinical trial. While this may indeed reflect real-world practice (i.e. includes neoadjuvant/adjuvant treatments of first-line patients) and the heterogeneity of the patient population, particularly during the interval just

following drug approval, this may in part also reflect data limitations. Patients considered as receiving palbociclib + letrozole as first-line may be misclassified if a metastatic diagnosis was not present in the data. In this case where a patient did not have a metastatic diagnosis, we assumed that the index date (date of metastatic diagnosis from which LOT was subsequently counted) began on the date of the palbociclib treatment initiation. The 49 first-line patients who were observed to have received prior therapy may actually be receiving palbociclib as LOT2 in which case the proportion of patients with prior systemic therapy would drop from 419/612 (68.5%) to 370/612 (60.5%).

Second, treatment orders for oral agents, including palbociclib, were not linked to an administrative claims record or dispensing pharmacy record. EMR systems capture treatment orders (for both IV and oral agents) through manual entry by the provider into structured fields within the EMR which describe the individual treatments prescribed and a description of the therapy course (i.e., dose and schedule). We noted that for patients receiving aromatase inhibitor therapy, including anastrozole and letrozole, there were often significant time intervals (>1 year) between the treatment order and any subsequent treatment order information. These data indicate that refills of these drugs were not captured as it is unlikely that a patient would go off therapy for such a significant amount of time. While this information limits the ability to accurately document the actual interval for which a patient was actively on-treatment (e.g., treatment interruptions could not be captured, true duration of treatment is unknown), it would not impact the assessment of LOT because any new treatment prescribed in theory should be entered into the EMR by the provider. In order to further qualify the LOT assignment and strengthen this assumption, we specified that treatment orders within 30 days constituted a combination treatment regimen. By doing so, we limited the potential for LOT misclassification which may have resulted from differential reporting of refill information by providers.

Finally, we observed that 68.1% of patients had a known starting dose of palbociclib while on treatment with palbociclib + letrozole. Most commonly we observed that course descriptions of treatment orders for patients without a known starting dose included language such as “1 tablet orally”. While additional information may have been noted in subsequent treatment orders we restricted this analysis only to those patients for whom the dose was recorded on the first treatment order to minimize bias in reporting starting dose.

In regard to laboratory monitoring with CBC, and subsequent evaluations of neutropenia based on laboratory results, we restricted analyses to those patients with at least one valid CBC test including results. Of the 612 patients initiating therapy on palbociclib + letrozole, 57.4% (n=345) of patients had at least one CBC laboratory result. The lack of CBC monitoring for 42.6% of patients is a reflection of the multiple EMR systems feeding data into the EMR database. Certain systems may capture laboratory data through scanned reports and may not be electronically transmitted into the providers EMR. These data are not available through the structured laboratory fields contained within the EMR database. As previously described, no chart review was planned to capture laboratory data that may be available within clinical progress notes. As a result, it was necessary therefore to limit the assessment of CBC evaluations to those patients with available laboratory data. A comparison of the demographic or clinical characteristics of patients with and without laboratory evaluations was not conducted, however, we observed that the distribution of

patients with at least one CBC test result was between 55.4%-60.2% when evaluated by number of cycles complete. This indicates that the frequency of testing was not related to characteristics or treatment patterns of patients and therefore no selection bias imposed by limiting the assessment to those patients with a known CBC test and result.

11.3. Interpretation

This is the first, to our knowledge, real-world analysis of the characteristics, treatment patterns and occurrence of neutropenia conducted among patients prescribed palbociclib for the treatment of metastatic breast cancer. Palbociclib in combination with letrozole for the treatment of metastatic breast cancer was approved in the US in February 2015 with subsequent approval of palbociclib in combination with fulvestrant in February 2016. As such, we provide a full description of the findings for the palbociclib + letrozole cohort but have restricted to not interpreting any of the palbociclib + fulvestrant findings given its utilization would have been considered off-label at the time of treatment based on our study period.

The decreasing trend in use of palbociclib + letrozole in later lines of therapy is fairly typical for a newly approved agent. Initially, a bolus of patients who have no further therapeutic options may be treated with the novel agent inflating the number of those who receive treatment in later lines of therapy. This phenomenon was observed in this analysis where the proportion of fourth-line or greater usage was highest in the first months following approval and lowest nearly one-year post approval.

Per the US prescribing information (PI) for palbociclib (02/2015 revision) [8], providers are suggested to monitor CBC prior to the start of palbociclib therapy and at the beginning of each cycle as well as Day 14 of the first two cycles. Because of data limitations it was not possible to precisely determine adherence to this recommendation (i.e. whether a test had been done on the actual start date and 14 days following treatment initiation). However, we found that the mean number of CBC tests conducted during the first cycle was 2 indicating that providers are conducting the appropriate number of tests, if not at the exact recommended times, during the first cycle. In regard to the occurrence of neutropenia events, the rate of grade 3 and grade 4 neutropenia reported in the PI are 57% and 5%, respectively. By the sixth cycle, we observed 41.1% and 7.0% of patients with laboratory data consistent with grade 3 and grade 4 events, respectively. The slightly higher rate of grade 4 may be reflective of a more diverse real-world patient population with pre-existing disposition to neutropenia from experience of prior therapeutic intervention. However, we noted no difference in laboratory values consistent with neutropenia between patients with evidence of a neutropenic event prior to initiation of palbociclib + letrozole compared to those without a prior neutropenic event. The slightly lower rate of grade 3 neutropenia may be more reflective of a lack of sufficient follow-up time as we observed an increasing trend in rate of grade 3 events with increasing length of time (i.e., cycles) from initiation of palbociclib.

In this analysis, the median days to any neutropenia diagnosis was 26 which is longer than that reported in PALOMA-1 (15 days).[9] However, it is important to note that the treatment order date available through the EMR represents the earliest day possible that a patient may have begun ingesting palbociclib. Therefore, given that drug may not have been available to

patients on the day of the order, our estimate is conservative and may be shorter should the true date of treatment start been after the date of the treatment order.

We observed reactive dose reductions of palbociclib in 20.1% of patients treated with palbociclib + letrozole. In comparison to dose reductions reported in the clinical trial (36.0% dose reduction due to an AE; initiation at 125 mg), we observed a lower rate, 21.2% of patients who initiated at 125 mg, were dose reduced.[7] These data are not directly comparable due to the requirement of a diagnosis of an AE in the RCT. Of note, all dose reductions in this research occurred by the end of the sixth cycle in our population of patients therefore the extent to which a shorter follow-up has biased these results is expected to be limited. Of note, we also observed 5 patients who were upwardly dose titrated, receiving a higher dose than at initiation or who returned to the starting dose after a dose decrease. These data suggest that community-based providers are sufficiently monitoring patients for significant clinical events, including neutropenia, and successfully managing them to avoid dose reductions and maintain adherence to treatment.

11.4. Generalizability

This research is the first to examine patient characteristics, treatment patterns and neutropenia among female metastatic breast cancer patients treated with palbociclib. It should be noted that early use of palbociclib may not be generalizable to palbociclib treatment today since a large proportion of treatment may have been as salvage therapy after disease progression following other endocrine, targeted, or chemotherapy.

Patients were selected for study inclusion if they have received palbociclib in combination with letrozole (or fulvestrant) outside of the clinical trial setting. Restrictions related to known ER/HER2 status, menopause status, or ECOG performance status were not used.[7] Additionally, this analysis was not restricted to use of palbociclib + letrozole as initial endocrine therapy for metastatic breast cancer patients.

The patients selected from the EMR database appear more heterogeneous compared to the clinical trial population. The real-world cohort of patients receiving palbociclib + letrozole were older compared to patients receiving palbociclib in the phase III PALOMA-2 trial (50.3% versus 40.8% ≥ 65 years of age, respectively) and had a higher ECOG-PS score (22.1% among those with known ECOG-PS versus no patients with ECOG ≥ 2 in RCT). In terms of prior treatments, 68.5% of patients had a therapy prior to palbociclib + letrozole compared to 62.8% in the PALOMA-2 study.

Further data regarding the geographic location of a patient or where treated, including descriptions of the practice setting and providers, were not available for analysis from the EMR. The characteristics of the EMR database itself has been previously described.

12. OTHER INFORMATION

Not Applicable

13. CONCLUSIONS

Per palbociclib prescribing information: "IBRANCE is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) negative advanced breast cancer as initiation endocrine-based therapy for their metastatic disease." Overall, we found that 39.5% of patients initiating treatment with palbociclib + letrozole received the combination as their first-line treatment. Use as fourth-line or higher treatment declined over the year following initial approval correlating with an increase in use as a third-line treatment. The observed trend likely reflects the early utilization amongst patients with limited available other treatment options highlighting the need for earlier intervention with more efficacious and tolerable therapies.

The majority of patients initiated palbociclib at the 125 mg dose. Among all patients treated with palbociclib in combination with letrozole, 20.1% had their palbociclib dose reduced during the follow-up period with all dose reductions observed occurring by the 6th cycle. Of note, 5 patients were dose escalated during this period.

Observed CBC monitoring occurs as frequently as recommended in the product prescribing information, with on average patients receiving 2 CBC tests during their first cycle of treatment. The rate of grade 3 or 4 neutropenia events is consistent with the rates observed in the PALOMA-2 trial.[7] Almost all observed highest grade neutropenia lab values were recorded within 56 days of initiation of treatment with palbociclib + letrozole.

Further long-term follow-up of this cohort may serve to determine outcomes of therapy in a real-world population of patients treated with palbociclib.

14. REFERENCES

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15. SOURCE TABLES AND FIGURES FOR PALBOCICLIB + LETROZOLE ANALYSIS

15.1. Demographic and Clinical Characteristics of patients initiating palbociclib + letrozole

	Cumulative						Incident Cohorts											
	All		<65		≥ 65		Feb/ Mar ('15)		Apr/ May		Jun/ Jul		Aug/ Sep		Oct/ Nov		Dec/ Jan ('16)	
Total patients (n, %)	612	(100)	304	(49.7)	308	(50.3)	64	(10.5)	108	(17.6)	125	(20.4)	108	(17.6)	92	(15.0)	115	(18.8)
Age (mean, SD)																		
at advanced breast cancer diagnosis	61	(12)	52	(9)	70	(8)	59	(12)	62	(12)	63	(12)	59	(12)	60	(13)	62	(12)
at initiation of Palbociclib	64	(12)	55	(8)	74	(6)	63	(13)	65	(11)	66	(12)	62	(12)	64	(13)	65	(12)
≤64 (n, %)	304	(49.7)	304	(100)			39	(60.9)	51	(47.2)	55	(44.0)	63	(58.3)	43	(46.7)	53	(46.1)
65-74 (n, %)	182	(29.7)			182	(59.1)	14	(21.9)	33	(30.6)	43	(34.4)	26	(24.1)	28	(30.4)	38	(33.0)
≥75 (n, %)	126	(20.6)			126	(40.9)	11	(17.2)	24	(22.2)	27	(21.6)	19	(17.6)	21	(22.8)	24	(20.9)
Weight (lbs.) at initiation of palbociclib (mean, SD)	165	(37)	171	(39)	157	(31)	154	(25)	178	(27)	152	(25)	166	(21)	178	(56)	164	(38)
BMI (mean, SD)	28.2	(7.6)	29.4	(8.0)	27.0	(7.0)	28.1	(7.7)	27.7	(7.4)	27.8	(7.6)	28.8	(7.4)	28.8	(7.6)	28.2	(8.0)
Menopause (n, %)																		
post-menopausal	169	(27.6)	96	(31.6)	73	(24.0)	19	(29.7)	29	(26.9)	35	(28.0)	32	(29.6)	25	(27.2)	29	(25.2)
unknown	443	(72.4)	208	(68.4)	235	(76.0)	45	(70.3)	79	(73.1)	90	(72.0)	76	(70.4)	67	(72.8)	86	(74.8)
Histology (n, %)																		
invasive ductal	190	(31.0)	103	(33.9)	87	(28.2)	20	(31.3)	30	(27.8)	35	(28.0)	37	(34.3)	37	(40.2)	31	(27.0)
invasive lobular	7	(3.7)	4	(1.3)	3	(1.0)			1	(1.0)	3	(2.4)	1	(0.9)			2	(1.7)
unknown	415	(67.8)	197	(64.8)	218	(70.8)	44	(68.8)	77	(71.3)	87	(69.6)	70	(64.8)	55	(59.8)	82	(71.3)
Stage recorded in EMR† (n, %)																		
≤ Stage IIB	154	(25.2)	80	(26.3)	74	(24.0)	23	(35.9)	27	(25.0)	24	(19.2)	26	(24.1)	23	(25.0)	31	(27.0)
IIIA	44	(7.2)	22	(7.2)	22	(7.1)	4	(6.3)	9	(8.3)	5	(4.0)	10	(9.3)	8	(8.7)	8	(7.0)
IIIB	10	(1.6)	6	(1.6)	4	(1.3)			3	(2.8)	2	(1.6)	2	(1.9)	1	(1.1)	2	(1.7)

	Cumulative						Incident Cohorts											
	All		<65		≥ 65		Feb/ Mar ('15)		Apr/ May		Jun/ Jul		Aug/ Sep		Oct/ Nov		Dec/ Jan ('16)	
IIIC	27	(4.4)	14	(4.6)	13	(4.2)	2	(3.1)	1	(0.9)	7	(5.6)	4	(3.7)	6	(6.5)	7	(6.1)
IV	278	(45.4)	133	(43.8)	145	(47.1)	28	(43.8)	48	(44.4)	70	(56.0)	49	(45.4)	41	(44.6)	42	(36.5)
Unknown	99	(16.2)	49	(16.1)	50	(16.2)	7	(10.9)	20	(18.5)	17	(13.6)	17	(15.7)	13	(14.1)	25	(21.7)
ECOG at palbociclib treatment initiation (n, %)																		
0/1	348	(56.9)	188	(61.8)	160	(51.9)	35	(54.7)	65	(60.2)	69	(55.2)	65	(60.2)	50	(54.3)	64	(55.7)
2	77	(12.6)	28	(9.2)	49	(15.9)	7	(10.9)	11	(10.2)	17	(13.6)	11	(10.2)	13	(14.1)	18	(15.7)
≥3	18	(2.9)	7	(2.3)	11	(3.6)	2	(3.1)	1	(0.9)	6	(4.8)	3	(2.8)	3	(3.3)	3	(2.6)
Unknown	169	(27.6)	81	(26.6)	88	(28.6)	20	(31.3)	31	(28.7)	33	(26.4)	29	(26.9)	26	(28.3)	30	(26.1)
ER +/ HER2 -																		
Yes	428	(69.9)	217	(71.4)	211	(68.5)	46	(71.9)	78	(72.2)	86	(68.8)	75	(69.4)	61	(66.3)	82	(71.3)
Unknown	184	(30.1)	87	(28.6)	97	(31.5)	18	(28.1)	30	(27.8)	39	(31.2)	33	(30.6)	31	(33.7)	33	(28.7)
ER status (n, %)																		
Positive	505	(82.5)	249	(81.9)	256	(83.1)	52	(81.3)	93	(86.1)	102	(81.6)	90	(83.3)	73	(79.3)	95	(82.6)
Negative	33	(5.4)	15	(4.9)	18	(5.8)	4	(6.3)	5	(4.6)	10	(8.0)	7	(6.5)	3	(3.3)	4	(3.5)
Unknown	74	(12.1)	40	(13.2)	34	(11.0)	8	(12.5)	10	(9.3)	13	(10.4)	11	(10.2)	16	(17.4)	16	(13.9)
HER2 status (n, %)																		
Positive	38	(6.2)	17	(5.7)	21	(6.8)	2	(3.1)	10	(9.3)	3	(2.4)	7	(6.5)	6	(6.5)	10	(8.7)
Negative	465	(76.0)	237	(78.0)	228	(74.0)	49	(76.6)	83	(76.9)	99	(79.2)	83	(76.9)	65	(70.7)	86	(74.8)
Unknown	109	(17.8)	50	(16.4)	59	(19.2)	13	(20.3)	15	(13.9)	23	(18.4)	18	(16.7)	21	(22.8)	19	(16.5)
Metastases* location (n, %)																		
Bone	24	(3.9)	7	(2.3)	17	(5.5			4	(3.7)	4	(3.2)	7	(6.5)	5	(5.4)	4	(3.5)
Brain																		

	Cumulative						Incident Cohorts											
	All		<65		≥ 65		Feb/ Mar ('15)		Apr/ May		Jun/ Jul		Aug/ Sep		Oct/ Nov		Dec/ Jan ('16)	
Liver	7	(1.1)	3	(1.0)	4	(1.3)			2	(1.9)	1	(0.8)	3	(2.8)			1	(0.9)
Lung	3	(0.5)			3	(1.0)					2	(1.6)			1	(1.1)		
Lymph	1	(0.2)			1	(0.3)					1	(0.8						
Skin	1	(0.2)			1	(0.3)			1	(0.9)								
None/ Unknown	580	(95.8)	294	(96.7)	286	(92.9)	64	(100)	102	(94.4)	118	(94.4)	99	(91.7)	87	(94.6)	110	(95.7)

†Stage recorded in EMR at closest date to palbociclib initiation, restaging of patients does not typically occur.
* Not mutually exclusive, total across categories may be greater than total number of patients.

15.2. Line of therapy at initiation of palbociclib + letrozole by month of start.

	Cumulative						Month of Initiation of Palbociclib											
	All		<65		≥65		Feb/ Mar ('15)		Apr/ May		Jun/ Jul		Aug/ Sep		Oct/ Nov		Dec/ Jan ('16)	
Total patients (n, %)	612	(100)	304	(49.7)	308	(50.3)	64	(10.5)	108	(17.6)	125	(20.4)	108	(17.6)	92	(15.0)	115	(18.8)
1st LOT	242	(39.5)	120	(39.5)	122	(39.6)	23	(35.9)	45	(41.7)	53	(42.4)	45	(41.7)	33	(35.9)	43	(37.4)
Any Prior Endocrine	112	(46.3)	57	(47.5)	55	(45.1)	13	(56.5)	23	(51.1)	24	(45.3)	21	(46.7)	14	(42.4)	17	(39.5)
Any Prior Chemotherapy	37	(15.3)	21	(17.5)	16	(13.1)	2	(8.7)	6	(13.3)	9	(17.0)	7	(15.6)	3	(9.1)	10	(23.3)
2nd LOT	96	(15.7)	41	(13.5)	55	(17.9)	10	(15.6)	12	(11.1)	19	(15.2)	15	(13.9)	19	(20.7)	21	(18.3)
Any Prior Endocrine	72	(75.0)	25	(61.0)	47	(85.5)	7	(70.0)	10	(83.3)	14	(73.7)	11	(73.3)	15	(78.9)	15	(71.4)
Any Prior Chemotherapy	42	(43.8)	25	(61.0)	17	(30.9)	6	(60.0)	3	(25.0)	9	(47.4)	6	(40.0)	9	(47.4)	9	(42.9)
3rd LOT	80	(13.1)	40	(13.2)	40	(13.0)	5	(7.8)	10	(9.3)	18	(14.4)	12	(11.1)	12	(13.0)	23	(20.0)
Any Prior Endocrine	70	(87.5)	33	(82.5)	37	(92.5)	5	(100)	10	(100)	15	(83.3)	10	(83.3)	11	(91.7)	19	(82.6)
Any Prior Chemotherapy	56	(70.0)	36	(90.0)	20	(50.0)	3	(60.0)	6	(60.0)	13	(72.2)	11	(91.7)	8	(66.7)	15	(65.2)
≥4th LOT	194	(31.7)	103	(33.9)	91	(29.5)	26	(40.6)	41	(38.0)	35	(28.0)	36	(33.3)	28	(30.4)	28	(24.3)
Any Prior Endocrine	186	(95.9)	99	(96.1)	87	(95.6)	25	(96.2)	39	(95.1)	34	(97.1)	34	(94.4)	27	(96.4)	27	(96.4)
Any Prior Chemotherapy	169	(87.1)	94	(91.3)	75	(82.4)	23	(88.5)	35	(85.4)	29	(82.9)	35	(97.2)	22	(78.6)	25	(89.3)

Key: LOT – line of therapy.

15.3. Patient disposition at end of study period by line of therapy at palbociclib + letrozole initiation and length of follow-up.

Variable	Overall		Line of therapy at initiation of palbociclib+ letrozole							
			1st LOT				≥ 2nd LOT			
			< 6 mo f-up		≥ 6 mo f-up		< 6 mo f-up		≥ 6 mo f-up	
Total Patients (n, %)	612	(100)	107	(44.2)	135	(55.8)	191	(51.6)	179	(48.4)
Months of follow-up from initiation of palbociclib + letrozole to last medical/pharmacy record (mean, SD)	6.4	(3.9)	3.0	(2.0)	9.7	(2.3)	3.0	(1.7)	9.6	(2.3)
On treatment at end of study period (n, %)	482	(78.8)	72	(67.3)	128	(94.8)	119	(62.3)	163	(91.1)
Last recorded line of therapy palbociclib + letrozole	296	(48.4)	61	(57.0)	83	(61.5)	80	(41.9)	72	(40.2)
Patient received line of therapy following palbociclib + letrozole	186	(30.4)	11	(10.3)	45	(33.3)	39	(20.4)	91	(50.8)
Lost to follow-up (n, %) ¥	58	(9.5)	24	(22.4)	4	(3.0)	23	(12.0)	7	(3.9)
Last recorded line of therapy palbociclib + letrozole	35	(5.7)	17	(15.9)	2	(1.5)	16	(8.4)	-	
Patient received line of therapy following palbociclib + letrozole	23	(3.8)	7	(6.5)	2	(1.5)	7	(3.7)	7	(3.9)
Deceased (n, %)	72	(11.8)	11	(10.3)	3	(2.2)	49	(25.7)	9	(5.0)
Last recorded line of therapy palbociclib + letrozole	21	(3.4)	3	(2.8)	-		18	(9.4)	-	
Patient received line of therapy following palbociclib + letrozole	51	(8.3)	8	(7.5)	3	(2.2)	31	(16.2)	9	(5.0)

Key: f-up – follow-up; LOT – line of therapy; MO - month.
¥ No treatment/medical encounters within 90 days of end of study period.

15.4. Observed treatments in line of therapy prior to initiation of palbociclib + letrozole.[†]

Variable	Overall		Line of therapy at initiation of palbociclib + letrozole							
			1st LOT*		2nd LOT		3rd LOT		≥ 4th LOT	
Total patients (n, %)	612	(100)	242	(39.5)	96	(15.7)	80	(13.1)	194	(31.7)
Months from metastatic diagnosis to palbociclib treatment initiation (mean, SD)	36	(52)	11	(39)	31	(56)	39	(36)	67	(53)
Patients with line of therapy prior to palbociclib + letrozole (n, %)	419	(68.5)	49	(20.2)	96	(100)	80	(100)	194	(100)
Endocrine in LOT prior (n, %)	251	(41.0)	31	(12.8)	63	(65.6)	57	(71.3)	100	(51.5)
Monotherapy	184	(30.1)	30	(12.4)	52	(54.2)	47	(58.8)	55	(28.4)
Anastrozole	55	(9.0)	7	(2.9)	27	(28.1)	7	(8.8)	14	(7.2)
Tamoxifen	52	(8.5)	14	(5.8)	11	(11.5)	13	(16.3)	14	(7.2)
Fulvestrant	50	(8.2)	1	(0.4)	8	(8.3)	22	(27.5)	19	(9.8)
Exemestane	18	(2.9)	2	(0.8)	5	(5.2)	3	(3.8)	8	(4.1)
Letrozole	8	(1.3)	6	(2.5)	1	(1.0)	1	(1.3)		
Goserelin Acetate	1	(0.2)					1	(1.3)		
Combination	67	(10.9)	1	(0.4)	11	(11.5)	10	(12.5)	45	(23.2)
Everolimus + Exemestane	20	(3.3)			2	(2.1)	3	(3.8)	15	(7.7)
Anastrozole + Fulvestrant	8	(1.3)			2	(2.1)	2	(2.5)	4	(2.1)
Exemestane + Fulvestrant	5	(0.8)			1	(1.0)	1	(1.3)	3	(1.5)
Anastrozole + Trastuzumab	3	(0.5)	1	(0.4)	1	(1.0)			1	(0.5)
Anastrozole + Paclitaxel Protein-Bound	2	(0.3)			2	(2.1)				
Goserelin Acetate + Letrozole	2	(0.3)					2	(2.5)		
Fulvestrant + Letrozole	2	(0.3)			1	(1.0)	1	(1.3)		
Fulvestrant + Trastuzumab	2	(0.3)							2	(1.0)
Everolimus + Exemestane + Fulvestrant	2	(0.3)					1	(1.3)	1	(0.5)
Anastrozole + Letrozole	2	(0.3)							2	(1.0)
Exemestane + Paclitaxel + Pertuzumab + Trastuzumab	1	(0.2)							1	(0.5)
Cyclophosphamide + Docetaxel + Letrozole	1	(0.2)			1	(1.0)				
Cisplatin + Exemestane	1	(0.2)							1	(0.5)

Variable	Overall		Line of therapy at initiation of palbociclib + letrozole					
			1st LOT*		2nd LOT		3rd LOT		≥ 4th LOT	
Bevacizumab + Exemestane + Fulvestrant	1	(0.2)							1	(0.5)
Anastrozole + Carboplatin	1	(0.2)							1	(0.5)
Anastrozole + Everolimus	1	(0.2)							1	(0.5)
Capecitabine + Fulvestrant	1	(0.2)							1	(0.5)
Fulvestrant + Tamoxifen	1	(0.2)							1	(0.5)
Ofatumumab + Tamoxifen	1	(0.2)							1	(0.5)
Gemcitabine + Letrozole	1	(0.2)							1	(0.5)
Anastrozole + Everolimus + Exemestane + Fulvestrant	1	(0.2)							1	(0.5)
Anastrozole + Capecitabine + Fulvestrant	1	(0.2)							1	(0.5)
Capecitabine + Tamoxifen	1	(0.2)			1	(1.0)				
Exemestane + Everolimus	1	(0.2)							1	(0.5)
Paclitaxel + Tamoxifen	1	(0.2)							1	(0.5)
Anastrozole + Exemestane	1	(0.2)							1	(0.5)
Toremifene Citrate	1	(0.2)							1	(0.5)
Exemestane + Fulvestrant + Paclitaxel	1	(0.2)							1	(0.5)
Exemestane + Paclitaxel	1	(0.2)							1	(0.5)
Chemotherapy in LOT prior (n,%)	**207**	**(33.8)**	**18**	**(7.4)**	**39**	**(40.6)**	**27**	**(33.8)**	**123**	**(63.4)**
Capecitabine	36	(5.9)	3	(1.2)	5	(5.2)	6	(7.5)	22	(11.3)
Paclitaxel	22	(3.6)	2	(0.8)	6	(6.3)	5	(6.3)	9	(4.6)
Everolimus + Exemestane	20	(3.3)			2	(2.1)	3	(3.8)	15	(7.7)
Eribulin Mesylate	16	(2.6)	1	(0.4)			2	(2.5)	13	(6.7)
Paclitaxel Protein-Bound	15	(2.5)	2	(0.8)	4	(4.2)	2	(2.5)	7	(3.6)
Everolimus	11	(1.8)					1	(1.3)	10	(5.2)
Cyclophosphamide	10	(1.6)	1	(0.4)	6	(6.3)	1	(1.3)	2	(1.0)
Doxorubicin	6	(1.0)					1	(1.3)	5	(2.6)
Docetaxel	5	(0.8)	1	(0.4)	1	(1.0)			3	(1.5)
Cyclophosphamide + Docetaxel	5	(0.8)	1	(0.4)	3	(3.1)			1	(0.5)

Variable	Overall		Line of therapy at initiation of palbociclib + letrozole							
			1st LOT*		2nd LOT		3rd LOT		≥ 4th LOT	
Ixabepilone	5	(0.8)			1	(1.0)			4	(2.1)
Doxorubicin Liposomal	4	(0.7)							4	(2.1)
Bevacizumab + Paclitaxel	3	(0.5)			1	(1.0)	1	(1.3)	1	(0.5)
Vinorelbine Tartrate	3	(0.5)			1	(1.0)	1	(1.3)	1	(0.5)
Gemcitabine	3	(0.5)					1	(1.3)	2	(1.0)
Carboplatin + Paclitaxel	3	(0.5)	1	(0.4)	2	(2.1)				
Cyclophosphamide + Doxorubicin	3	(0.5)			2	(2.1)			1	(0.5)
Capecitabine + Ixabepilone	2	(0.3)	1	(0.4)					1	(0.5)
Anastrozole + Paclitaxel Protein-Bound	2	(0.3)			2	(2.1)				
Everolimus + Exemestane + Fulvestrant	2	(0.3)					1	(1.3)	1	(0.5)
Carboplatin	1	(0.2)							1	(0.5)
Ofatumumab + Paclitaxel	1	(0.2)	1	(0.4)						
Imatinib	1	(0.2)	1	(0.4)						
Cyclophosphamide + Doxorubicin + Paclitaxel	1	(0.2)	1	(0.4)						
Capecitabine + Tamoxifen	1	(0.2)			1	(1.0)				
Cisplatin + Exemestane	1	(0.2)							1	(0.5)
Gemcitabine + Letrozole	1	(0.2)							1	(0.5)
Docetaxel + Ofatumumab	1	(0.2)					1	(1.3)		
Lenalidomide	1	(0.2)	1	(0.4)						
Bevacizumab + Exemestane + Fulvestrant	1	(0.2)							1	(0.5)
Capecitabine + Paclitaxel	1	(0.2)							1	(0.5)
Anastrozole + Capecitabine + Fulvestrant	1	(0.2)							1	(0.5)
Trastuzumab + Vinorelbine Tartrate	1	(0.2)	1	(0.4)						
Doxorubicin Liposomal + Methotrexate	1	(0.2)							1	(0.5)
Anastrozole + Everolimus + Exemestane + Fulvestrant	1	(0.2)							1	(0.5)
Epirubicin	1	(0.2)							1	(0.5)
Gemcitabine + Paclitaxel Protein-Bound	1	(0.2)							1	(0.5)

Variable	Overall		Line of therapy at initiation of palbociclib + letrozole					
			1st LOT*		2nd LOT		3rd LOT		≥ 4th LOT	
Anastrozole + Everolimus	1	(0.2)							1	(0.5)
Cyclophosphamide + Docetaxel + Letrozole	1	(0.2)			1	(1.0)				
Anastrozole + Carboplatin	1	(0.2)							1	(0.5)
Ofatumumab	1	(0.2)							1	(0.5)
Capecitabine + Fulvestrant	1	(0.2)							1	(0.5)
Ofatumumab + Tamoxifen	1	(0.2)							1	(0.5)
Carboplatin	1	(0.2)							1	(0.5)
Paclitaxel + Tamoxifen	1	(0.2)							1	(0.5)
Exemestane + Everolimus	1	(0.2)							1	(0.5)
Pertuzumab	1	(0.2)					1	(1.3)		
Exemestane + Fulvestrant + Paclitaxel	1	(0.2)							1	(0.5)
Cyclophosphamide + Docetaxel + Ofatumumab	1	(0.2)			1	(1.0)				
Exemestane + Paclitaxel	1	(0.2)							1	(0.5)
Exemestane + Paclitaxel + Pertuzumab + Trastuzumab	1	(0.2)							1	(0.5)

Key: LOT – line of therapy.
†Categories not mutually exclusive, column total may sum to > 100% as regimens with chemotherapy and endocrine were grouped in both combination endocrine and chemotherapy subgroups.
* For LOT1, includes treatments received prior to development of metastatic disease if patient data contained within the EMR.

15.5. Observed treatments following palbociclib + letrozole[†].

	Overall		Line of therapy at initiation of palbociclib + letrozole							
			1st LOT				≥ 2nd LOT			
			< 6 mo f-up		≥ 6 mo f-up		< 6 mo f-up		≥ 6 mo f-up	
Total Patients (n, %)	612	(100)	107	(44.2)	135	(55.8)	191	(51.6)	179	(48.4)
Months of follow-up from palbociclib treatment initiation (mean, SD)	6.4	(3.9)	3.0	(2.0)	9.7	(2.3)	3.0	(1.7)	9.6	(2.3)
Patients receiving new treatment regimen post-palbociclib (n, %)	236	(38.6)	22	(20.6)	52	(38.5)	57	(29.8)	105	(58.7)
Switch to Endocrine (n, %)	134	(21.9)	15	(14.0)	34	(25.2)	28	(14.7)	57	(31.8)
Monotherapy	73	(11.9)	8	(7.5)	27	(20.0)	10	(5.2)	28	(15.6)
Fulvestrant	39	(6.4)	6	(5.6)	10	(7.4)	9	(4.7)	14	(7.8)
Letrozole	20	(3.3)	1	(0.9)	8	(5.9)	1	(0.5)	10	(5.6)
Tamoxifen	6	(1.0)			3	(2.2)			3	(1.7)
Anastrozole	5	(0.8)	1	(0.9)	4	(3.0)				
Exemestane	3	(0.5)			2	(1.5)			1	(0.6)
Combination	61	(10.0)	7	(6.5)	7	(5.2)	18	(9.4)	29	(16.2)
Fulvestrant + Palbociclib	10	(1.6)	1	(0.9)	1	(0.7)	3	(1.6)	5	(2.8)
Everolimus + Exemestane	6	(1.0)	1	(0.9)	1	(0.7)	2		2	(1.1)
Fulvestrant + Letrozole	4	(0.7)	1	(0.9)	2	(1.5)			1	(0.6)
Fulvestrant + Letrozole + Palbociclib	4	(0.7)					1	(0.5)	3	(1.7)
Anastrozole + Letrozole + Palbociclib	3	(0.5)					1	(0.5)	2	(1.1)
Exemestane + Letrozole + Palbociclib	3	(0.5)							3	(1.7)
Letrozole + Palbociclib + Tamoxifen	3	(0.5)	1	(0.9)			1	(0.5)	1	(0.6)
Anastrozole + Palbociclib	2	(0.3)	1	(0.9)	1	(0.7)				
Capecitabine + Letrozole + Palbociclib	2	(0.3)					1	(0.5)	1	(0.6)
Docetaxel + Letrozole + Pertuzumab + Trastuzumab	2	(0.3)	1	(0.9)			1	(0.5)		
Eribulin Mesylate + Letrozole + Palbociclib	2	(0.3)					1	(0.5)	1	(0.6)
Gemcitabine + Letrozole	2	(0.3)			1	(0.7)			1	(0.6)
Goserelin Acetate	2	(0.3)					1	(0.5)	1	(0.6)
Letrozole + Paclitaxel	2	(0.3)					2	(1.0)		
Anastrozole + Lenalidomide	1	(0.2)							1	(0.6)

Capecitabine + Letrozole	1	(0.2)			1	(0.7)				
Doxorubicin + Tamoxifen	1	(0.2)							1	(0.6)
Eribulin Mesylate + Letrozole	1	(0.2)							1	(0.6)
Everolimus + Exemestane + Letrozole	1	(0.2)							1	(0.6)
Everolimus + Exemestane + Letrozole + Palbociclib	1	(0.2)							1	(0.6)
Everolimus + Exemestane + Palbociclib	1	(0.2)							1	(0.6)
Everolimus + Letrozole	1	(0.2)	1	(0.9)						
Goserelin Acetate + Letrozole + Palbociclib	1	(0.2)					1	(0.5)		
Letrozole	1	(0.2)					1	(0.5)		
Letrozole + Paclitaxel + Palbociclib	1	(0.2)							1	(0.6)
Letrozole + Paclitaxel Protein-Bound	1	(0.2)							1	(0.6)
Palbociclib + Tamoxifen	1	(0.2)					1	(0.5)		
Toremifene Citrate	1	(0.2)					1	(0.5)		
Switch to Chemotherapy (n, %)	153	(25.0)	13	(12.1)	23	(17.0)	43	(22.5)	74	(41.3)
Capecitabine	24	(3.9)	1	(0.9)	4	(3.0)	6	(3.1)	13	(7.3)
Paclitaxel Protein-Bound	12	(2.0)			2	(1.5)	5	(2.6)	5	(2.8)
Eribulin Mesylate	11	(1.8)			4	(3.0)	3	(1.6)	4	(2.2)
Fulvestrant + Palbociclib	10	(1.6)	1	(0.9)	1	(0.7)	3	(1.6)	5	(2.8)
Paclitaxel	10	(1.6)	2	(1.9)	2	(1.5)	3	(1.6)	3	(1.7)
Doxorubicin	6	(1.0)							6	(3.4)
Everolimus + Exemestane	6	(1.0)	1	(0.9)	1	(0.7)	2	(1.0)	2	(1.1)
Carboplatin + Paclitaxel	5	(0.8)	1	(0.9)	2	(1.5)	1	(0.5)	1	(0.6)
Ixabepilone	4	(0.7)	1	(0.9)	1	(0.7)			2	(1.1)
Fulvestrant + Letrozole + Palbociclib	4	(0.7)					1	(0.5)	3	(1.7)
Vinorelbine Tartrate	4	(0.7)					1	(0.5)	3	(1.7)
Gemcitabine	3	(0.5)					2	(1.0)	1	(0.6)
Exemestane + Letrozole + Palbociclib	3	(0.5)							3	(1.7)
Anastrozole + Letrozole + Palbociclib	3	(0.5)					1	(0.5)	2	(1.1)
Letrozole + Palbociclib + Tamoxifen	3	(0.5)	1	(0.9)			1	(0.5)	1	(0.6)
Anastrozole + Palbociclib	2	(0.3)	1	(0.9)	1	(0.7)				
Docetaxel + Letrozole + Pertuzumab + Trastuzumab	2	(0.3)	1	(0.9)			1	(0.5)		

Capecitabine + Letrozole + Palbociclib	2	(0.3)					1	(0.5)	1	(0.6)
Letrozole + Paclitaxel	2	(0.3)					2	(1.0)		
Gemcitabine + Letrozole	2	(0.3)			1	(0.7)			1	(0.6)
Everolimus	2	(0.3)			1	(0.7)	1	(0.5)		
Cyclophosphamide	2	(0.3)							2	(1.1)
Eribulin Mesylate + Letrozole + Palbociclib	2	(0.3)					1	(0.5)	1	(0.6)
Carboplatin + Gemcitabine	2	(0.3)							2	(1.1)
Capecitabine + Palbociclib	1	(0.2)							1	(0.6)
Carboplatin + Epirubicin	1	(0.2)					1	(0.5)		
Cytarabine Liposome	1	(0.2)					1	(0.5)		
Anastrozole + Lenalidomide	1	(0.2)							1	(0.6)
Gemcitabine Hcl + Ofatumumab	1	(0.2)	1	(0.9)						
Carboplatin + Gemcitabine Hcl	1	(0.2)					1	(0.5)		
Letrozole + Paclitaxel + Palbociclib	1	(0.2)							1	(0.6)
Capecitabine + Ixabepilone	1	(0.2)							1	(0.6)
Carboplatin	1	(0.2)							1	(0.6)
Everolimus + Exemestane + Letrozole	1	(0.2)							1	(0.6)
Cyclophosphamide + Epirubicin	1	(0.2)			1	(0.7)				
Palbociclib + Tamoxifen	1	(0.2)					1	(0.5)		
Gemcitabine Hcl + Palbociclib	1	(0.2)	1	(0.9)						
Everolimus + Exemestane + Palbociclib	1	(0.2)							1	(0.6)
Eribulin Mesylate + Letrozole	1	(0.2)							1	(0.6)
Everolimus + Letrozole	1	(0.2)	1	(0.9)						
Letrozole + Paclitaxel Protein-Bound	1	(0.2)							1	(0.6)
Bevacizumab + Paclitaxel Protein-Bound	1	(0.2)					1	(0.5)		
Ofatumumab + Paclitaxel	1	(0.2)			1	(0.7)				
Capecitabine + Letrozole	1	(0.2)			1	(0.7)				
Paclitaxel + Palbociclib	1	(0.2)					1	(0.5)		
Doxorubicin + Tamoxifen	1	(0.2)							1	(0.6)
Pertuzumab	1	(0.2)					1	(0.5)		
Doxorubicin Liposomal	1	(0.2)							1	(0.6)

Everolimus + Exemestane + Letrozole + Palbociclib	1	(0.2)					1	(0.6)
Eribulin Mesylate + Palbociclib	1	(0.2)			1	(0.5)		
Eribulin Mesylate + Pertuzumab + Trastuzumab	1	(0.2)					1	(0.6)

Key: F-up – follow-up; LOT – line of therapy; MO – months.
[†]Categories not mutually exclusive, column total may sum to > 100% as regimens with chemotherapy and endocrine were grouped in both combination endocrine and chemotherapy subgroups.

15.6. Initiation dose of palbociclib and patterns of dose reductions among patients treated with palbociclib + letrozole.

	Overall		Number of palbociclib cycles received†					
			6 cycles¥		4 cycles$^{\alpha}$		2 cycles$^{\mu}$	
Total patients	612	(100)	336	(54.9)	445	(72.7)	524	(85.6)
Patients with known starting dose	417	(68.1)	269	(80.1)	323	(72.6)	367	(70.0)
Patients with unknown starting dose	195	(31.9)	67	(19.9)	122	(27.4)	157	(30.0)
Starting dose (n, %) (among patients with known starting dose)								
125 mg	367	(88.0)	237	(88.1)	283	(87.6)	321	(87.5)
100 mg	46	(11.0)	30	(11.2)	38	(11.8)	42	(11.4)
75 mg	4	(1.0)	2	(0.7)	2	(0.6)	4	(1.1)
Number of dose reductions (n, %) (among patients with known starting dose)								
None	333	(79.9)	185	(68.8)	240	(74.3)	309	(84.2)
>=1	84	(20.1)	84	(31.2)	83	(25.7)	58	(15.8)
Type of first dose reduction (n, %) (among patients with known starting dose)								
Reduction from 125 mg to 100 mg	65	(15.6)	65	(24.2)	64	(19.8)	45	(12.3)
Reduction from 100 mg to 75 mg	6	(1.4)	6	(2.2)	6	(1.9)	5	(1.4)
Reduction from 125 mg to 75 mg	13	(3.1)	13	(4.8)	13	(4.0)	8	(2.2)
Days to first dose reduction (mean, SD)	48	(31)	48	(31)	48	(31)	46	(31)

†Number of cycles approximated by time since initiation of treatment of palbociclib as cycle/refill dates not available in EMR.

¥Interval from initiation of palbociclib + letrozole through 168 days post initiation among those considered on palbociclib + letrozole at day 168 post initiation.

$^{\alpha}$Interval from initiation of palbociclib + letrozole through 112 days post initiation among those considered on palbociclib + letrozole at day 112 post initiation.

$^{\mu}$Interval from initiation of palbociclib + letrozole through 56 days post initiation among those considered on palbociclib + letrozole at day 56 post initiation.

15.7. Supportive care drugs used during treatment with palbociclib among patients treated with palbociclib + letrozole.

Variable	Overall		Line of therapy at initiation of palbociclib + letrozole							
			1st LOT				≥ 2nd LOT			
			< 6 mo f-up		≥ 6 mo f-up		< 6 mo f-up		≥ 6 mo f-up	
Total patients	612	(100)	107	(44.2)	135	(55.8)	191	(51.6)	179	(48.4)
Any supportive care drug	392	(64.1)	69	(64.5)	94	(69.6)	110	(57.6)	119	(66.5)
Bone preserving agents	255	(41.7)								
Denosumab	163	(26.6)	31	(29.0)	44	(32.6)	39	(20.4)	49	(27.4)
Zoledronic Acid	97	(15.8)	14	(13.1)	27	(20.0)	24	(12.6)	32	(17.9)
Alendronate Sodium	1	(0.2)					1	(0.5)		
Pamidronate Disodium	1	(0.2)			1	(0.7)				
Antiemetic	172	(28.1)								
Prochlorperazine Maleate	65	(10.6)	14	(13.1)	17	(12.6)	15	(7.9)	19	(10.6)
Ondansetron	61	(10.0)	11	(10.3)	19	(14.1)	16	(8.4)	15	(8.4)
Ondansetron Hcl	46	(7.5)	12	(11.2)	11	(8.1)	16	(8.4)	7	(3.9)
Promethazine Hcl	14	(2.3)	2	(1.9)	3	(2.2)	4	(2.1)	5	(2.8)
Dronabinol	8	(1.3)					5	(2.6)	3	(1.7)
Metoclopramide Hcl	6	(1.0)	2	(1.9)			3	(1.6)	1	(0.6)
Granisetron	5	(0.8)	1	(0.9)			2	(1.0)	2	(1.1)
Hydroxyzine Hcl	4	(0.7)	1	(0.9)			1	(0.5)	2	(1.1)
Fosaprepitant Dimeglumine	2	(0.3)							2	(1.1)
Palonosetron	1	(0.2)							1	(0.6)
Prochlorperazine Edisylate	1	(0.2)	1	(0.9)						
Pain	45	(7.4)								
Oxycodone Hcl	28	(4.6)	4	(3.7)	6	(4.4)	8	(4.2)	10	(5.6)
Gabapentin	15	(2.5)	1	(0.9)	2	(1.5)	6	(3.1)	6	(3.4)
Morphine Sulfate	4	(0.7)			3	(2.2)			1	(0.6)
Celecoxib	2	(0.3)							2	(1.1)
Corticosteroid	39	(6.4)								

Variable	Overall		Line of therapy at initiation of palbociclib + letrozole							
			1st LOT				≥ 2nd LOT			
			< 6 mo f-up		≥ 6 mo f-up		< 6 mo f-up		≥ 6 mo f-up	
Dexamethasone Sod Phosphate	13	(2.1)	2	(1.9)	1	(0.7)	5	(2.6)	5	(2.8)
Dexamethasone	10	(1.6)	1	(0.9)	2	(1.5)	4	(2.1)	3	(1.7)
Prednisone	8	(1.3)	1	(0.9)	2	(1.5)	4	(2.1)	1	(0.6)
Hydrocortisone	5	(0.8)					2	(1.0)	3	(1.7)
Triamcinolone Acetonide	4	(0.7)	1	(0.9)	2	(1.5)	1	(0.5)		
Methylprednisolone	2	(0.3)					1	(0.5)	1	(0.6)
Anticoagulant	19	(3.1)								
Rivaroxaban	9	(1.5)	2	(1.9)	1	(0.7)	5	(2.6)	1	(0.6)
Enoxaparin Sodium	5	(0.8)	1	(0.9)	2	(1.5)	1	(0.5)	1	(0.6)
Alteplase	4	(0.7)	1	(0.9)					3	(1.7)
Warfarin Sodium	3	(0.5)			2	(1.5)			1	(0.6)
Fondaparinux Sodium	2	(0.3)	1	(0.9)					1	(0.6)
Proton pump inhibitor	16	(2.6)								
Pantoprazole Sodium	13	(2.1)	3	(2.8)	4	(3.0)	2	(1.0)	4	(2.2)
Cimetidine	2	(0.3)							2	(1.1)
Ranitidine Hcl	1	(0.2)					1	(0.5)		
Antibiotic	12	(2.0)								
Doxycycline Hyclate	3	(0.5)			1	(0.7)	2	(1.0)		
Ciprofloxacin Hcl	3	(0.5)			1	(0.7)	1	(0.5)	1	(0.6)
Cephalexin	3	(0.5)					1	(0.5)	2	(1.1)
Penicillin V Potassium	2	(0.3)					1	(0.5)	1	(0.6)
Metronidazole	1	(0.2)							1	(0.6)
Diuretic										
Furosemide	15	(2.5)	1	(0.9)	2	(1.5)	8	(4.2)	4	(2.2)
GCSF	12	(2.0)								
Filgrastim	7	(1.1)			3	(2.2)	2	(1.0)	2	(1.1)
Pegfilgrastim	5	(0.8)			1	(0.7)	1	(0.5)	3	(1.7)

Variable	Overall		Line of therapy at initiation of palbociclib + letrozole							
			1st LOT				≥ 2nd LOT			
			< 6 mo f-up		≥ 6 mo f-up		< 6 mo f-up		≥ 6 mo f-up	
Erythropoetin Stimulating Factor										
Epoetin Alfa	12	(2.0)			3	(2.2)	3	(1.6)	6	(3.4)
Insomnia										
Temazepam	7	(1.1)	2	(1.9)	2	(1.5)	1	(0.5)	2	(1.1)
Gastric protective agent										
Sucralfate	4	(0.7)	1	(0.9)	2	(1.5)			1	(0.6)
Thyroid hormone										
Levothyroxine Sodium	3	(0.5)					1	(0.5)	2	(1.1)

Key: F-up – follow-up; LOT – line of therapy; MO – months.

15.8. Frequency (n, %) of adverse event diagnoses during palbociclib + letrozole treatment by time since initiation of palbociclib.

	Time since initiation of palbociclib†					
	Cycles 1-6¥		Cycles 1-4α		Cycles 1-2μ	
Total Patients	400	(65.4)	460	(75.2)	522	(85.3)
Any AE diagnosis	112	(28.0)	89	(19.3)	58	(11.1)
Number of AEs diagnosed during palbociclib + letrozole treatment						
1	82	(20.5)	65	(14.1)	46	(8.8)
2	21	(5.3)	16	(3.5)	10	(1.9)
≥ 3	9	(2.3)	8	(1.7)	2	(0.4)
Anemia	12	(3.0)	10	(2.2)	5	(1.0)
Anorexia	2	(0.5)	2	(0.4)	1	(0.2)
Diarrhea	8	(2.0)	6	(1.3)	4	(0.8)
Fatigue	33	(8.3)	25	(5.4)	10	(1.9)
Leukopenia	19	(4.8)	18	(3.9)	10	(1.9)
Mucositis	4	(1.0)	3	(0.7)	2	(0.4)
Nausea	33	(8.3)	28	(6.1)	17	(3.3)
Neuropathy	3	(0.8)	2	(0.4)	1	(0.2)
Pain	18	(4.5)	11	(2.4)	8	(1.5)
Rash	4	(1.0)	4	(0.9)	4	(0.8)
Respiratory infections	4	(1.0)	3	(0.7)	1	(0.2)
Skin reaction	-		-		-	
Thrombocytopenia	16	(4.0)	11	(2.4)	9	(1.7)

†All patients assumed to be receiving treatment throughout the interval following initiation. Number of patients in each subgroup may vary from other tables as selection criteria (i.e. for table 15.6 patient required to have known starting dose) may be different.

¥Interval from initiation of palbociclib + letrozole through 168 days post initiation among those considered on palbociclib + letrozole at day 168 post initiation and those who experienced an event prior to the end of the interval.

α Interval from initiation of palbociclib + letrozole through 112 days post initiation among those considered on palbociclib + letrozole at day 112 post initiation and those who experienced an event prior to the end of the interval.

μ Interval from initiation of palbociclib + letrozole through 56 days post initiation among those considered on palbociclib + letrozole at day 56 post initiation and those who experienced an event prior to the end of the interval.

15.9. CBC laboratory evaluations during palbociclib + letrozole treatment and occurrence, timing and grade of lab value consistent with neutropenia[†].

	All Cycles		Cycles 1-6[¥]		Cycles 1-4[α]		Cycles 1-2[µ]	
Total patients	612	(100.0)	497	(81.2)	551	(90.0)	575	(94.0)
Patients with ≥ one CBC during time period	351	(57.4)	299	(60.2)	316	(57.4)	316	(55.0)
Number of CBC tests (mean, SD)[‡]	6.0	(5.7)	5.3	(4.5)	4.7	(3.6)	3.3	(2.2)
Lab value consistent with neutropenia* while on palbociclib (n, %)	262	(74.6)	262	(91.0)	262	(85.3)	243	(76.9)
Days to first neutropenia episode (mean, SD)	28.4	(19.6)	28.4	(19.6)	28.4	(19.6)	24.2	(12.6)
Highest grade Neutropenia (n, % of patients with test)								
Grade 1 (ANC 1500-1999)	45	(12.8)	48	(16.1)	52	(16.5)	47	(14.9)
Grade 2 (ANC 1000-1499)	72	(20.5)	70	(23.4)	67	(21.2)	66	(20.9)
Grade 3 (ANC 500-999)	124	(35.3)	123	(41.1)	122	(38.6)	111	(35.1)
Grade 4 (ANC < 500)	21	(6.0)	21	(7.0)	21	(6.6)	19	(6.0)

Key: ANC - absolute neutrophil count

†Only patients with at least one lab test result counted in frequency of CBC tests, neutrophil count during palbociclib treatment and grade of neutropenia. All patients assumed to be receiving treatment throughout the interval following initiation. Number of patients in each subgroup may vary from other tables as selection criteria (i.e. for table 15.6 patient required to have known starting dose) may be different.

*Neutropenia = neutrophil % divided by 100, multiply value by WBC quantity (neutrophil value in K/µl), and multiply by 1000 to convert to mm3.

[¥]Interval from initiation of palbociclib + letrozole through 168 days post initiation among those considered on palbociclib + letrozole at day 168 post initiation and those who received test/experienced event prior to the end of the interval.

[α] Interval from initiation of palbociclib + letrozole through 112 days post initiation among those considered on palbociclib + letrozole at day 112 post initiation and those who received test/experienced event prior to the end of the interval.

[µ] Interval from initiation of palbociclib + letrozole through 56 days post initiation among those considered on palbociclib + letrozole at day 56 post initiation and those who received test/experienced event prior to the end of the interval.

16. SOURCE TABLES AND FIGURES FOR PALBOCICLIB + FULVESTRANT ANALYSIS

16.1. Demographic and Clinical Characteristics of patients initiating palbociclib + fulvestrant

	Cumulative						Incident Cohorts											
	All		<65		≥ 65		Feb/ Mar ('15)		Apr/ May		Jun/ Jul		Aug/ Sep		Oct/ Nov		Dec/ Jan ('16)	
Total patients (n, %)	151	(100)	73	(48.3)	78	(51.7)	5	(3.3)	6	(4)	24	(15.9)	35	(23.2)	40	(26.5)	41	(27.2)
Age (mean, SD)																		
at advanced breast cancer diagnosis	61	(13.2)	51	(8.5)	71	(9.0)	68	(11.9)	66	(15.1)	58	(13.2)	62	(12.5)	59	(14.7)	61	(12.2)
at initiation of palbociclib	65	(12.6)	54	(7.7)	75	(6.7)	71	(11.8)	69	(10.3)	62	(12.1)	66	(12.4)	64	(13.8)	64	(12.3)
≤64 (n, %)	73	(48.3)	73	(100)	-	-	2	(40.0)	3	(50.0)	12	(50.0)	15	(42.9)	20	(50.0)	21	(51.2)
65-74 (n, %)	43	(28.5)	-	-	43	(55.1)	1	(20.0)	1	(16.7)	8	(33.3)	13	(37.1)	10	(25.0)	10	(24.4)
≥75 (n, %)	35	(23.2)	-	-	35	(44.9)	2	(40.0)	2	(33.3)	4	(16.7)	7	(20.0)	10	(25.0)	10	(24.4)
Weight (lbs.) at initiation of palbociclib (mean, SD)	163	(47.7)	170	(51.4)	155	(42.8)	165	(52.3)	139	(36.5)	155	(29.6)	161	(39.7)	163	(49.4)	172	(60.7)
BMI (mean, SD)	28	(8.2)	30	(9.1)	27	(7.0)	27	(7.4)	25	(5.9)	26	(5.3)	28	(6.9)	28	(8.8)	30	(10.2)
Menopause (n, %)																		
Post-menopausal	33	(22)	16	(21.9)	17	(21.8)			1	(16.7)	6	(25)	7	(20)	14	(35)	5	(12.2)
Unknown	118	(78)	57	(88.1)	61	(88.2)	5	(100)	5	(83.3)	18	(75)	28	(80)	26	(65)	36	(87.8)
Histology (n, %)																		
Invasive ductal	40	(26.5)	19	(26.0)	21	(26.9)			1	(16.7)	10	(41.7)	13	(37.1)	8	(20.0)	8	(19.5)
Invasive lobular	1	(0.7)	1	(1.4)							1	(4.2)						
Unknown	110	(72.8)	53	(72.6)	57	(73.1)	5	(100)	5	(83.3)	13	(54.2)	22	(62.9)	32	(80.0)	33	(80.5)
Stage recorded in EMR† (n, %)																		
≤ Stage IIB	35	(23.2)	18	(24.7)	17	(21.8)			1	(16.7)	4	(16.7)	8	(22.9)	9	(22.5)	13	(31.7)

	Cumulative						Incident Cohorts											
	All		<65		≥ 65		Feb/ Mar ('15)		Apr/ May		Jun/ Jul		Aug/ Sep		Oct/ Nov		Dec/ Jan ('16)	
IIIA	13	(8.6)	11	(15.1)	2	(2.6)			2	(33.3)	2	(8.3)	4	(11.4)	2	(5.0)	3	(7.3)
IIIB	5	(3.3)	2	(2.7)	3	(3.8)	1	(20.0)					1	(2.9)	1	(2.5)	2	(4.9)
IIIC	4	(2.6)	1	(1.4)	3	(3.8)					1	(4.2)	1	(2.9)	1	(2.5)	1	(2.4)
IV	54	(35.8)	26	(35.6)	28	(35.9)	3	(60.0)	2	(33.3)	12	(50)	15	(42.9)	16	(40.0)	6	(14.6)
Unknown	40	(26.5)	15	(20.5)	25	(32.1)	1	(20.0)	1	(16.7)	5	(20.8)	6	(17.1)	11	(27.5)	16	(39.0)
ECOG at palbociclib treatment initiation (n, %)																		
0/1	99	(65.6)	55	(75.3)	44	(56.4)	2	(40.0)	3	(50.0)	15	(62.5)	28	(80.0)	29	(72.5)	22	(53.7)
2	16	(10.6)	4	(5.5)	12	(15.4)	2	(40.0)			4	(16.7)	4	(11.4)	1	(2.5)	5	(12.2)
≥3	1	(0.7)	1	(1.4)											1	(2.5)		
Unknown	35	(23.2)	13	(17.8)	22	(28.2)	1	(20.0)	3	(50.0)	5	(20.8)	3	(8.6)	9	(22.5)	14	(34.1)
ER +/ HER2 -																		
Yes	87	(57.6)	47	(64.4)	40	(51.3)	1	(20.0)	6	(100)	11	(45.8)	23	(65.7)	23	(57.5)	23	(56.1)
Unknown	64	(42.4)	26	(35.6)	38	(48.7)	4	(80.0)			13	(54.2)	12	(34.3)	17	(42.5)	18	(43.9)
ER status (n, %)																		
Positive	116	(76.8)	60	(82.2)	56	(71.8)	2	(40.0)	6	(100)	17	(70.8)	31	(88.6)	29	(72.5)	31	(75.6)
Negative	16	(10.6)	5	(6.8)	11	(14.1)	1	(20.0)			6	(25)	2	(5.7)	3	(7.5)	4	(9.8)
Unknown	19	(12.6)	8	(11)	11	(14.1)	2	(40.0)			1	(4.2)	2	(5.7)	8	(20.0)	6	(14.6)
HER2 status (n, %)																		
Positive	14	(9.3)	7	(9.6)	7	(9)	1	(20.0)			3	(12.5)	4	(11.4)	3	(7.5)	3	(7.3)
Negative	100	(66.2)	51	(69.9)	49	(62.8)	2	(40.0)	6	(100)	15	(62.5)	25	(71.4)	25	(62.5)	27	(65.9)
Unknown	37	(24.5)	15	(20.5)	22	(28.2)	2	(40.0)			6	(25.0)	6	(17.1)	12	(30.0)	11	(26.8)
Metastases* location (n, %)																		

	Cumulative						Incident Cohorts											
	All		<65		≥ 65		Feb/ Mar ('15)		Apr/ May		Jun/ Jul		Aug/ Sep		Oct/ Nov		Dec/ Jan ('16)	
Bone	1	(0.7)			1	(1.3)									1	(2.5)		
Brain																		
Liver	1	(0.7)			1	(1.3)									1	(2.5)		
Lung	1	(0.7)			1	(1.3)									1	(2.5)		
Lymph	1	(0.7)	1	(1.4)									1	(2.9)				
Skin																		
None/ Unknown	147	(97.4)	72	(98.6)	75	(96.2)	5	(100)	6	(100)	24	(100)	34	(97.1)	37	(92.5)	41	(100)

†Stage recorded in EMR at closest date to palbociclib initiation, restaging of patients does not typically occur.
* Not mutually exclusive, total across categories may be greater than total number of patients.

16.2. Line of therapy at initiation of palbociclib + fulvestrant by month of start.

	Cumulative						Month of Initiation of Palbociclib											
	All		<65		≥65		Feb/ Mar ('15)		Apr/ May		Jun/ Jul		Aug/ Sep		Oct/ Nov		Dec/ Jan ('16)	
Total Patients (n, %)	151	(100)	73	(48.3)	78	(51.7)	5	(3.3)	6	(4)	24	(15.9)	35	(23.2)	40	(26.5)	41	(27.2)
1st LOT	46	(30.5)	21	(13.9)	25	(16.6)	1	(20.0)	2	(33.3)	4	(16.7)	6	(17.1)	15	(37.5)	18	(43.9)
Any Prior Endocrine	35	(76.1)	16	(76.2)	19	(76.0)	1	(100)	2	(100)	3	(75.0)	4	(66.7)	11	(73.3)	14	(77.8)
Any Prior Chemotherapy	8	(17.4)	6	(28.6)	1	(8.0)					1	(25.0)	1	(16.7)	2	(13.3)	4	(22.2)
2nd LOT	29	(19.2)	10	(6.6)	19	(12.6)	3	(60.0)	3	(50.0)	5	(20.8)	6	(17.1)	4	(10)	8	(19.5)
Any Prior Endocrine	27	(93.1)	9	(90.0)	18	(94.7)	3	(100)	3	(100)	5	(100)	5	(83.3)	4	(100)	7	(87.5)
Any Prior Chemotherapy	7	(24.1)	4	(40.0)	3	(15.8)							1	(16.7)	1	(25.0)	5	(62.5)
3rd LOT	23	(15.2)	10	(6.6)	13	(8.6)					5	(20.8)	7	(20.0)	7	(17.5)	4	(9.8)
Any Prior Endocrine	23	(100)	10	(100)	13	(100)					5	(100)	7	(100)	7	(100)	4	(100)
Any Prior Chemotherapy	9	(39.1)	4	(40.0)	5	(38.5)					2	(40)	3	(42.9)	3	(42.9)	1	(25.0)
≥4th LOT	53	(35.1)	32	(21.2)	21	(13.9)	1	(20)	1	(16.7)	10	(41.7)	16	(45.7)	14	(35)	11	(26.8)
Any Prior Endocrine	51	(96.2)	31	(96.9)	20	(95.2)			1	(100)	10	(100)	16	(100)	13	(92.9)	11	(100)
Any Prior Chemotherapy	42	(79.2)	26	(81.3)	16	(76.2)	1	(100)	1	(100)	9	(90.0)	8	(50.0)	12	(85.7)	11	(100)

Key: LOT – line of therapy.

16.3. Patient disposition at end of study period by line of therapy at palbociclib + fulvestrant initiation and length of follow-up.

Variable	Overall		Line of therapy at initiation of palbociclib + fulvestrant							
			1st LOT				≥ 2nd LOT			
			< 6 mo f-up		≥ 6 mo f-up		< 6 mo f-up		≥ 6 mo f-up	
Total Patients (n, %)	151	(100)	33	(21.9)	13	(8.6)	58	(38.4)	47	(31.1)
Months of follow-up from initiation of palbociclib + fulvestrant to last medical/pharmacy record (mean, SD)	5.3	(3.0)	3.1	(1.8)	8.7	(2.1)	3.4	(1.6)	8.2	(1.5)
On treatment at end of study period (n, %)	130	(86.1)	27	(81.8)	13	(100)	45	(77.6)	45	(95.7)
Last recorded line of therapy palbociclib + fulvestrant	91	(60.3)	23	(69.7)	9	(69.2)	33	(56.9)	26	(55.3)
Patient received line of therapy following palbociclib + fulvestrant	39	(25.8)	4	(12.1)	4	(30.8)	12	(20.7)	19	(40.4)
Lost to follow-up (n, %) ¥	5	(3.3)	2	(6.1)			1	(1.7)	2	(4.3)
Last recorded line of therapy palbociclib + fulvestrant										
Patient received line of therapy following palbociclib + fulvestrant	5	(100)	2	(100)			1	(100)	2	(100)
Deceased (n, %)	16	(10.6)	4	(12.1)			12	(20.7)		
Last recorded line of therapy palbociclib + fulvestrant										
Patient received line of therapy following palbociclib + fulvestrant	16	(100)	4	(100)			12	(100)		

Key: f-up – follow-up; LOT – line of therapy; MO - month.
¥ No treatment/medical encounters within 90 days of end of study period.

16.4. Observed treatments in line of therapy prior to initiation of palbociclib + fulvestrant.†

Variable	Overall		Line of therapy at initiation of palbociclib + fulvestrant							
			1st LOT*		2nd LOT		3rd LOT		≥ 4th LOT	
Total patients (n, %)	151	(100)	46	(30.5)	29	(19.2)	23	(15.2)	53	(35.1)
Months from metastatic diagnosis to palbociclib treatment initiation (mean, SD)	38	(56.4)	16	(58.4)	35	(51.7)	41	(30.7)	59	(59.2)
Patients with line of therapy prior to palbociclib + fulvestrant (n, %)	143	(94.7)	38	(82.6)	29	(100)	23	(100)	53	(100)
Endocrine in LOT prior (n, %)	71	(47.0)			22	(75.9)	21	(73.9)	28	(52.8)
Monotherapy	56	(78.9)			20	(90.0)	12	(57.1)	24	(85.7)
Anastrozole	13	(23.2)			6	(30.0)	3	(25.0)	4	(16.7)
Tamoxifen	6	(10.7)			2	(10.0)	1	(8.3)	3	(12.5)
Fulvestrant	1	(1.8)			1	(5.0)				
Exemestane	24	(42.9)			3	(15.0)	6	(50)	15	(62.5)
Letrozole	11	(19.6)			7	(35.0)	2	(16.7)	2	(8.3)
Goserelin Acetate	1	(1.8)			1	(5.0)				
Combination	15	(21.1)			2	(10.0)	9	(42.9)	4	(14.8)
Everolimus + Exemestane	7	(46.7)					4		3	(75.0)
Anastrozole + Fulvestrant	2	(13.3)			1	(50.0)	1	(4.3)		
Exemestane + Fulvestrant										
Anastrozole + Trastuzumab										
Anastrozole + Paclitaxel Protein-Bound										
Goserelin Acetate + Letrozole	1	(6.7)					1	(4.3)		
Fulvestrant + Letrozole	4	(26.7)			1	(50.0)	2	(8.7)	1	(25.0)
Fulvestrant + Trastuzumab										
Everolimus + Exemestane + Fulvestrant										
Anastrozole + Letrozole	1	(6.7)					1	(4.3)		
Exemestane + Paclitaxel + Pertuzumab + Trastuzumab										
Cyclophosphamide + Docetaxel + Letrozole										
Cisplatin + Exemestane										

Variable	Overall		Line of therapy at initiation of palbociclib + fulvestrant					
			1st LOT*		2nd LOT		3rd LOT	≥ 4th LOT
Bevacizumab + Exemestane + Fulvestrant								
Anastrozole + Carboplatin								
Anastrozole + Everolimus								
Capecitabine + Fulvestrant								
Fulvestrant + Tamoxifen								
Ofatumumab + Tamoxifen								
Gemcitabine + Letrozole								
Anastrozole + Everolimus + Exemestane + Fulvestrant								
Anastrozole + Capecitabine + Fulvestrant								
Capecitabine + Tamoxifen								
Exemestane + Everolimus								
Paclitaxel + Tamoxifen								
Anastrozole + Exemestane								
Toremifene Citrate								
Exemestane + Fulvestrant + Paclitaxel								
Exemestane + Paclitaxel								
Chemotherapy in LOT prior (n,%)	34	(23.8)			6	(20.7)	6 (26.1)	22 **(41.5)**
Capecitabine	5	(13.9)					1 (16.7)	4 (18.2)
Paclitaxel	1	(2.8)						1 (4.5)
Everolimus + Exemestane	7	(19.4)					4 (66.7)	3 (13.6)
Eribulin Mesylate	4	(11.1)						4 (18.2)
Paclitaxel Protein-Bound	4	(11.1)			1	(16.7)		3 (13.6)
Everolimus	3	(8.3)			1	(16.7)		2 (9.1)
Cyclophosphamide								
Doxorubicin	2	(5.6)			1	(16.7)		1 (4.5)
Docetaxel								
Cyclophosphamide + Docetaxel								

Variable	Overall		Line of therapy at initiation of palbociclib + fulvestrant							
			1st LOT*		2nd LOT		3rd LOT		≥ 4th LOT	
Ixabepilone										
Doxorubicin Liposomal	2	(5.6)			1	(16.7)			1	(4.5)
Bevacizumab + Paclitaxel										
Vinorelbine Tartrate	3	(8.3)			1	(16.7)	1	(16.7)	1	(4.5)
Gemcitabine	1	(2.8)							1	(4.5)
Carboplatin + Paclitaxel	1	(2.8)			1	(16.7)				
Cyclophosphamide + Doxorubicin										
Capecitabine + Ixabepilone	1	(2.8)							1	(4.5)
Anastrozole + Paclitaxel Protein-Bound										
Everolimus + Exemestane + Fulvestrant										
Carboplatin										
Ofatumumab + Paclitaxel										
Imatinib										
Cyclophosphamide + Doxorubicin + Paclitaxel										
Capecitabine + Tamoxifen										
Cisplatin + Exemestane										
Gemcitabine + Letrozole										
Docetaxel + Ofatumumab										
Lenalidomide										
Bevacizumab + Exemestane + Fulvestrant										
Capecitabine + Paclitaxel										
Anastrozole + Capecitabine + Fulvestrant										
Trastuzumab + Vinorelbine Tartrate										
Doxorubicin Liposomal + Methotrexate										
Anastrozole + Everolimus + Exemestane + Fulvestrant										
Epirubicin										
Gemcitabine + Paclitaxel Protein-Bound										

Variable	Overall	Line of therapy at initiation of palbociclib + fulvestrant			
		1st LOT*	2nd LOT	3rd LOT	≥ 4th LOT
Anastrozole + Everolimus					
Cyclophosphamide + Docetaxel + Letrozole					
Anastrozole + Carboplatin					
Ofatumumab					
Capecitabine + Fulvestrant					
Ofatumumab + Tamoxifen					
Carboplatin					
Paclitaxel + Tamoxifen					
Exemestane + Everolimus					
Pertuzumab					
Exemestane + Fulvestrant + Paclitaxel					
Cyclophosphamide + Docetaxel + Ofatumumab					
Exemestane + Paclitaxel					
Exemestane + Paclitaxel + Pertuzumab + Trastuzumab					

Key: LOT – line of therapy.
†Categories not mutually exclusive, column total may sum to > 100% as regimens with chemotherapy and endocrine were grouped in both combination endocrine and chemotherapy subgroups.
* For LOT 1, includes treatments received prior to development of metastatic disease if patient data contained within the EMR.

16.5. Observed treatments following palbociclib + fulvestrant†.

Variable	Overall		LOT at initiation of palbociclib + fulvestrant							
			1st LOT				≥ 2nd LOT			
			< 6 mo f-up		≥ 6 mo f-up		< 6 mo f-up		≥ 6 mo f-up	
Total Patients (n, %)	151	(100)	33	(21.9)	13	(8.6)	58	(38.4)	47	(31.1)
Months of follow-up from palbociclib treatment initiation (mean, SD)	5.3	(3.0)	3.1	(1.8)	8.7	(2.1)	3.4	(1.6)	8.2	(1.5)
Patients receiving new treatment regimen post-palbociclib (n, %)	60	(39.7)	10	(30.3)	4	(30.8)	25	(43.1)	21	(44.7)
Switch to Endocrine (n,%)	7	(50.0)					3	(42.9)	4	(57.1)
Monotherapy	1	(14.3)					1	(33.3)		
Fulvestrant	3	(42.9)					2	(66.7)	1	(25.0)
Letrozole	1	(14.3)							1	(250)
Tamoxifen										
Anastrozole	2	(28.6)							2	(50.0)
Exemestane	7	(50.0)					3	(42.9)	4	(57.1)
Combination	7	(50.0)	2	(28.6)	1	(14.3)	2	(28.6)	2	(28.6)
Fulvestrant + Palbociclib	1	(14.3)							1	(50.0)
Everolimus + Exemestane	1	(14.3)					1	(50.0)		
Fulvestrant + Letrozole	2	(28.6)	1	(50.0)					1	(50.0)
Fulvestrant + Letrozole + Palbociclib	1	(14.3)	1	(50.0)						
Anastrozole + Letrozole + Palbociclib										
Exemestane + Letrozole + Palbociclib										
Letrozole + Palbociclib + Tamoxifen										
Anastrozole + Palbociclib	1	(14.3)			1	(100)				
Capecitabine + Letrozole + Palbociclib										
Docetaxel + Letrozole + Pertuzumab + Trastuzumab										
Eribulin Mesylate + Letrozole + Palbociclib										
Gemcitabine + Letrozole										
Goserelin Acetate										
Letrozole + Paclitaxel										

Variable	Overall		LOT at initiation of palbociclib + fulvestrant					
			1st LOT				≥ 2nd LOT	
			< 6 mo f-up		≥ 6 mo f-up		< 6 mo f-up	≥ 6 mo f-up
Anastrozole + Lenalidomide								
Capecitabine + Letrozole								
Doxorubicin + Tamoxifen								
Eribulin Mesylate + Letrozole								
Everolimus + Exemestane + Letrozole								
Everolimus + Exemestane + Letrozole + Palbociclib								
Everolimus + Exemestane + Palbociclib								
Everolimus + Letrozole								
Goserelin Acetate + Letrozole + Palbociclib								
Letrozole								
Letrozole + Paclitaxel + Palbociclib								
Letrozole + Paclitaxel Protein-Bound								
Palbociclib + Tamoxifen	1	(14.3)					1	(50.0)		
Toremifene Citrate								
Switch to Chemotherapy (n,%)	23		2	(8.7)	3	(13)	8	(34.8)	10	(43.5)
Capecitabine	5	(21.7)	1	(50.0)			2	(25.0)	2	(20.0)
Paclitaxel Protein-Bound								
Eribulin Mesylate	3	(13.0)					2	(25.0)	1	(10.0)
Fulvestrant + Palbociclib	1	(4.3)							1	(10.0)
Paclitaxel	3	(13.0)			1	(33.3)	1	(12.5)	1	(10.0)
Doxorubicin								
Everolimus + Exemestane	1	(4.3)					1	(12.5)		
Carboplatin + Paclitaxel								
Ixabepilone								
Fulvestrant + Letrozole + Palbociclib	1	(4.3)			1	(33.3)				
Vinorelbine Tartrate								
Gemcitabine	1	(4.3)							1	(10.0)

Variable	Overall	LOT at initiation of palbociclib + fulvestrant			
		1st LOT		≥ 2nd LOT	
		< 6 mo f-up	≥ 6 mo f-up	< 6 mo f-up	≥ 6 mo f-up
Exemestane + Letrozole + Palbociclib					
Anastrozole + Letrozole + Palbociclib					
Letrozole + Palbociclib + Tamoxifen					
Anastrozole + Palbociclib	1 (4.3)		1 (33.3)		
Docetaxel + Letrozole + Pertuzumab + Trastuzumab					
Capecitabine + Letrozole + Palbociclib					
Letrozole + Paclitaxel					
Gemcitabine + Letrozole					
Everolimus					
Cyclophosphamide	1 (4.3)				1 (10.0)
Eribulin Mesylate + Letrozole + Palbociclib					
Carboplatin + Gemcitabine	1 (4.3)				1 (10.0)
Capecitabine + Palbociclib	1 (4.3)	1 (50.0)			
Carboplatin + Epirubicin					
Cytarabine Liposome					
Anastrozole + Lenalidomide					
Gemcitabine Hcl + Ofatumumab					
Carboplatin + Gemcitabine Hcl					
Letrozole + Paclitaxel + Palbociclib					
Capecitabine + Ixabepilone	1 (4.3)				1 (10.0)
Carboplatin	1 (4.3)			1 (12.5)	
Everolimus + Exemestane + Letrozole					
Cyclophosphamide + Epirubicin					
Palbociclib + Tamoxifen	1 (4.3)			1 (12.5)	
Gemcitabine Hcl + Palbociclib					
Everolimus + Exemestane + Palbociclib					
Eribulin Mesylate + Letrozole					

Variable	Overall	LOT at initiation of palbociclib + fulvestrant			
		1st LOT		≥ 2nd LOT	
		< 6 mo f-up	≥ 6 mo f-up	< 6 mo f-up	≥ 6 mo f-up
Everolimus + Letrozole Letrozole + Paclitaxel Protein-Bound Bevacizumab + Paclitaxel Protein-Bound Ofatumumab + Paclitaxel Capecitabine + Letrozole Paclitaxel + Palbociclib Doxorubicin + Tamoxifen Pertuzumab Doxorubicin Liposomal Everolimus + Exemestane + Letrozole + Palbociclib Eribulin Mesylate + Palbociclib Eribulin Mesylate + Pertuzumab + Trastuzumab	1 (4.3)				1 (10.0)

Key: F-up – follow-up; LOT – line of therapy; MO – months.
†Categories not mutually exclusive, column total may sum to > 100% as regimens with chemotherapy and endocrine were grouped in both combination endocrine and chemotherapy subgroups.

16.6. Initiation dose of palbociclib and patterns of dose reductions among patients treated with palbociclib + fulvestrant.

	Overall		Number of palbociclib cycles received†					
			6 cycles¥		4 cycles$^{\alpha}$		2 cycles$^{\mu}$	
Total patients	151	(100)	65	(43)	104	(68.9)	130	(86.1)
Patients with known starting dose	149	(98.7)	63	(96.9)	102	(98.1)	128	(98.5)
Patients with unknown starting dose	2	(1.3)	2	(3.1)	2	(1.9)	2	(1.5)
Starting dose (n, %) (among patients with known starting dose)								
125 mg	127	(84.1)	57	(87.7)	92	(88.5)	113	(86.9)
100 mg	21	(13.9)	6	(9.2)	10	(9.6)	15	(11.5)
75 mg	1	(0.7)	0	(0)	0	(0)	1	(0.8)
Number of dose reductions (n, %) (among patients with known starting dose)								
None	117	(77.5)	41	(63.1)	76	(73.1)	103	(79.2)
>=1	34	(22.5)	24	(36.9)	28	(26.9)	27	(20.8)
Type of first dose reduction (n, %) (among patients with known starting dose)								
Reduction from 125 mg to 100 mg	24	(70.6)	15	(62.5)	19	(67.9)	23	(85.2)
Reduction from 100 mg to 75 mg	8	(23.5)	8	(33.3)	8	(28.6)	8	(29.6)
Reduction from 125 mg to 75 mg	2	(5.9)	1	(4.2)	1	(3.6)	1	(3.7)
Days to first dose reduction (mean, SD)	45.1	(20.3)	49.7	(22.7)	47.3	(21.4)	46.4	(20.3)

†Number of cycles approximated by time since initiation of treatment of palbociclib as cycle/refill dates not available in EMR.

¥Interval from initiation of palbociclib + fulvestrant through 168 days post initiation among those considered on palbociclib + fulvestrant at day 168 post initiation.

$^{\alpha}$Interval from initiation of palbociclib + fulvestrant through 112 days post initiation among those considered on palbociclib + fulvestrant at day 112 post initiation.

$^{\mu}$Interval from initiation of palbociclib + fulvestrant through 56 days post initiation among those considered on palbociclib + fulvestrant at day 56 post initiation.

16.7. Supportive care drugs used during treatment with palbociclib among patients treated with palbociclib + fulvestrant.

Variable	Overall		Line of therapy at initiation of palbociclib + fulvestrant							
			1st LOT				≥ 2nd LOT			
			< 6 mo f-up		≥ 6 mo f-up		< 6 mo f-up		≥ 6 mo f-up	
Total patients	151	(100)	33	(21.9)	13	(8.6)	58	(38.4)	47	(31.1)
Any supportive care drug	115	(76.2)	18	(54.5)	12	(92.3)	44	(75.9)	41	(87.2)
Bone preserving agents										
Denosumab	55	(47.8)	7	(38.9)	7	(58.3)	19	(43.2)	22	(53.7)
Zoledronic Acid	25	(21.7)	6	(33.3)	1	(8.3)	10	(22.7)	8	(19.5)
Alendronate Sodium	2	(1.7)	1	(5.6)			1	(2.3)		
Pamidronate Disodium	1	(0.9)					1	(2.3)		
Antiemetic										
Prochlorperazine Maleate	27	(23.5)	5	(27.8)	3	(25)	9	(20.5)	10	(24.4)
Ondansetron	14	(12.2)	2	(11.1)	1	(8.3)	4	(9.1)	7	(17.1)
Ondansetron Hcl	17	(14.8)	4	(22.2)	1	(8.3)	8	(18.2)	4	(9.8)
Promethazine Hcl	4	(3.5)	1	(5.6)			1	(2.3)	2	(4.9)
Dronabinol	2	(1.7)	1	(5.6)					1	(2.4)
Metoclopramide Hcl	2	(1.7)					1	(2.3)	1	(2.4)
Granisetron	9	(7.8)	1	(5.6)			2	(4.5)	6	(14.6)
Hydroxyzine Hcl	1	(0.9)							1	(2.4)
Fosaprepitant Dimeglumine	2	(1.7)							2	(4.9)
Palonosetron	6	(5.2)					4	(9.1)	2	(4.9)
Prochlorperazine Edisylate										
Pain										
Oxycodone Hcl	10	(8.7)			1	(8.3)	7	(15.9)	2	(4.9)
Gabapentin	5	(4.3)					2	(4.5)	3	(7.3)
Morphine Sulfate	1	(0.9)					1	(2.3)		
Celecoxib	2	(1.7)							2	(4.9)
Corticosteroid										

Variable	Overall		Line of therapy at initiation of palbociclib + fulvestrant							
			1st LOT				≥ 2nd LOT			
			< 6 mo f-up		≥ 6 mo f-up		< 6 mo f-up		≥ 6 mo f-up	
Dexamethasone Sod Phosphate	13	(11.3)	1	(5.6)	1	(8.3)	4	(9.1)	7	(17.1)
Dexamethasone	7	(6.1)			1	(8.3)	3	(6.8)	3	(7.3)
Prednisone	1	(0.9)			1	(8.3)				
Hydrocortisone	1	(0.9)							1	(2.4)
Triamcinolone Acetonide	3	(2.6)			2	(16.7)	1	(2.3)		
Methylprednisolone										
Anticoagulant										
Rivaroxaban	3	(2.6)					2	(4.5)	1	(2.4)
Enoxaparin Sodium	5	(4.3)	1	(5.6)			3	(6.8)	1	(2.4)
Alteplase	3	(2.6)					1	(2.3)	2	(4.9)
Warfarin Sodium	3	(2.6)			1	(8.3)	1	(2.3)	1	(2.4)
Fondaparinux Sodium										
Proton pump inhibitor										
Pantoprazole Sodium	1	(0.9)					1	(2.3)		
Cimetidine	1	(0.9)			1	(8.3)				
Ranitidine Hcl	1	(0.9)							1	(2.4)
Antibiotic										
Doxycycline Hyclate	1	(0.9)							1	(2.4)
Ciprofloxacin Hcl	3	(2.6)			1	(8.3)			2	(4.9)
Cephalexin										
Penicillin V Potassium	1	(0.9)							1	(2.4)
Metronidazole	1	(0.9)							1	(2.4)
Diuretic										
Furosemide	7	(6.1)	1	(5.6)	0	(0)	4	(9.1)	2	(4.9)
GCSF										
Filgrastim	3	(2.6)							3	(7.3)
Pegfilgrastim	5	(4.3)							5	(12.2)

Variable	Overall		Line of therapy at initiation of palbociclib + fulvestrant							
			1st LOT				≥ 2nd LOT			
			< 6 mo f-up		≥ 6 mo f-up		< 6 mo f-up		≥ 6 mo f-up	
Erythropoetin Stimulating Factor										
Epoetin Alfa	3	(2.6)					2	(4.5)	1	(2.4)
Insomnia										
Temazepam	1	(0.9)							1	(2.4)
Gastric protective agent										
Sucralfate										
Thyroid hormone										
Levothyroxine Sodium										

Key: F-up – follow-up; LOT – line of therapy; MO – months.

16.8. Frequency (n, %) of adverse event diagnoses during palbociclib + fulvestrant treatment by number of cycles received.

	Time since initiation of palbociclib†					
	Cycles 1-6¥		Cycles 1-4α		Cycles 1-2μ	
Total Patients	65	(43)	104	(68.9)	130	(86.1)
Any AE diagnosis	19	(14.6)	12	(11.5)	7	(10.8)
Number of AEs diagnosed during palbociclib + fulvestrant treatment						
1	14	(73.7)	8	(66.7)	6	(85.7)
2	3	(15.8)	4	(33.3)	1	(14.3)
≥ 3	2	(10.5)				
Anemia	4	(21.1)	1	(8.3)		
Anorexia	1	(5.3)	1	(8.3)		
Diarrhea	1	(5.3)	1	(8.3)	1	(14.3)
Fatigue	6	(31.6)	5	(41.7)	2	(28.6)
Leukopenia	1	(5.3)	1	(8.3)		
Mucositis						
Nausea	4	(21.1)	3	(25)	2	(28.6)
Neuropathy						
Pain	3	(15.8)	1	(8.3)	1	(14.3)
Rash						
Respiratory infections	3	(15.8)	1	(8.3)		
Skin reaction						
Thrombocytopenia	3	(15.8)	2	(16.7)	2	(28.6)

*All patients assumed to be receiving treatment throughout the interval following initiation.
¥Interval from initiation of palbociclib + fulvestrant through 168 days post initiation among those considered on palbociclib + fulvestrant at day 168 post initiation and those who experienced an event prior to the end of the interval.
α Interval from initiation of palbociclib + fulvestrant through 112 days post initiation among those considered on palbociclib + fulvestrant at day 112 post initiation and those who experienced an event prior to the end of the interval.
μ Interval from initiation of palbociclib + fulvestrant through 56 days post initiation among those considered on palbociclib + fulvestrant at day 56 post initiation and those who experienced an event prior to the end of the interval.

16.9. CBC laboratory evaluations during palbociclib + fulvestrant treatment and occurrence, timing and grade of neutropenia.

	All Cycles	Cycles 1-6¥	Cycles 1-4α	Cycles 1-2μ

	All Cycles		Cycles 1-6[¥]		Cycles 1-4[α]		Cycles 1-2[µ]	
Total patients	151	(100)	65	(43)	104	(68.9)	130	(86.1)
Patients with ≥ one CBC during time period	115	(76.2)	50	(76.9)	76	(73.1)	101	(77.7)
Number of CBC tests (mean, SD)[‡]	3.3	(3.4)	4.7	(4.6)	3.8	(3.9)	3.5	(3.5)
Lab value consistent with neutropenia* while on palbociclib (n, %)	53	(46.1)	23	(46)	36	(47.4)	48	(47.5)
Days to first neutropenia episode (mean, SD)	34.0	(26.3)	47.7	(40.9)	35.8	(29.7)	33.9	(27.6)
Highest grade Neutropenia (n, % of patients with test)								
Grade 1 (ANC 1500-1999)	16	(30.2)	6	(26.1)	13	(36.1)	15	(31.3)
Grade 2 (ANC 1000-1499)	18	(34)	8	(34.8)	11	(30.6)	15	(31.3)
Grade 3 (ANC 500-999)	12	(22.6)	6	(26.1)	8	(22.2)	12	(25.0)
Grade 4 (ANC < 500)	6	(11.3)	3	(13.0)	4	(11.1)	6	(12.5)

Key: ANC - absolute neutrophil count

‡ Only patients with at least one lab test result counted in frequency of CBC tests, neutrophil count during palbociclib treatment and grade of neutropenia.

*Neutropenia = divide neutrophil % by 100, multiply value by WBC quantity (neutrophil value in K/µl), and multiply by 1000 to convert to mm3.

[¥] Interval from initiation of palbociclib + fulvestrant through 168 days post initiation among those considered on palbociclib + fulvestrant at day 168 post initiation and those who received test/experienced event prior to the end of the interval.

[α] Interval from initiation of palbociclib + fulvestrant through 112 days post initiation among those considered on palbociclib + fulvestrant at day 112 post initiation and those who received test/experienced event prior to the end of the interval.

[µ] Interval from initiation of palbociclib + fulvestrant through 56 days post initiation among those considered on palbociclib + fulvestrant at day 56 post initiation and those who received test/experienced event prior to the end of the interval.

Document Approval Record

Document Name:	A5481067 CT24-GSOP-RF27 2.0 NI Study Report
Document Title:	Descriptive Analyses of Clinical Characteristics and Treatment Patterns of Breast Cancer Patients Initiating Palbociclib (Ibrance®) Treatment in the US Community Oncology Setting

Signed By:	Date(GMT)	Signing Capacity
De Bernardi, Barbara	29-Mar-2017 16:34:48	Business Line Approver

APPENDIX 1. SIGNATURES

PROTOCOL NUMBER: A5481067

TITLE OF STUDY: Descriptive Analyses of Clinical Characteristics and Treatment Patterns of Breast Cancer Patients Initiating Palbociclib (Ibrance®) Treatment in the US Community Oncology Setting

Confirmation: I confirm that this Non-Interventional (NI) study report, which is final in content and has been printed from its definitive source, is a complete and accurate representation of the data and statistical analyses from this study.

Pfizer NI study lead

Melea Ward, PhD, PharmD, BCPS

Signature: Melea Ward **Date:** 28 February 2017

If no external scientists were accountable for scientific and operational conduct of the study, the box below should be deleted. Boxes may be added to accommodate additional scientists as needed.

Epidemiologist accountable for scientific and operational conduct of study

Jonathan Karl Kish, PhD MPH

Signature: **Date: 9 December 2016**

If the approval(s) for this study report were completed electronically within the Global Management Document System (GDMS), all text below should be deleted. Boxes may be added to accommodate any additional approvers, in accordance with CT24-GSOP.

Approval of non-interventional study report

US Oncology Outcomes & Evidence Team Lead
Global Health and Value

Timothy Bell

Signature: **Date:** 2/26/17

Study information

Title	Descriptive Analyses of Clinical Characteristics and Treatment Patterns of Breast Cancer Patients Initiating Palbociclib (Ibrance®) Treatment in the US Community Oncology Setting
Protocol number	A5481067
Protocol version identifier	V1
Date of last version of protocol	December 3rd, 2015
EU Post Authorisation Study (PAS) register number	N/A
Active substance	Palbociclib
Medicinal product	Ibrance
Research question and objectives	Palbociclib (Ibrance®) was launched in the United States in February 2015. This study will describe the characteristics of patients initiating treatment with palbociclib in terms of demographic and clinical characteristics, real-world treatment patterns (line of therapy, concomitant use of other chemotherapy/hormonal therapy/supportive drugs), dosing patterns, and adverse event/neutropenia-related outcomes (frequency of monitoring incidence, time to event) among female patients with breast cancer following US approval.
Author	Jonathan Kish, PhD, MPH Director, Health Economics and Outcomes Research 2515 McKinney Avenue Suite 1600, Dallas, TX 75201 313.570.8220 mobile E: jonathan.kish@cardinalhealth.com

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
CBC	Complete blood count
CDK	Cyclin-dependent kinase
DNA	Deoxyribonucleic acid
ECOG	Eastern oncology cooperative group
EMR	Electronic medical records
ER	Estrogen receptor
FDA	Food and Drug Administration
HER2	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HR	Hormone receptor
IRB	Institutional Review Board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MBC	Metastatic breast cancer
NCCN	National Comprehensive Cancer Network
OS	Overall survival
PFS	Progression-free survival
PHI	Personal Health Information
QC	Quality control

Abbreviation	Definition
SAP	Statistical Analysis Plan
US	United States

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Giovanni Zanotti, PharmD, MSc	Director, Global Outcomes & Evidence, Oncology	Pfizer Inc.	235E 42nd, New York, NY, 10017
Jonathan Kish, PhD, MPH	Director, Health Economics and Outcomes Research	Cardinal Health	2515 McKinney Avenue Suite 1600, Dallas, TX 75201
Hsing-Ting Yu, MPH	Sr. Project Manager, Health Economics and Outcomes Research	Cardinal Health	2515 McKinney Avenue Suite 1600, Dallas, TX 75201

3. AMENDMENTS AND UPDATES

None

4. MILESTONES

Milestone	Planned date
Project kick off	27 October 2015
Study protocol finalization	4 December 2015
Statistical Analysis Plan (SAP) finalization	11 December 2015
Data cleaning and analytic cohort formation, analysis, and reporting	
1st data cut (through September 2015)	25 November 2015
1st descriptive analysis	8 January 2016
1st report	22 January 2016
2nd data cut (through November 2015)	5 February 2016
2nd descriptive analysis	4 March 2016
2nd report	1 April 2016
Final data cut (through February 2016)	6 May 2016
Final descriptive analysis	3 June 2016
Final report	1 July 2016

5. RATIONALE AND BACKGROUND

In the United States (US), breast cancer is the leading cause of cancer-related deaths among women aged 20-59 years. In 2015, it is estimated that 29% of all new cancer cases among US women will be breast cancer, amounting to an estimated 234,190 new cases and 40,730 deaths.[1] Although the overall mortality rate due to breast cancer has been declining in recent decades, the incidence rate has steadily increased.[2]

Because treatment decisions and outcomes can vary based on tumor characteristics, the National Comprehensive Cancer Network (NCCN) guidelines recommend testing all patients for hormonal and human epidermal growth factor receptor 2 (HER2) status. Treatment for localized breast cancer typically consists of surgery and radiation therapy, followed by adjuvant chemotherapy, endocrine therapy, and/or biological therapy, if needed. Patients who are diagnosed with metastatic breast cancer (MBC) are treated with chemotherapy or targeted therapy, and specific hormonal or anti-HER2 agents are used in patients with hormone receptor (HR)-positive or HER2-positive disease. Single-agent or combination chemotherapy for MBC often includes anthracyclines, taxanes, microtubule inhibitors, or other agents. Some commonly used targeted agents include trastuzumab, pertuzumab, lapatinib, and everolimus [2]

Palbociclib is an oral, , cyclin-dependent kinase (CDK) 4/6 inhibitor, which prevents deoxyribonucleic acid (DNA) replication by prohibiting progression from G1 to S phase during cell division, thereby preventing tumor cell proliferation through cell cycle control. The US Food and Drug Administration (FDA) granted palbociclib Breakthrough Therapy Designation for breast cancer in April 2013, and the rolling NDA was completed in August 2014. Accelerated approval for palbociclib as frontline treatment in postmenopausal women with estrogen receptor (ER)-positive/HER2-negative MBC was granted in February 2015, after the randomized phase II PALOMA-1 trial demonstrated that the addition of palbociclib to letrozole significantly improved progression-free survival (PFS) in patients with advanced ER-positive/HER2-negative breast cancer (median PFS, 20.2 months vs. 10.2 months; hazard ratio [HR] = 0.448; P = .0004).[3] Grade 3/4 adverse events that occurred more frequently in the palbociclib arm included neutropenia (54% vs. 1%), leukopenia (19% vs. 0), and fatigue (4% vs. 1%).

Pfizer is interested in gathering real-world data describing the population of patients treated with palbociclib in the community oncology setting. This research will evaluate clinical characteristics and treatment sequencing of patients prescribed palbociclib to support the medical strategies being pursued by Pfizer.

6. RESEARCH QUESTION AND OBJECTIVES

The goals of this research are to evaluate the real-world treatment sequencing, dosing patterns, and occurrence of adverse events (AEs)/neutropenia among female breast cancer patients initiating treatment with palbociclib following drug approval (February 1, 2015). More specifically, Electronic Medical Records (EMR) data will be utilized to achieve the following research objectives:

1. Characterize the demographic and clinical characteristics of patients at the initiation of treatment with palbociclib.
2. Describe palbociclib utilization by line of therapy.
3. Assess the frequency, timing, and rationale (occurrence of diagnosed AEs) of palbociclib dose reduction/titration, dose interruption/delay or discontinuation by line of therapy.
4. Quantify frequency of complete blood count (CBC) including white blood cell count (WBC) monitoring including the incidence of neutropenia and time to neutropenia treatment during the three time intervals: anytime prior to palbociclib initiation, within 3 months prior to palbociclib initiation, and during palbociclib treatment.
5. Describe utilization of chemotherapy, hormonal therapy, and other supportive pharmacological agents pre-treatment, concomitantly, and post-treatment with palbociclib.

7. RESEARCH METHODS

7.1. Study design

This is a retrospective observational study of female patients diagnosed with breast cancer and newly initiating treatment with palbociclib in the community oncology setting in the US. Female patients who meet the inclusion criteria will be retrospectively selected from an EMR database. This study will describe the patient characteristics in terms of demographic and clinical characteristics, real-world treatment patterns including line of therapy, dosing patterns (dose at initiation, dose titration or reduction, and timing of dose modifications), concomitant use of other chemotherapy/hormonal therapy/supportive drugs), laboratory monitoring patterns (CBC and WBC), and AE/neutropenia-related outcomes including incidence, time to event, and association with dosing modifications and discontinuations among female breast cancer patients during the 12-month period following drug approval (February 1, 2015).

7.2. Setting

Female breast cancer patients newly initiating treatment with palbociclib between February 1, 2015 and January 31, 2016 will be selected for the study from the EMR database. The index date for the analysis is the date of first prescription for palbociclib. EMR data will be extracted for each patient backward in time to the first date of diagnosis for breast cancer and forward up to one year following treatment initiation. Patients meeting all of the following criteria will be selected for analysis.

7.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Received at least one prescription for palbociclib during the index period.

2. Diagnosed with breast cancer (ICD-9 CM 174.x) anytime prior to or on the date of first prescription for palbociclib.
3. Female sex.
4. At least 18 years of age at date of breast cancer diagnosis.

7.2.2. Exclusion criteria

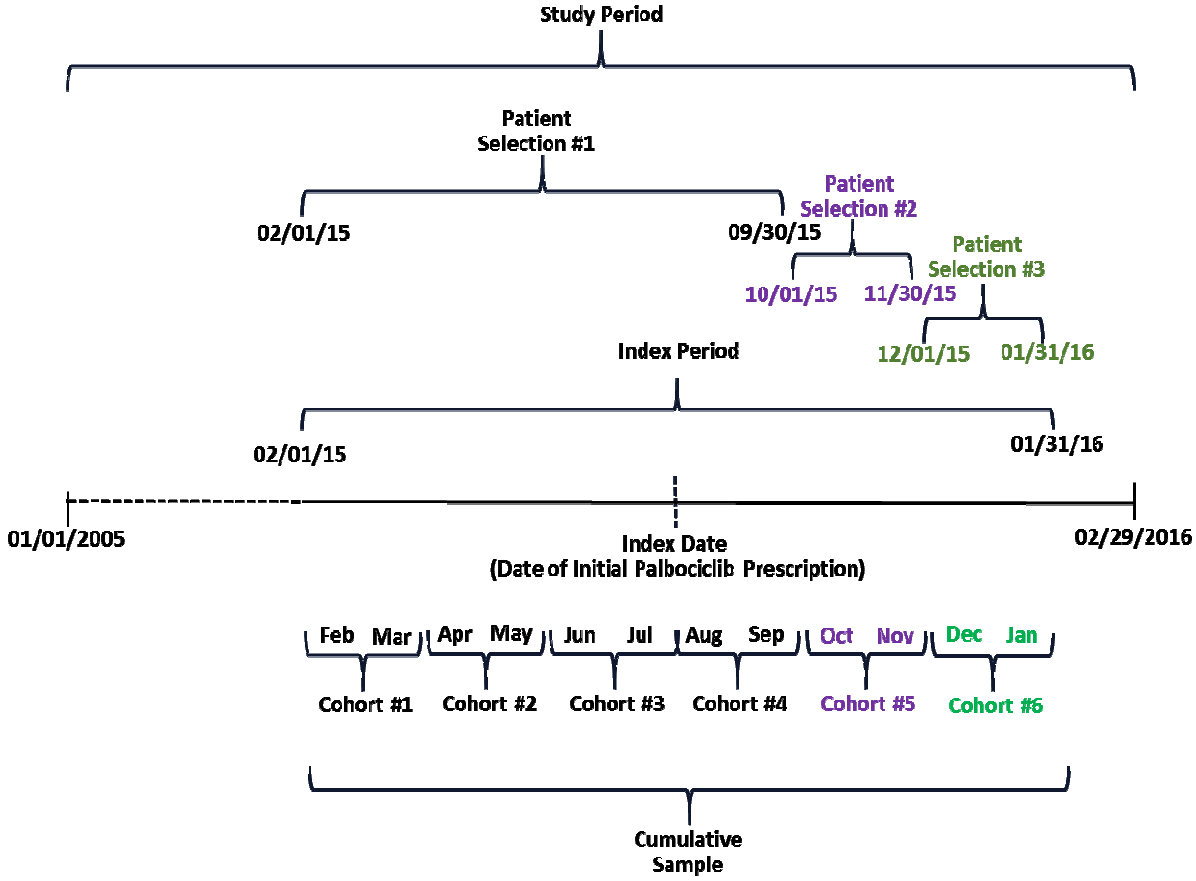
Patients meeting any of the following criteria will not be included in the study:

1. Diagnosis or treatment of a second primary malignancy anytime during the study period.
2. Receiving a prescription for palbociclib prior to the index period.
3. Participation in any palbociclib clinical trial during the study period.

7.2.3. Analytical Cohort Formation

To fulfil the study objectives, patients will be selected from the EMR dataset at three time points. The initial patient selection will include those patients treated with palbociclib anytime between February 1, 2015 and September 30, 2015. Subsequently, the dataset will be refreshed at two future time points to select incident patients initiating palbociclib therapy and obtain follow-up information on prevalent study subjects already included in the dataset. The index date will be the date of first prescription for palbociclib. Analyses will be reported for each successive two-month interval following the launch of palbociclib in the US on February 1, 2015 leading to the formation of six period-specific analysis cohorts (eg, cohort 1 = index date anytime between February 1, 2015 and March 31, 2015; cohort 2 = index date anytime between April 1, 2015 and May 30, 2015; through cohort 6 = index date anytime between December 1, 2015 and January 31, 2016). Cumulative results will be presented for the total patient sample in the dataset after each incident cohort analysis (eg, summary results for cohort 1-2, 1-3, 1-4, 1-5 and complete sample including cohorts 1-6). All analyses will be performed on all incident and cumulative cohorts. In order to evaluate outcomes of interest following treatment initiation for the last cohort (cohort 6), data abstraction will be extended to include February 2016 data. A stratified analysis will be conducted for each analytical cohort to compare analysis measures among patients with <6 or ≥6 months of follow-up. As this analysis is descriptive in nature, no formal statistical comparison will be made between analytic cohorts. Figure 1 illustrates the study time period, patient selection intervals, and analysis cohorts.

Figure 1. Study Period Diagram



7.3. Variables

The following measures will be calculated to support each of the research objectives:

Objective 1 – Frequency of demographic and clinical characteristics (see Table 1 variables) of patients for each of the analytic cohorts.

Objective 2 – Frequency of use of palbociclib by line of therapy through the following measures:

- Proportion of use as first-line therapy;
- Proportion of use as second-line therapy;
- Proportion of use as third-line therapy;
- Proportion of use as fourth-line therapy;
- Proportion of use as fifth or higher-line therapy.

Objective 3 – Frequency of palbociclib dose reductions/titrations, reason for dose reduction (adverse event of interest or not), time to dose reduction by palbociclib line of therapy and duration of treatment interruption/dose delay through the following measures:

- Frequency of any dose reduction;

- Frequency of reduction from 125 mg to 100 mg;
- Frequency of reduction from 125 mg to 75 mg;
- Frequency of reduction from 100 mg to 75 mg;
- Time to first dose reduction;
- Duration of time at dose lower than first prescription;
- Time to second dose reduction;
- Time to treatment discontinuation by palbociclib;
- Proportion of treament discontinuations due to any and/or specific adverse events (based on ICD-9-CM diagnosis codes);
- Proportion of dose reductions due to any and/or specific adverse events (based on ICD-9-CM diagnosis codes);
- Proportion of dose reductions due to neutropenia;
- Average time of treatment interruption/delay.

Objective 4 – Frequency of laboratory evaluations (CBC including WBC) to evaluate incidence and time to diagnosis of neutropenia among patients with and without a diagnosis of neutropenia prior to palbociclib treatment initiation through the following measures:

- Diagnosis of neutropenia prior to first palbociclib prescription during the following time intervals:
    - Anytime prior to first prescription;
    - Within 3 months prior to first prescription;
    - In prior line of therapy (if applicable).
- Mean number of neutropenia events (by diagnosis) before and during palbociclib treatment by line of therapy.
- Time to first diagnosis of neutropenia during palbociclib treatment.
- Frequency of CBC/WBC laboratory evaluations during first palbociclib cycle (ie, within 30 days of palbociclib initiation).
- Frequency of CBC/WBC laboratory evaluations during second palbociclib cycle (ie, >30 and ≤60 days following palbociclib initiation).
- Proportion of patients with absolute neutrophil count <500 and <1000 during palbociclib treatment by line of therapy.

Objective 5 – Utilization of other chemotherapy, hormonal therapy, and supportive care (both overall and by individual drugs/agents) through the following measures:

- Proportion receiving any and/or each recorded chemotherapy, hormonal and supportive care drugs for advanced/metastatic breast cancer during the following timeframes:
    - Anytime prior to palbociclib treatment initiation;
    - Within 6 months following palbociclib treatment initiation.
- Proportion receiving any and/or each recorded chemotherapy and/or hormonal drugs at start of (±14 days) palbociclib treatment initiation.
- Proportion receiving any and/or each recorded supportive care medications during the following timeframes:

  - Anytime during palbociclib treatment;
  - At start of (±14 days) first palbociclib prescription;
  - At start of (±14 days) second palbociclib prescription.
- Proportion receiving any and/or each recorded chemotherapy or hormonal drug therapy as their first therapy subsequent to palbociclib treatment discontinuation.

Demographic, clinical and treatment related variables, variable descriptions, the time point(s) of data collection in regard to each variable, and the source of the data (structured or unstructured elements of the EMR) to calculate the outcome measures are shown in Table 1. Variables collected at diagnosis will be collected from the first recorded claim/record available for the patient with a breast cancer diagnosis. Diagnosis of advanced disease will be assessed through evaluation of stage data contained in structured fields. Variables collected at palbociclib treatment initiation will be collected from the claim/record on or closest to the date of the first recorded prescription for palbociclib. The EMR contains both structured and unstructured data. The unstructured data will be searched using keywords for those elements not collected in the structured fields. Where the structured data does not contain the variable of interest, single keyword searches of the patient clinical/progress notes will be performed to identify the patient status in regard to the variable of interest.

Table 1. Demographic, Clinical and Treatment Related Variables

Variable	Collection Point	Operational
Age	• At advanced/metastatic breast cancer diagnosis • At palbociclib treatment initiation	Structured data field
Region of residence	• At palbociclib treatment initiation	Structured data field
Weight	• At palbociclib treatment initiation	Structured data field
Diagnosis of advanced breast cancer	• Date on which occurs	Based on ICD-9 diagnosis codes
Diagnosis of metastatic breast cancer	• Date on which occurs	Based on ICD-9 diagnosis codes
Location of Metastatic Disease	• At palbociclib treatment initiation	Based on ICD-9 diagnosis codes
Number of metastases	• Anytime during study period	Based on different ICD-9 diagnosis codes
Menopausal status	• At advanced/metastatic breast cancer diagnosis	Unstructured keyword search of progress notes
Histology	• At advanced/metastatic breast cancer diagnosis	Based on ICD-9 diagnosis codes
Stage at diagnosis	• At advanced/metastatic breast cancer diagnosis • At palbociclib treatment initiation	Structured data field
TNM Stage	• At palbociclib treatment initiation • At palbociclib treatment discontinuation	Structured data field
ECOG Performance Status	• At palbociclib treatment initiation	Structured data field
Karnofsky Score	• At palbociclib treatment initiation	Structured data field
ER Receptor Status	• Most recent evaluation	Structured data field
PR Receptor Status	• Most recent evaluation	Structured data field

Variable	Collection Point	Operational
HER2 Receptor Status	• Most recent evaluation	Structured data field
Palbociclib treatment date	• Date of each prescription order for palbociclib	Structured data field
Palbociclib dose	• At each prescription order	Structured data field
Chemotherapy treatment date	• Date of each order/prescription for chemotherapy drugs	Structured data field
Hormonal therapy treatment date	• Date of each order/prescription for Hormonal therapy drugs	Structured data field
Supportive care treatment date	• Date of each order/prescription for Supportive care drugs	Structured data field
Adverse event diagnosis	• Date of any occurrence during palbociclib treatment	Events based on ICD-9 diagnosis codes
CBC Lab test	• Closest data prior to and any instance during palbociclib combination treatment	Structured data field
WBC quantity	• Date of tests and results anytime during study period	Structured data field
WBC neutrophil percentage	• Date of tests and results anytime during study period	Structured data field
Diagnosis of neutropenia	• Any time during study period	• Structured data fields (ICD-9 diagnosis code and/or WBC laboratory results) • Unstructured keyword search of progress notes

7.4. Data sources

EMR data are sourced from multiple community oncology practice sites across the US. Practices provide data through up to 23 distinct EMR systems; the data are then collected and aggregated to a common data standard. Included in the database are the records for over 2 million patients treated since 2005 by over 975 oncologists at 81 practice sites in 25 states across the US. These data include commercial, Medicare, and Medicaid covered patients. Treatment history is captured for both intravenous and oral chemotherapy medications. Both structured data fields and unstructured data are available for research purposes with single-keyword natural language processing available to search the unstructured data elements. All data are linked for a given patient, and all data are de-identified to protect Personal Health Information (PHI) in accordance with the Health Insurance Portability and Accountability Act (HIPAA). As such, access to patient/clinical progress notes is not available for manual human review.

7.5. Study size

A preliminary feasibility assessment was performed to determine the number of patients receiving palbociclib treatment. The following table illustrates the number of patients within the dataset who initiated treatment with palbociclib and were diagnosed with breast cancer.

Table 2. Number of Prevalent Patients Prescribed Palbociclib per Month in 2015

Month in 2015	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP
Number of patients prescribed palbociclib	345	376	423	436	455	480	475	481

Study analyses are descriptive in nature and thus no formal power calculations have been conducted.

7.6. Data management

Patient-level EMR data are provided to Cardinal Health Specialty Solutions (CHSS) by the data vendor. Only de-identified records are transferred. Data management consists of validity checks to ensure that complete records of patients are received and to identify potential outliers and structural data problems. Initial assessments will be made by visualizations: histograms, bar charts, and box plots of variables. Reasonable thresholds will be set to identify extreme outliers (eg, 1.5 * interquartile range). Assumptions of normal distributions of the analysis variables will be evaluated. The overall approach to missing data will be informed by the EMA Guideline on Missing Data in Confirmatory Clinical Trials.[7] All data management and statistical analyses will be conducted using Statistical Analysis Software (SAS v. 9.3)

7.7. Data analysis

The analysis to be conducted is descriptive in nature. Patients initiating treatment with palbociclib will be grouped by month according to the date of the first treatment administration of palbociclib and subsequently aggregated into two-month groups to form the incident population analysis subgroups. These two month intervals will be divided as follows: February 1–March 31, 2015 (incident subgroup #1); April 1–May 30, 2015 (incident subgroup #2); June 1–July 30, 2015 (incident subgroup #3); August 1–September 30, 2015 (incident subgroup #4); October 1–November 30, 2015 (incident subgroup #5); December 1–January 31, 2016 (incident subgroup #6). All analyses will be performed on these subgroups in addition to the complete analysis set (at the end of the study period) with incremental cumulative updates throughout. Stratified analyses will also be conducted for the following subgroups on the prevalent cohort: 1) <65 years of age and ≥65 years of age at diagnosis of advanced or metastatic breast cancer and 2) palbociclib line of therapy (1^{st}, 2^{nd}, $\geq 3^{rd}$). Analysis of each incident cohort will be stratified by length of follow-up (<6 months versus ≥6 months after palbociclib treatment initiation).

Descriptive statistics will be reported for continuous variables (eg, age) using means, medians, standard deviation, and range. Categorical variables (eg, gender, payer type) will be reported using frequencies and proportions. Differences in categorical outcomes across subgroups will be evaluated with Chi-square or Fischer exact test and for continuous outcome variables using a t-test or Wilcoxon rank-sum test (medians), as appropriate. For time to event endpoints, patients will be censored at the date of last follow-up. No other inferential statistical analyses are planned for this study. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP

may modify the analyses plans outlined in the protocol, if required; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

7.8. Quality control

Data are provided to CHSS as patient-level analytical files. To ensure quality control of the data, CHSS will undertake a set of quality control (QC) measures upon retrieval of the data and throughout the study process to ensure validity. Specifically, there are four levels of QC performed:

1. Demographics and Clinical Characteristics

Checks on coding for specific diseases and subtypes of diseases including specific biomarker and mutations are conducted using ICD-9 codes and structured data inputs using both current and retrospective retired codes. Completion rates for specified inclusion and exclusion fields are checked to determine if additional algorithms need to be developed to identify patients. Line of therapy determination is conducted with both automated and manual clinical review to determine appropriate drug lines, and combinations of therapy and drug regimens are compared to accepted NCCN guidelines within CHSS's treatment library.

2. Outcome Measures

Rules are developed to ensure that the appropriate outcomes variables are calculated from the available data. Derived variables rules and missing data imputation rules are created and recorded in the SAP. A check for duplicates is conducted and rules for removing duplicate data are created in addition to rules for dealing with multiple data points for a specific variable. Drug administration dates and verified min and max dates for drug administration are finalized for both medical and pharmacy data and applied to calculate treatment durations.

3. Adapting Algorithms

The goal is to determine the extent and type of algorithms that need to be utilized to appropriately improve the data quality. Algorithms to identify disease sub-classifications not based on ICD-9 codes are developed and validated as needed, using clinical input and review of the existing literature. Expert review of this process is an essential part of this process. Rules to assign diagnosis, place of service, etc., are developed at this time.

4. Validation

The goal is to determine reliability and consistency of data sources between studies and within studies over time. Consistency checks are conducted upon final database creation for both internal and external consistency. Potential sensitivity analysis data points are identified.

7.9. Limitations of the research methods

One limitation of EMR data is that the source data are confined to community practice, and therefore treatment in hospital or ambulatory care is not captured. Additionally, the level of documentation by the provider into the EMR may vary across practice sites and cannot be guaranteed prior to analysis. Biomarker testing and results are available only if contained in the structured or searchable EMR data, and availability of data may also not be guaranteed.

7.10. Other aspects

Not applicable.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient information and consent

This research involves no risk to the patient as there is no intervention involved. The study will utilize Cardinal Health's oncology-specific EMR database to describe drug utilization categorization of palbociclib in oncology patients. No patients will be contacted at any point during the study. Furthermore, at no point during the study will we have access to or hold protected health information. The database complies with all aspects of the HIPAA 1996.

8.2. Patient withdrawal

Not applicable.

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

With the use of an existing de-identified database, IRB oversight was deemed inapplicable under Health and Human Services 45 CFR 46.101 (a) (4). To ensure the integrity of future publications, IRB Exemption Determination will be obtained.

8.4. Ethical conduct of the study

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

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

A pharmacovigilance valid adverse event (AE) report must contain at a minimum the following four elements: an identifiable patient (includes subject/consumer), a suspect product, an event, and an identifiable reporter. Because this study utilizes secondary data collection, it is not feasible to make an assessment of causality (i.e., a definitive statement of causality by a healthcare provider linking drug administration to the AE as recorded in the medical chart at an individual case level). Therefore, reporting of AEs is not applicable for this study per CT24-GSOP-RF06 *Safety Reporting Language: Secondary Data Study – Does Not Include Protocol-Required Human Review of Unstructured Data.*

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A study report detailing the study design and findings will be submitted to Pfizer upon completion of analyses. Abstracts for submission to any conference may be initiated once descriptive results from initial analysis are reviewed. Drafting of a manuscript suitable for submission to a peer-reviewed journal is optional.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

11. REFERENCES

1. Siegel et al. Cancer statistics, 2015. *CA Cancer J Clin* 2015; 65:5-29.
2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast Cancer. Version 3.2015. Available at: nccn.org. Accessed August 5, 2015.
3. Finn et al. *Lancet Oncol* 2015; 16:25-35.
4. Turner et al. *N Engl J Med* 2015; 373:209-219.
5. ClinicalTrials.gov website. Available at: clinicaltrials.gov. Accessed August 5, 2015.

12. LIST OF TABLES

13. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Statistical Analysis Plan (SAP)

For Non-Interventional Studies

Non-Interventional Study Protocol

A5481067

Descriptive Analyses of Clinical Characteristics and Treatment Patterns of Breast Cancer Patients Initiating Palbociclib (Ibrance®) Treatment in the US Community Oncology Setting

Statistical Analysis Plan (SAP)

Version: 2

Author: Jonathan Kish (Cardinal Health – Dallas, TX)

Date: 21-DEC-2015

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

In the United States (US), breast cancer (BC) is the leading cause of cancer-related deaths among women aged 20-59 years. In 2015, it is estimated that 29% of all new cancer cases among US women will be BC, amounting to an estimated 234,190 new cases and 40,730 deaths.[1] Although the overall mortality rate due to BC has been declining in recent decades, the incidence rate has steadily increased.[2]

Because treatment decisions and outcomes can vary based on tumor characteristics, the National Comprehensive Cancer Network (NCCN) guidelines recommend testing all patients for hormonal and human epidermal growth factor receptor 2 (HER2) status. Treatment for localized BC typically consists of surgery and radiation therapy, followed by adjuvant chemotherapy, endocrine therapy, and/or biological therapy, if needed. Patients who are diagnosed with metastatic BC (MBC) are treated with chemotherapy or targeted therapy, and specific hormonal or anti-HER2 agents are used in patients with hormone receptor (HR)-positive or HER2-positive disease. Single-agent or combination chemotherapy for MBC often includes anthracyclines, taxanes, microtubule inhibitors, or other agents. Some commonly used targeted agents include trastuzumab, pertuzumab, lapatinib, and everolimus.[2]

Palbociclib is an oral, , cyclin-dependent kinase (CDK) 4/6 inhibitor, which prevents deoxyribonucleic acid (DNA) replication by prohibiting progression from G1 to S phase during cell division, thereby preventing tumor cell proliferation through cell cycle control. The US Food and Drug Administration (FDA) granted palbociclib Breakthrough Therapy Designation for BC in April 2013, and the rolling NDA was completed in August 2014. Accelerated approval for palbociclib as frontline treatment in postmenopausal women with estrogen receptor (ER)-positive/HER2-negative MBC was granted in February 2015, after the randomized phase II PALOMA-1 trial demonstrated that the addition of palbociclib to letrozole significantly improved progression-free survival (PFS) in patients with advanced ER-positive/HER2-negative BC (median PFS, 20.2 months vs. 10.2 months; hazard ratio [HR] = 0.448; P = .0004).[3] Grade 3/4 adverse events that occurred more frequently in the palbociclib arm included neutropenia (54% vs. 1%), leukopenia (19% vs. 0), and fatigue (4% vs. 1%).

Pfizer is interested in gathering real-world data describing the population of patients treated with palbociclib in the community oncology setting. This research will evaluate clinical characteristics and treatment sequencing of patients prescribed palbociclib to support the medical strategies being pursued by Pfizer.

2.1. Study Design

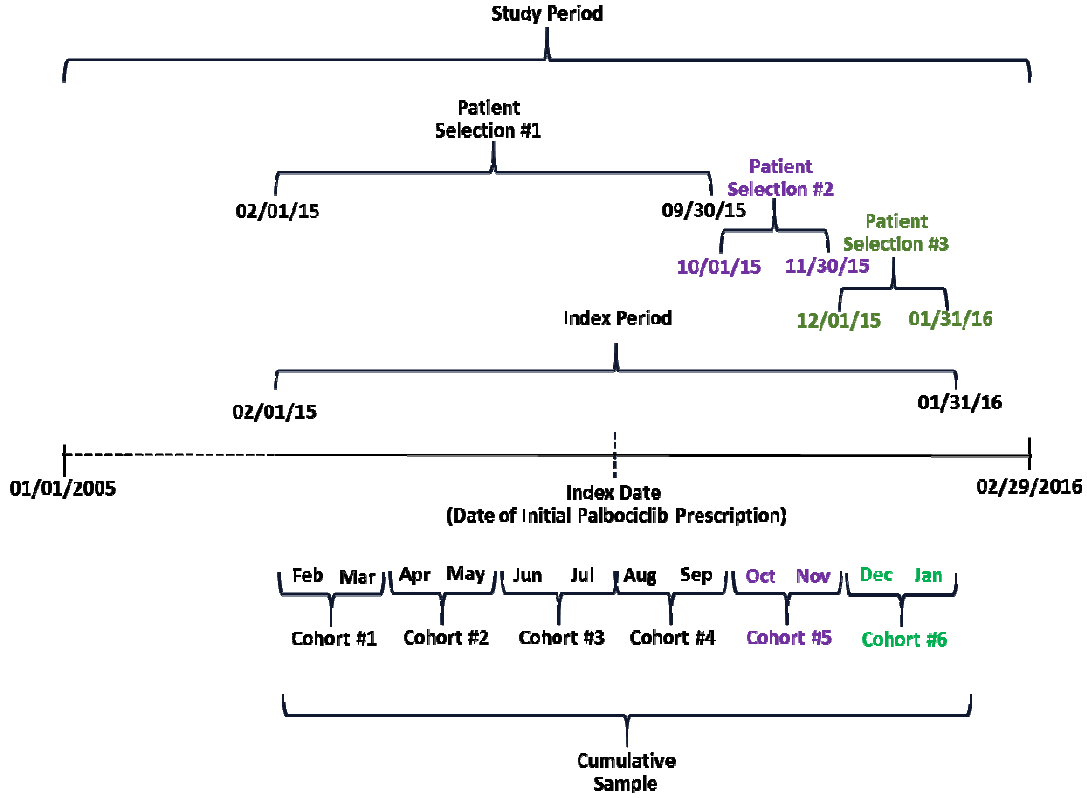
This is a retrospective observational study of female patients diagnosed with BC and newly initiating treatment with palbociclib in the community oncology setting in the US.

Female patients who meet the inclusion criteria will be retrospectively selected from an EMR database. This study will describe the patient characteristics in terms of demographic and clinical characteristics, real-world treatment patterns including line of therapy, dosing patterns (dose at initiation, dose titration or reduction, and timing of dose modifications), concomitant use of other chemotherapy/hormonal therapy/supportive drugs), laboratory monitoring patterns (white blood cell count [WBC]), and adverse event [AE]/neutropenia-related outcomes including incidence, time to event, and association with dosing modifications and discontinuations among female BC patients during the 12-month period following drug approval (February 1, 2015).

To fulfil the study objectives, patients will be selected from the EMR dataset at three time points. The initial patient selection will include those patients treated with palbociclib anytime between February 1, 2015 and September 30, 2015. Subsequently, the dataset will be refreshed at two future time points to select incident patients initiating palbociclib therapy and obtain follow-up information on prevalent study subjects already included in the dataset. The index date will be the date of first prescription for palbociclib. Analyses will be reported for each successive two-month interval following the approval of palbociclib in the US on February 1, 2015 leading to the formation of six period-specific analysis cohorts (eg, cohort 1 = index date anytime between February 1, 2015 and March 31, 2015; cohort 2 = index date anytime between April 1, 2015 and May 30, 2015; through cohort 6 = index date anytime between December 1, 2015 and January 31, 2016). Cumulative results will be presented for the total patient sample in the dataset after each incident cohort analysis (eg, summary results for cohort 1-2, 1-3, 1-4, 1-5 and complete sample including cohorts 1-6). All analyses will be performed on all incident and cumulative cohorts. In order to evaluate outcomes of interest following treatment initiation for the last cohort (cohort 6), data abstraction will be extended to include February 2016 data. As this analysis is descriptive in nature, no formal statistical comparison will be made between analytic cohorts. Figure 1 illustrates the study time period, patient selection intervals, and analysis cohorts.

EMR data are sourced from multiple community oncology practice sites across the US. Practices provide data through up to 23 distinct EMR systems; the data are then collected and aggregated to a common data standard. Included in the database are the records for over 2 million patients treated since 2005 by over 975 oncologists at 81 practice sites in 25 states across the US. These data include commercial, Medicare, and Medicaid covered patients. Treatment history is captured for both intravenous and oral chemotherapy medications. Both structured data fields and unstructured data are available for research purposes with single-keyword natural language processing available to search the unstructured data elements. All data are linked for a given patient, and all data are de-identified to protect Personal Health Information (PHI) in accordance with the Health Insurance Portability and Accountability Act (HIPAA). As such, access to patient/clinical progress notes is not available for manual human review.

Figure 1. Study Period Diagram



2.2. Study Objectives

The goals of this research are to evaluate the real-world utilization, treatment sequencing and experience of neutropenia among female BC patients initiating treatment with palbociclib during the 12-month period following drug approval (February 1, 2015). More specifically, EMR data from female BC patients treated in the community oncology setting will be utilized to achieve the following research objectives:

1. Characterize the demographic and clinical characteristics of patients at the initiation of treatment with palbociclib.

2. Describe palbociclib utilization by line of therapy.

3. Assess the frequency, timing, and rationale (occurrence of diagnosed AEs) of palbociclib dose modification (reduction/titration, subsequent resumption of initiation dose, dose interruption/delay or discontinuation) by line of therapy.

4. Quantify frequency of complete blood count (CBC) including WBC monitoring including the incidence of neutropenia and time to neutropenia treatment during the three time intervals: anytime prior to palbociclib initiation, within 3 months prior to palbociclib initiation, and during palbociclib treatment.
5. Describe utilization of chemotherapy, hormonal therapy, and other supportive pharmacological agents pre-treatment, concomitantly, and post-treatment with palbociclib.

3. INTERIM ANALYSES

Two interim reported will be generated prior to the final report following each of the initial two data cuts. The first report will include analysis of cohorts 1-4 including data through September 30, 2015. Subsequently, the next interim report will include updated analysis for cohorts 1-4 and first analysis of cohort 5. The final report will included updated analysis for cohorts 1-5 and analysis of cohort 6. There is an approximate 45 day lag between the end date of the analysis cohort and the publication of the updated results to Pfizer. The final report will be generated upon availability, cleaning and analysis of data from cohort 6 and will serve as the final cumulative analysis point for all cohorts.

4. HYPOTHESES AND DECISION RULES

Not applicable.

4.1. Statistical Hypotheses

The study is descriptive in nature and is not designed to test any hypotheses regarding between group differences.

4.2. Statistical decision rules

Not applicable

5. ANALYSIS SETS/ POPULATIONS

5.1. Base Cohort

All female BC patients newly initiating treatment with palbociclib between February 1, 2015 and January 31, 2016 will be included from the EMR database. The index date for the analysis is the date of first treatment administration of palbociclib. EMR data will be extracted for each patient backward in time to the first date of diagnosis for BC and forward up to 1-year following treatment initiation. Patients meeting all of the following inclusion criteria and none of the exclusion criteria will form the base cohort, all palbociclib treated patients, for analysis:

5.1.1. Inclusion criteria

1. Received at least one prescription for palbociclib during the index period;
2. At least 18 years of age at date of BC diagnosis (ICD-9 CM 174.x);
3. Female sex.

5.1.2. Exclusion criteria

1. Diagnosis or treatment of a second primary malignancy anytime during the study period;
2. Received a prescription for palbociclib prior to February 1, 2015;
3. Received systemic therapy as part of an interventional clinical trial.

5.2. On-Label Cohort

In addition to those inclusion and exclusion criteria specified for the creation of the base cohort, the following additional criteria will be used to select the "on-label" cohort. The on-label cohort consists of all female breast cancer patients who have received palbociclib in line with the FDA-approved indication for Ibrance®:

1. Treated with palbociclib in combination with letrozole;
2. Post-menopausal at the date of palbociclib treatment initiation;
3. Diagnosed with locally advanced (stage III) or metastatic (stage IV) BC;
4. Diagnosed with ER+/HER2- BC.

5.3. Safety analysis set

Not applicable.

5.4. Other analysis set

Not applicable.

5.5. Subgroups

In both the all palbociclib and on-label analysis sets patients will be grouped by month according to the date of the first treatment administration of palbociclib and subsequently aggregated into two month groups to form the incident population analysis cohorts. These two month intervals will be divided as follows: February 1 – March 31, 2015 (incident subgroup #1); April 1 – May 30, 2015 (incident subgroup #2); June 1 – July 30, 2015 (incident subgroup #3); August 1 – September 30, 2015 (incident subgroup #4); October 1 – November 30, 2015 (incident subgroup #5); December 1 – January 31, 2016 (incident subgroup #6).

Within each bi-monthly population groups, patients will be stratified independently into the following subgroups: 1) <65 years of age at diagnosis, ≥65 years of age at diagnosis; 2) palbociclib line of therapy (1^{st}, 2^{nd}, $\geq 3^{rd}$) and 3) length of follow-up (<6 months, ≥6 months). The latter subgroup analysis will only be considered in relation to study objectives 1 and 3-5.

6. VARIABLES AND ENDPOINTS

6.1. Variables

Demographic, clinical and treatment related variables, variable descriptions, the time point(s) of data collection in regard to each variable, and the source of the data (structured or unstructured elements of the EMR) to calculate the outcome measures are shown in Table 1. Variables collected at diagnosis will be collected from the first recorded claim/record available for the patient with a BC diagnosis. Diagnosis of advanced disease will be assessed through evaluation of stage data contained in structured fields. Variables collected at palbociclib treatment initiation will be collected from the claim/record on or closest to the date of the first recorded prescription for palbociclib. The EMR contains both structured and unstructured data. The unstructured data will be searched using keywords for those elements not collected in the structured fields. Where the structured data does not contain the variable of interest, single keyword searches of the patient clinical/progress notes will be performed to identify the patient status in regard to the variable of interest. For example, the keywords "premenopaus*", "perimenopaus*", and "postmenapaus*" (where asterisk indicates any characters following the root word would be included) and spelling variations, such as "pre-menopaus*", will be used to identify patient menopausal status. A detailed list of keywords to be evaluated is provided in Appendix 1.

Table 1. Demographic and Clinical Variables and Descriptions

Variable	Description	Collection Point	Operational
Age	Continuous	• At advanced/ metastatic BC diagnosis • At palbociclib treatment initiation	Structured data field
Weight	Continuous, kg	• At palbociclib treatment initiation	Structured data field
Total number of metastases	Continuous	• Anytime during study period	Based on unique ICD-9 diagnosis codes (Appendix 3)
Location of Metastatic Disease	• Bone • Brain • Liver • Lung • Lymph • Other	• At palbociclib treatment initiation	Based on ICD-9 diagnosis codes (Appendix 3)
Date of diagnosis of metastatic BC	Date, includes all patients with any distant metastasis	• At first occurrence	Based on first date of distant metastasis or stage IV
Date of diagnosis of locally advanced BC	Numeric, includes patients without a metastatic BC diagnosis	• At first occurrence	Based on first date of advanced BC diagnosis and/or stage III
Menopausal status	• premenopausal • perimenopausal • postmenopausal	• At advanced/ metastatic breast cancer diagnosis	Unstructured keyword search of progress notes (Appendix 1)

Table 1. Demographic and Clinical Variables and Descriptions

Variable	Description	Collection Point	Operational
	• unknown		
Histology	• ductal carcinoma in situ • inflammatory carcinoma • invasive ductal carcinoma • invasive lobular carcinoma • invasive mammary • lobular carcinoma in situ • tubular carcinoma • undifferentiated • unknown	• At advanced/ metastatic breast cancer diagnosis	Based on ICD-9 diagnosis codes (Appendix 2)
Stage	• 0 • 0, ductal carcinoma in situ • I • IA • IB • IIA • IIB • IIIA • IIIB • IIIC • IV • Unknown	• At diagnosis • At palbociclib treatment initiation	Structured data field
TNM Stage	• T: T1 - T4 including prefix and suffix • N: N1 - N4 including prefix and suffix • M: M0 - M1 including prefix and suffix • Unknown	• At palbociclib treatment initiation • At palbociclib treatment discontinuation	Combined from each of T, N and M structured date fields
ECOG Performance Status	• 0 • 1 • 2 • ≥3	• At palbociclib treatment initiation	Structured data field
Karnofsky Score	Ordinal, in 10 step increments from 10-100	• At palbociclib treatment initiation	Structured data field
ER Receptor Status	• Positive • Negative • unknown	• Most recent evaluation	Structured data field
PR Receptor Status	• Positive • Negative • unknown	• Most recent evaluation	Structured data field
HER2 Receptor Status	• Positive • Negative • unknown	• Most recent evaluation	Structured data field
Palbociclib treatment initiation date	Date, first prescription order for palbociclib	• First prescription order (index date)	Structured data field

Table 1. Demographic and Clinical Variables and Descriptions

Variable	Description	Collection Point	Operational
Palbociclib dose	• 125 mg • 100 mg • 75 mg • unknown	• At each prescription order	Structured data field
Reason for dose change	• Adverse event other than neutropenia • Neutropenia • Unknown	• Within 15 days of new prescription order	Based on presence of ICD-9 Adverse event diagnosis code/ neutropenia diagnosis
Palbociclib treatment discontinuation date	End date of last cycle of palbociclib	• Last prescription order in study period	Last order plus days of supply including refills and time off therapy
Palbociclib treatment duration	Time (days) between first palbociclib prescription to discontinuation date	• Per palbociclib line of therapy	Includes time associated with letrozole when prescribed in conjunction with letrozole
Use of chemotherapy	Identify occurrence of treatment with any chemotherapy drugs listed in Appendix 4	• see Endpoints for description of time intervals	Structured data field
Use of hormonal therapy	Identify occurrence of treatment with any chemotherapy drugs listed in Appendix 4	• see Endpoints for description of time intervals	Structured data field
Use of supportive care medications	Identify occurrence of treatment with any chemotherapy drugs listed in Appendix 5	• see Endpoints for description of time intervals	Structured data field
Adverse event diagnosis	Date of diagnosis collected for each event	• Each occurrence during treatment with palbociclib	Events based on ICD-9 diagnosis codes (Appendix 3)
WBC Count Lab test	Data flag/ Date of test collected for each WBC count test and % neutrophil test	• Closest data prior to palbociclib treatment initiation • Any instance during palbociclib treatment	Structured data field
WBC quantity	Numeric, x 10^9 L	• Date of tests and results anytime during study period	
WBC neutrophil percentage	Numeric, %	• Date of tests and results anytime during study period	
Absolute Neutrophil Count Grade	• Grade 0 : Normal • Grade 1 : 1500-2000 • Grade 2 : 1000-1499 • Grade 3 : 500-999 • Grade 4 : <500	• Anytime during follow-up when both white blood cell (WBC) quantity and neutrophil %	Calculated based on conversion† of WBC count and neutrophil %

Table 1. Demographic and Clinical Variables and Descriptions

Variable	Description	Collection Point	Operational
		present	
Diagnosis of neutropenia	Date collected for each occurrence	• Any time during study period	Either ICD-9 diagnosis codes (structured), ANC, or keyword search (Appendix 1) of clinical progress notes

† Conversion: divide neutrophil % by 100, multiply value by WBC quantity (neutrophil value in K/µl), and multiply by 1000 to convert to mm^3

6.2. Endpoints

The following measures will be calculated to support each of the research objectives:

Objective 1 – Frequency of demographic and clinical characteristics (see Table 1 variables) of patients for each of the analytic cohorts.

Objective 2 – Frequency of use of palbociclib by line of therapy through the following measures:

- Proportion of use as first-line therapy;
- Proportion of use as second-line therapy;
- Proportion of use as third-line therapy;
- Proportion of use as fourth-line therapy;
- Proportion of use as fifth or higher-line therapy.

Patient medical records will be evaluated from the initiation of treatment with palbociclib back to the date of the date of their first diagnosis for BC to appropriately determine the line of therapy at which palbociclib was initiated. Line of therapy will be calculated based on the cumulative treatment pattern from both diagnosis of BC and separately from the time of diagnosis of advanced/metastatic BC. Palbociclib treatment initiation is defined as the date of the first prescription for palbociclib for the base cohort and as the date of the first prescription for either palbociclib or letrozole when used in combination for the on-label cohort. Palbociclib treatment discontinuation is defined as the last date of any palbociclib prescription plus the days of supply taken from the course description field. For example, "125.0 mg Oral every 1 day for 21 times" will be translated as discontinuation date 21 days following the prescription order. For each prescription the FDA-approved prescribing information is used to calculate the total days on therapy which would include once daily for 21 days followed by a 7 day time off treatment. The total time on therapy would be 28 days. Therefore, one cycle of treatment will be completed after 28 days following the initial prescribing date.

For line of therapy calculations, the first regimen observed following the diagnosis of breast cancer or advanced/metastatic BC (depending on analytical cohort) will be assigned as line 1. Treatment regimen assignments (combination therapy) are done by

grouping chemotherapy drugs into treatment regimens given the dates of administration fall within 30 days of each other and the drugs are representative of known prescribed therapies. Changes in terms of the addition or removal of a drug that occur beyond 30 days trigger drug combination reassignment and potentially increment the line of therapy. Exceptions are made for known sequential therapies, which are accounted for by the distinct grouping rules, and for drugs used in the maintenance setting. Administrations of the same cycle within 90 days of each other are considered part of the same regimen and line of therapy given the same drugs were used (to account for potential breaks in therapy as a result of intolerability and/or drug holidays). Regimen modifications that occur within 60 days of the prior cycle are grouped into the same regimen and are not counted as a new line. Addition of a new agent constitutes an advance to the next line of therapy. Given the time period of approval for palbociclib in combination with letrozole, patients initiating therapy on letrozole and transitioning to a combined letrozole + palbociclib treatment regimen will not be considered as having received a new line of therapy unless the patients received letrozole for more than 90 days prior to initiating palbociclib or if there is a gap in treatment of more than 30 days between the last date of treatment with letrozole and the subsequent initiation of letrozole + palbociclib.

Initially, if the same regimen is given after a 90+ day break, the patient is considered to still be receiving the same line of treatment however the treatment break is not included in any duration of therapy calculation. Any instance of 90+ day breaks in therapy constitute a manual review of the patients data to determine if sufficient information exists (ie, intolerability, progression, etc.) to deem whether the resumption should constitute a new line of therapy. If no such information exists, the patient will not have the line of therapy increased upon resumption of the treatment regimen. Example: if a patient was treated with first-line docetaxel (line 1) and then received the next treatment of docetaxel 90+ days later, the resumption is still considered to be line 1 provided there is no evidence of an adverse event/progression. Had the next treatment included an agent different from that previously included in the treatment regimen, the line of therapy would be incremented by 1 and would be considered line 2. Similarly, removal of one agent from a treatment regimen does not constitute the end of a line of therapy if the removal is temporary meaning that the full treatment regimen is resumed within 90 days of the last date of full treatment regimen.

Line of therapy assignment is done first programmatically through a SAS programmed algorithm using the following variables from the structured EMR data:

Table 2. Example of Structured Data for a Chemotherapy Drug Received by a Patient

Drug Name	Course Description	Cycle Number	Cycle Day	Order Date
Docetaxel	134 mg (at 75 mg/m2) Intravenous daily over 60 minutes for 1 day	1	1	03-14-2012

Following the automatic line of therapy scrubbing, the treatment sequence, and line of therapy assignments are then reviewed by clinical personnel including oncology nurses, physicians or other appropriately trained staff to determine if any modifications are necessary based upon the previously described criteria.

Objective #3 – Frequency of palbociclib dose reductions/titrations, reason for dose reduction (adverse event of interest or not), time to dose reduction by palbociclib line of therapy and duration of treatment interruption/dose delay through the following measures:

- Frequency of any dose reduction;
- Frequency of reduction from 125 mg to 100 mg;
- Frequency of reduction from 125 mg to 75 mg;
- Frequency of reduction from 100 mg to 75 mg;
- Time to first dose reduction;
- Frequency of escalation from modified dose to higher dose;
- Time between lower dose and resumption of any higher dose;
- Duration of time at dose lower than first prescription;
- Time to second dose reduction;
- Proportion of dose reductions due to any and/or specific adverse events (based on ICD-9-CM diagnosis codes);
- Frequency of palbociclib treatment discontinuation;
- Time to palbociclib treatment discontinuation;
- Proportion of palbociclib treatment discontinuations due to any and/or specific adverse events (based on ICD-9-CM diagnosis codes);
- Proportion of dose reductions due to neutropenia;
- Time to first dose reduction due to neutropenia;
- Average time of treatment interruption/delay.

The starting dose order for palbociclib will be collected from the course description field of the treatment order form in the EMR. A dose reduction is defined as any prescribed palbociclib treatment at a lower dose than that of the index palbociclib treatment. The time to first dose reduction will be calculated from the date of the index palbociclib treatment to the date of the prescription for the lower dosage form (either 125 mg to 100 mg or 100 mg to 75 mg). Time to second dose reduction will be from the date of the index palbociclib prescription to the 75 mg dose. Additionally, frequency and time to event will be calculated for patients resuming a higher dose of palbociclib following any dose reduction. Patterns in dose reduction and resumption will be assessed.

The proportion of dose reductions due to an adverse event will be calculated. A dose reduction occurring within 30 days post of the diagnosis of an adverse event will be considered a dose reduction due to an AE. A dose reduction due to neutropenia will be said to have occurred when there is a confirmed diagnosis of neutropenia (see objective #4 for definition of neutropenia diagnosis) within 30 days of the date of dose reduction.

Objective #4 – Frequency of laboratory evaluations (CBC including WBC) to evaluate incidence and time to diagnosis of neutropenia among patients with and without a diagnosis of neutropenia prior to palbociclib treatment initiation through the following measures:

- Diagnosis of neutropenia prior to first palbociclib prescription during the following time intervals:
  - Anytime prior to first prescription;
  - Within 3 months prior to first palbociclib prescription;
  - In prior line of therapy (if applicable);
- Mean number of neutropenia events (by diagnosis) before and during palbociclib treatment by line of therapy;
- Time to first diagnosis of neutropenia during palbociclib treatment.
- Frequency of WBC laboratory evaluations during first palbociclib cycle (ie, within 30 days of palbociclib initiation);
- Frequency of WBC laboratory evaluations during second palbociclib cycle (ie, >30 and ≤60 days following palbociclib initiation);
- Proportion of patients with absolute neutrophil count <500 and <1000 during palbociclib treatment by line of therapy.

The date and results of each WBC count and % neutrophil lab test will be collected from the structured data elements of the EMR. Within these results, a conversion between the WBC count and % neutrophil will be used for analysis of the diagnosis of neutropenia (see *Table 1* footnote). The date of diagnosis of neutropenia is the first occurrence of any of the following: 1) an ICD-9 based diagnosis of neutropenia; 2) a calculation (based on previously described algorithm of WBC count and % neutrophil) resulting in an absolute neutrophil count <1000; or 3) the presence of the keyword neutropenia (and other derivatives – see Appendix 1) in a clinical progress note. Only patients with at least one known calculated neutrophil count value will be included in any analysis related to neutropenia.

Objective #5

Utilization of other chemotherapy, hormonal therapy, and supportive care (both overall and by individual drugs/agents) through the following measures:

- Proportion receiving any and/or each recorded chemotherapy, hormonal and supportive care drugs for advanced/metastatic breast cancer during the following timeframes:
  - Anytime prior to palbociclib treatment initiation;
  - Within 6 months following palbociclib treatment initiation.
- Proportion receiving any and/or each recorded chemotherapy and/or hormonal drugs at start of (±14 days) palbociclib treatment initiation.

- Proportion receiving any and/or each recorded supportive care medications during the following timeframes:
  - Anytime during palbociclib treatment;
  - At start of (±14 days) first palbociclib prescription;
  - At start of (±14 days) second palbociclib prescription;
- Proportion receiving any and/or each recorded chemotherapy or hormonal drug therapy as their first therapy subsequent to palbociclib treatment discontinuation.

6.3. Safety Endpoints

A pharmacovigilance valid adverse event (AE) report must contain at a minimum the following four elements: an identifiable patient (includes subject/consumer), a suspect product, an event, and an identifiable reporter. Because this study utilizes secondary data collection, it is not feasible to make an assessment of causality (ie, a definitive statement of causality by a healthcare provider linking drug administration to the AE as recorded in the medical chart at an individual case level). Therefore, reporting of AEs is not applicable for this study per CT24-GSOP-RF06 *Safety Reporting Language: Secondary Data Study – Does Not Include Protocol-Required Human Review of Unstructured Data.*

6.4. Other endpoints

Not applicable.

6.5. Covariates

Not applicable.

7. HANDLING OF MISSING VALUES

The overall approach to missing data will be informed from the EMA Guideline on Missing Data in Confirmatory Clinical Trials.[6] Because this is a retrospective, observational analysis on a large starting sample, preference will be given to list wise deletion where data are incomplete. Subset analyses may prove limiting for the sample, and if Pfizer is in agreement, mean substitution or imputation may be used on case-by-case basis.

Full case data may be further restricted due to checks included during the data assessment process (ie, data cleaning). These checks include the following processes: evaluation of impossible drug administrations due to combination of agents or violation of possible min/max dosing, cell values that are negative or impossible, cell values that are in the incorrect format (eg, text entry in a numeric field), and date values out of range (eg, future administration dates). Depending on the extent and nature of the error, mean substitution or imputation, with Pfizer agreement may be considered.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical methods

Descriptive statistics will be reported for continuous variables (eg, age) using means, medians and standard deviations. Categorical variables (eg, region, histology, stage) will be reported using frequencies and proportions. In case of missing observations, the calculation of percentages will always include the missing category. Counts of missing observations will thus be included in the denominator and presented as a separate category. Differences in categorical outcomes across subgroups will be evaluated with Chi-square or Fischer exact test and for continuous outcome variables using a t-test or Wilcoxon rank-sum test (medians), as appropriate. For time to event endpoints, patients will be censored at the date of last follow-up. Time to event will be calculated and illustrated using the Kaplan Meier methods. No other inferential statistical analysis are planned for this study.

8.2. Statistical Analyses

The goals of the study are to describe the real-world patient demographic, clinical and treatment characteristics of the population of patients initiating treatment with palbociclib. All analyses will be primarily descriptive in nature as described in section 8.1. Any pair-wise testing between the subgroups of interest will be made using chi-square and student's t-test sample size permitting.

8.2.1. Safety Analyses

Not applicable.

9. LIST OF TABLES AND TABLE SHELLS

Please note, each table will be constructed separately for the base cohort and on-label cohorts. Cumulative results are shown separately in tables 6-7 but will be combined into single tables for any reports.

TABLE 1. PATIENT COHORT SELECTION ATTRITION TABLE

Inclusion Criteria	Base Cohort	On-Label Cohort
Received at least one prescription for palbociclib during the index period		
Diagnosed with BC (ICD-9 CM 174.x) anytime prior to or on the date of first prescription for palbociclib		
At least 18 years of age at date of BC diagnosis		
Diagnosed with advanced/metastatic breast cancer prior to or at time of palbociclib treatment initiation		
Post-menopausal at time of palbociclib treatment initiation		
ER + / HER2 – receptor status		
Prescribed palbociclib in combination with letrozole		
Total Sample		
Exclusion criteria		
Diagnosed or treatment of a second primary malignancy anytime during the study period		
Prescribed palbociclib prior to February 1, 2015		
Participation in any clinical trial during the study period		
Final Sample		

TABLE 2. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS AT ADVANCED BC DIAGNOSIA AND PALBOCICLIB TREATMENT INITATION

Characteristic	**BC Diagnosis**	**Advanced BC Diagnosis**	**Palbociclib Initiation**
All patients			
Age (mean, med, SD)			
Weight (mean, med, SD)			
Region of residence (n, %)			
Menopausal status (n, %)			
Histology (n, %)			
AJCC Stage (n, %)			
TNM Stage (n, %)			
ECOG Perf. Status (n, %)			
Karnofsky score (n, %)			
ER receptor status (n, %)			
PR receptor status (n, %)			
HER2 receptor status (n, %)			
ER +/ HER2 -			
Number of metastases (n, %)			
Location of metastases (n, %)			

TABLE 3. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS BY PALBOCICLIB START DATE COHORT

	Incident Cohorts						Cumulative		
	Feb/ Mar	Apr/ May	Jun/ Jul	Aug/ Sep	Oct/ Nov	Dec/ Jan ('16)	All	<65	≥65
Number of patients newly prescribed palbociclib									
Age (mean, med, SD)									
Weight (mean, med, SD)									
Region of residence (n, %)									
Menopausal status (n, %)									
Histology (n, %)									
Stage at diagnosis (n, %)									
ECOG Perf. Status (n, %)									
Karnofsky score (n, %)									
ER receptor status (n, %)									
PR receptor status (n, %)									
HER2 receptor status (n, %)									
Number of metastases (n, %)									
Location of metastases (n, %)									

TABLE 4. CHARACTERISTICS OF PABLOCICLIB TREATMENT BY START DATE

Characteristic	Incident Cohort						Cumulative		
	Feb/ Mar	Apr/ May	Jun/ Jul	Aug/ Sep	Oct/ Nov	Dec/ Jan ('16)	All	<65	≥65
Palbociclib use by LOT (n, %) 1st line 2nd line 3rd line 4th line 5th+ line									
Palbociclib dose reduction (n, %) Any dose reduction Reduction from 125 mg to 100 mg Reduction from 100 mg to 75 mg Reduction from 125 mg to 75 mg No dose reduction									
Dose reductions due to AE (n, %) Dose reductions due to specific AE - *see Appendix 3* (n, %) Dose reductions due to neutropenia (n, %) Mean duration of treatment delay, days (mean, med, SD)									
Time to first dose reduction, days (mean, med, SD) Duration of first dose reduction, days (mean, med, SD) Time to second dose reduction, days (mean, med, SD) Time to palbociclib treatment discontinuation, days (mean, med, SD)									
Resume higher dose? (n, %) of those with dose reduction									
Time from lowered dose to resumption of higher dose (mean, med, SD)									

TABLE 5. RECEIPT OF OTHER CHEMOTHERAPY, HORMONAL DRUGS AND SUPPORTIVE CARE AGENTS

Characteristic	Incident Cohort						Cumulative		
	Feb/ Mar	Apr/ May	Jun/ Jul	Aug/ Sep	Oct/ Nov	Dec/ Jan ('16)	All	<65	≥65
	N (%)								
Receipt of any chemotherapy or hormonal drug (*reported overall and by drug - see Appendix 4*): - Anytime prior to palbociclib treatment initiation - Within 6 months prior to palbociclib treatment initiation - At start of palbociclib treatment imitation (+/- 14 days, only following drugs evaluated)									
Receipt of any supportive care drug (*reported overall and by drug - see Appendix 5*): - Anytime during palbociclib treatment - During first palbociclib prescription - During second palbociclib prescription									
Chemotherapy/ hormonal drug after palbociclib treatment discontinuation (see Appendix 4 – reported overall and by drug)									

TABLE 6. FREQUENCY AND CHARACTERISTICS OF NEUTROPENIA AMONG PALBOCICLIB PATIENTS

Characteristic	Incident Cohort						Cumulative		
	Feb/ Mar	Apr/ May	Jun/ Jul	Aug/ Sep	Oct/ Nov	Dec/ Jan ('16)	All	<65	≥65
Pre-palbociclib neutropenia diagnosis (n, %) Anytime prior Within 3 months In prior line of therapy									
Pre-palbociclib neutropenia diagnosis (mean, med, SD) Anytime prior Within 3 months In prior line of therapy									
On palbociclib neutropenia diagnosis N, % Mean, med, SD Time to neutropenia diagnosis, days (mean, med, SD)									
Lowest neutrophil count during palbociclib treatment Mean < 1000 (n, %) < 500									
Cumulative frequency of CBC/WBC tests (mean, med, SD) First palbociclib cycle Second palbociclib cycle									
Resume higher dose? (n, %) of those with dose reduction due to neutropenia									
Time from lowered dose to resumption of higher dose (mean, med, SD)									

TABLE 7. LAYOUT OF INCREMENTAL CUMULATIVE ANALYSIS TABLES

Characteristic	Cohorts 1-2	Cohorts 1-3	Cohorts 1-4	Cohorts 1-5	Cohorts 1-6	
					<6 months	≥6 months
Replicate outcomes from in Tables 2 -6						

TABLE 8. LAYOUT OF LINE OF THERAPY SUBGROUP ANALYSIS TABLES

	< 6 months follow-up			≥ 6 months follow-up		
	LOT1	LOT 2	LOT ≥3	LOT1	LOT 2	LOT ≥3
Replicate outcomes from in Tables 2 -6						

10. REFERENCES

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5. ClinicalTrials.gov website. Available at: clinicaltrials.gov. Accessed August 5, 2015.

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11. APPENDICES

Appendix 1. KEYWORDS SEARCH TERMS FOR VARIABLES

Variable	Keywords
Menopausal Status	premenopausal, perimenopausal, postmenopausal
Neutropenia	neutropenia, neutropenic, febrile neutropenia
Metastatic	metastatic, metastases
Response	progression, recurrence
Tumor Hormone Receptors	ER, estrogen receptor, PR, progesterone receptor, HER 2, HER2 neu

Appendix 2. METASTATIC DISEAE ICD-9 DIAGNOSIS CODES

Metastasis Label	Code	Description
Lung	197.0	Secondary malignant neoplasm of lung
Mediastinum	197.1	Secondary malignant neoplasm of mediastinum
Pleura	197.2	Secondary malignant neoplasm of pleura
Respiratory	197.3	Secondary malignant neoplasm of other respiratory organs
Colon	197.4	Secondary malignant neoplasm of small intestine including duodenum
Colon	197.5	Secondary malignant neoplasm of large intestine and rectum
Peritoneal	197.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
Liver	197.7	Malignant neoplasm of liver, secondary
Digestive Organs	197.8	Secondary malignant neoplasm of other digestive organs and spleen
Renal	198.0	Secondary malignant neoplasm of kidney
Urinary Organs	198.1	Secondary malignant neoplasm of other urinary organs
Skin	198.2	Secondary malignant neoplasm of skin
Brain	198.3	Secondary malignant neoplasm of brain and spinal cord
Nervous System	198.4	Secondary malignant neoplasm of other parts of nervous system
Bone	198.5	Secondary malignant neoplasm of bone and bone marrow
Ovary	198.6	Secondary malignant neoplasm of ovary
Adrenal	198.7	Secondary malignant neoplasm of adrenal gland
Genital	198.82	Secondary malignant neoplasm of genital organs
Lymph	196.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face, and neck
Lymph	196.1	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes
Lymph	196.2	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
Lymph	196.3	Secondary and unspecified malignant neoplasm of lymph nodes of axilla and upper limb
Lymph	196.5	Secondary and unspecified malignant neoplasm of lymph nodes of inguinal region and lower limb
Lymph	196.6	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
Lymph	196.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple sites
Lymph	196.9	Secondary and unspecified malignant neoplasm of lymph nodes, site unspecified

Appendix 3. ADVERSE EVENT ICD-9 DIAGNOSIS CODES

Adverse Event	ICD-9 CM Code
Anemia	285.3
Anorexia	783
Arrhythmia	427.9
Arterial thrombosis	444.09
Atrial fibrillation	427.31
Bleeding due to intrinsic circulating anticoagulants	286.5
Bleeding acquired coagulation factor deficiency	286.7
Bleeding Other and unspecified coagulation defects	286.9
Bleeding unspecified	459.0
Bradycardia	427.89
Chest pain	786.50, 786.59
Dehydration	276.51
Diarrhea	787.91
Dyspnea	786.00, 786.09
Edema	782.3
Fatigue	780.79
Hepatic failure	572.8, 571.9
Hyponatremia	276.1
Tumor Lysis Syndrome	277.88
Left ventricular dysfunction	429.9
Leukopenia	288.5
Mucositis	528.01
Nausea	787.02, 787.01
Neuropathy	356.8
Neutropenia	288.03
Pain	338.19, 338.29, 338.3
Rash	782.1
Severe hypersensitivity	995
Thrombocytopenia	287.30, 287.4, 287.49, 287.5
Venous thrombosis	453.4
Vomiting	787.03
Pneumonitis	51630, 51632, 51634, 51635, 51636, 51639
Respiratory infections	465, 4658, 4659, 466, 46611, 46619 465.9
Skin reactions	69510, 69511, 69512, 69519, 69550, 69551, 69552, 69553, 69554, 69555, 69556, 69557, 69558, 69559, 6959, 70901, 6961, 6968

Appendix 4. CHEMOTHERAPY/ HORMONAL TREATMENTS OF INTEREST

Abiraterone acetate, po solid
Ado-trastuzumab emtansine, inj
Anakinra, syringe
Anastrozole, po solid
BKM120 invest or placebo, po solid
Bevacizumab or placebo, inj
Bevacizumab, inj
Bicalutamide, po solid
Capecitabine, po solid
Carboplatin, inj
Cisplatin, inj
Cyclophosphamide, inj
Dasatinib, po solid
Docetaxel, inj
Doxorubicin hcl liposomal [Lipodox], inj
Doxorubicin hcl peg-liposomal, inj
Doxorubicin hcl, inj
EZN-2208 invest, inj
Epirubicin hcl, inj
Eribulin mesylate, inj
Everolimus, po solid
Exemestane, po solid
Fluorouracil CIV, inj
Fluorouracil, inj
Fluoxymesterone, po solid
Fulvestrant, syringe
GDC-0941 invest or placebo, po solid
GW572016 invest, po solid
Gemcitabine hcl, inj
Goserelin acetate
Irinotecan hcl, inj
Ixabepilone, inj
LEE011 invest or placebo, po solid
Lapatinib ditosylate, po solid
Letrozole or placebo, po solid
Letrozole, po solid
Leucovorin calcium, inj
Leuprolide acetate, inj
Leuprolide acetate, syringe
Lucitanib invest, po solid
MDV3100 invest or placebo, po solid

Megestrol acetate, po liq
Megestrol acetate, po solid
Methotrexate sodium, inj
Methotrexate sodium, po solid
NKTR-102 invest, inj
Oxaliplatin, inj
PD 0332991 invest, po solid
PD-0332991 invest or placebo, po solid
Paclitaxel protein-bound, inj
Paclitaxel, inj
Paclitaxel,semi-synthetic, inj
Pertuzumab, inj
Ramucirumab invest, inj
Study Drug invest, po solid
Tamoxifen citrate or placebo, po solid
Tamoxifen citrate, po solid
Testosterone cypionate, inj
Toremifene citrate, po solid
Trastuzumab, inj
Vinorelbine tartrate, inj

Appendix 5. SUPPORTIVE CARE TREATMENTS OF INTEREST

Alendronate sodium, po solid
Alteplase, inj
Aprepitant, po solid
Atropine sulfate, inj
Ceftriaxone sodium, inj
Celecoxib, po solid
Cephalexin, po solid
Cimetidine hcl, inj
Cimetidine, po solid
Ciprofloxacin hcl, po solid
Dabigatran etexilate mesylate, po solid
Daptomycin, inj
Darbepoetin alfa in polysorbat, inj
Darbepoetin alfa in polysorbat, syringe
Denosumab, inj
Denosumab, syringe
Dexamethasone or Placebo, po solid
Dexamethasone sod phosphate, inj
Dexamethasone, po liq
Dexamethasone, po solid
Doxycycline hyclate, po solid
Doxycycline or placebo, po solid (doxycycline monohydrate)
Dronabinol, po solid
Enoxaparin sodium, syringe
Epoetin alfa, inj
Filgrastim, inj
Filgrastim, syringe
Fludrocortisone acetate, po solid
Flurazepam hcl, po solid
Fondaparinux sodium, syringe
Fosaprepitant dimeglumine, inj
Furosemide, inj
Furosemide, po solid
Gabapentin, po solid
Granisetron hcl, inj
Granisetron hcl, po solid
Granisetron, top
Heparin lock flush, inj (heparin sodium,porcine)
Heparin sodium,porcine, inj
Heparin sodium,porcine, syringe
Heparin sodium,porcine/pf, syringe

Hydrocortisone sod succinate, inj
Hydrocortisone, po solid
Hydrocortisone, top
Hydroxyzine hcl, po solid
Ibandronate sodium, inj
Immune globulin,g(igg)/maltose, inj
Levothyroxine sodium, po solid
Meperidine hcl, inj
Methylprednisolone acetate, inj
Methylprednisolone sod succ, inj
Methylprednisolone, po solid
Metoclopramide hcl, po solid
Metolazone, po solid
Metronidazole, po solid
Morphine sulfate, inj
Morphine sulfate, po liq
Morphine sulfate, po solid
Octreotide acetate, inj
Ondansetron
Ondansetron hcl, inj
Ondansetron hcl, po solid
Oxycodone hcl, po solid
Oxycodone hcl/acetaminophen, po solid
Palonosetron hcl, inj
Pamidronate disodium, inj
Pantoprazole sodium, po solid
Pegfilgrastim, inj
Pegfilgrastim, syringe
Penicillin V potassium, po solid
Prednisolone acetate, drops
Prednisolone sod phosphate, drops
Prednisolone, po solid
Prednisone, po solid
Prochlorperazine edisylate, inj
Prochlorperazine maleate, po solid
Prochlorperazine maleate, sup
Prochlorperazine or placebo, po solid
Promethazine hcl, inj
Promethazine hcl, po solid
Promethazine hcl, sup
Ranitidine hcl, inj
Ranitidine hcl, po solid
Rivaroxaban, po solid

Sargramostim, inj
Scopolamine hydrobromide, top
Sucralfate, po liq
Sucralfate, po solid
Temazepam, po solid
Triamcinolone acetonide, inj
Vancomycin hcl, inj
Warfarin sodium, po solid
Z-Pak (Zithromax), po solid (azithromycin)
Zoledronic acid, inj
Zoledronic acid/mannitol&water