Study Information

Title	Real-world treatment patterns and effectiveness of Palbociclib in combination with an aromatase inhibitor as initial endocrine based therapy in metastatic/advanced breast cancer
Protocol number	A5481122
Protocol version identifier	Amendment 1
Date of last version of protocol	22 January 2019
Active substance	L01XE33 Palbociclib (IBRANCE;® PD-0332991)
Medicinal product	Palbociclib (IBRANCE;® PD-0332991)
Research Question & Objectives	**Primary objectives** • To describe demographic and clinical characteristics of metastatic/advanced (MBC) patients who were treated with Palbociclib + an aromatase inhibitor (AI) as initial endocrine based therapy. • To describe treatment patterns of Palbociclib + AI as initial endocrine based therapy for MBC. • To examine effectiveness of Palbociclib + AI as initial endocrine based therapy for MBC, including real world progression free survival (rwPFS), overall survival (OS), and real world tumor response (rwTR). **Secondary objectives** • To examine effectiveness of Palbociclib + AI as initial endocrine based therapy for MBC by subgroups such as age, ECOG performance, metastatic status, menopausal status, and prior therapy. • To examine the time from Palbociclib + AI

	initiation to the next line of anti-cancer treatment and time to first use of chemotherapy. CCI [redacted]
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AI	Aromatase inhibitor
ASCO	American Society of Clinical Oncology
BC	Breast cancer
BRCA	BReast CAncer susceptibility gene
CDK	Cyclin-dependent kinase
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen receptor
ET	Endocrine therapy
EHR	Electronic health record
FDA	US Food and Drug Administration
GPO	Group Purchasing Organization
GPP	Good Pharmacoepidemiology Practices
HR+	Hormone receptor-positive
HCP	Health Care Professional
HER	Human Epidermal Growth Factor Receptor
HIPPA	Health Insurance Portability and Accountability Act
HR	Hormone receptor
ICD	International Classification of Diseases
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IPTW	Inverse probability treatment weighting
LHRH	Luteinizing hormone releasing hormone
LOT	Line of therapy
MBC	Metastatic breast cancer
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NI	Non-interventional
OS	Overall survival
PR	Progesterone receptor
PS	Propensity score
QC	Quality Control
rwDOT	Real-world duration of treatment
rwPFS	Real-world progression-free survival
rwTR	Real-world tumor response
SAP	Statistical analysis plan
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results
SQL	Structured Query Language
US	United States

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: Real-world treatment patterns and effectiveness of Palbociclib in combination with an aromatase inhibitor as initial endocrine based therapy in metastatic/advanced breast cancer

Date of Abstract: 10 November 2019

Amendment 1

Name and affiliation of the main author:
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Rationale and Background:

Palbociclib, the first oral cyclin-dependent kinase (CDK) 4/6 inhibitor, is approved for HR+/HER2–metastatic/advanced breast cancer (MBC) in combination with an aromatase inhibitor or fulvestrant. Improved median PFS was observed with Palbociclib plus Letrozole as first-line therapy (PALOMA-2) and with Fulvestrant in patients who have failed prior endocrine therapy (PALOMA-3). Since its approval in February 2015, Palbociclib has been prescribed for more than 100,000patients. Recent real-world studies support the effectiveness of Palbociclib-based therapy in HR+/HER2– MBC patients. It is important to better understand a treatment's benefits and risks in a real world setting as published real-world studies to date have limitations including small cohorts, short duration of

follow-up, inconsistent definitions of outcomes, and lack of a comparator. Electronic health record (EHR) data are collected as part of routine clinical practice and enable quick access to richer health information (as compared to claims database) in a timely manner (as compared to primary data collection) in a relatively large population. Utilizing Flatiron Health's longitudinal, demographically and geographically diverse database derived from electronic health record (EHR)data from over 265 cancer clinics (~800 sites of care), the current study is designed to describe patient characteristics, treatment patterns and effectiveness of Palbociclib in combination with an aromatase inhibitor (AI) as initial endocrine based therapy in HR+/HER2- MBC.

Research question and objectives:

This study aims to describe patient characteristics, treatment patterns and effectiveness in HR+/HER2- MBC patients initiating Palbociclib + AI as initial endocrine based therapy during the period of February/3/2015 through August/31/2018 (or 3 months prior to study cut-off date) in the United States (US) real-world clinical practice setting.

Primary Objectives

- To describe demographic and clinical characteristics of metastatic/advanced (MBC) patients who were treated with Palbociclib + AI as initial endocrine based therapy.
- To describe treatment patterns of Palbociclib + AI as initial endocrine based therapy for MBC.
- To examine effectiveness of Palbociclib + AI as initial endocrine based therapy for MBC, including real world progression free survival (rwPFS), overall survival (OS), and real world tumor response (rwTR).

Secondary objectives

- To examine effectiveness of Palbociclib + AI as initial endocrine based therapy for MBC by subgroups such as age, ECOG performance, metastatic status, menopausal status, and prior therapy.
- To examine the time from Palbociclib + AI initiation to the next line of anti-cancer treatment and time to first use of chemotherapy.

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Study design: This is a retrospective cohort study utilizing data derived from the Flatiron Health Analytic Database to describe patient characteristics, treatment patterns and effectiveness of Palbociclib + AI as initial endocrine based therapy in HR+/HER2- MBC during the period of February/3/2015 through August/31/2018 (or 3 months prior to study cut-off date) in the US real-world clinical practice setting. The date of the first Palbociclib

+ AI line of therapy after February 3, 2015 is defined as the index date. Patients will be evaluated retrospectively from index date to November 30, 2018 (or study cut-off date), or death, whichever came first.

Population Setting: This study uses secondary de-identified Flatiron Healthcare Analytic data that involve patients who have been diagnosed with MBC in the United States.

Study Population: Female patients will be eligible for analysis if they were aged 18 or above at MBC diagnosis, HR+/HER2- as confirmed by a test before or up to 60 days after the date of MBC diagnosis, and were treated with Pablociclib + AI or Letrozole alone for MBC during the period from February 2015 through August 2018 (or 3 months prior to study cut-off date). Eligible patients will be identified from the Flatiron Health Analytic Database.

Variables: Variables will be obtained from both structured and unstructured data using Flatiron's technology-enabled data processing. The following variables will be included for the analyses: demographics (eg, age, race, ethnicity, region), baseline clinical characteristics (eg, date of diagnosis of MBC, HR+/HER2- status, ECOG performance status, disease stage at initial diagnosis, site of metastasis, and number of disease sites), treatment patterns (eg, AI therapy partner, starting dose, dose adjustment, duration of treatment, discontinuation, and reasons for dose adjustment and discontinuation), and effectiveness (real-world progression-free survival, overall survival, real-world tumor response, time to next line of anti-cancer treatment, and time to chemotherapy).

Data source

Flatiron Health's longitudinal, demographically and geographically diverse database derived from electronic health record (EHR) data from over 265 cancer clinics (~800 sites of care) including more than 2 million active US cancer patients.

Study Size: Based on an initial feasibility assessment using Flatiron Health Analytic Database between February 2015 – November 2018, there are 1,367 HR+/HER2- MBC patients who received Palbociclib + AI (including 1,221 Pablociclib + Letrozole, 70 Palbociclib + Anastrozole, and 76 Palbociclib + Exemestane) and 627 patients who received Letrozole monotherapy in the database. All patients satisfying inclusion and exclusion criteria will be included in the statistical analyses.

Data Analysis: Descriptive analyses will be performed to describe baseline demographics and clinical characteristics, treatment patterns, and effectiveness outcomes for patients receiving Palbociclib + AI as initial endocrine based therapy for MBC. Kaplan-Meier curves and landmark analyses will be performed to estimate real-world progression-free survival, overall survival, real-world tumor response, and time to chemotherapy from Palbociclib + AI

initiation. Subgroup analyses will be conducted according to age, ECOG performance, metastatic status, menopausal status, and prior therapy.

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Milestones: Data analysis will be conducted once data/related variables are available, and the final study report will be completed on Oct 27, 2021.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	10 November 2019	Section 8-9	Index period was changed from ’31 August 2018 (or 3 months prior to study cut-off date)’ and study end date was changed from November 30 to study cut-off date.	To be consistent with Flatiron’s data cut-off date.
		Section 9.2.1	Inclusion criterion #5. 1. “letrozole alone” was added. 2. “first line therapy” was added.	1. To include letrozole cohort. 2. To specify “initial endocrine based therapy” in the study to be consistent with PALOMA 2.
		Section 9.2.2	Exclusion criteria were updated	Follow Flatiron’s protocol.
		Section 9.3	Follow-up period, rwPFS, and OS were clarified	Follow Flatiron’s protocol.
		Section 9.3	Change Palbociclib +AI to index treatment	To be applicable to letrozole cohort.
		Section 6	Final report changed to 10/27/2021	Further analyses need to be done and to be consistent with complete date in clinicaltrial.gov.

6. MILESTONES

Milestone	Planned date (mm/dd/yyyy)
Completion of feasibility assessment using Flatiron Health Analytic Databases	*22 January 2019*
Analyses for primary objectives	*25 January 2019*
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Final study report	*27 October 2027*

7. RATIONALE AND BACKGROUND

Breast cancer is the most common cancer in women and the second most common cancer overall. In 2016, there were approximately 3.5 million women living with a history of breast cancer (BC) in the US.[1] It is estimated that 154,794 American women living with metastatic BC in the US in 2017 and that 3 in 4 initially diagnosed with early stage BC will progress to MBC.[2] Hormone receptor-positive (HR+) breast cancer is the most commonly diagnosed subtype (~70-80%), and it is potentially sensitive to endocrine therapy.[3]

Palbociclib, the first oral CDK4/6 inhibitor, is approved for HR+/HER2– advanced and metastatic breast cancer in combination with an aromatase inhibitor or Fulvestrant. Palbociclib is approved in the US based on improved median PFS demonstrated in 3 pivotal clinical trials: PALOMA-1 and PALOMA 2 (initial endocrine based therapy) and PALOMA-3 (after progression following endocrine therapy). Approval was first granted based on findings from the phase II PALOMA-1 trial[4] in February 2015. 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.[5,6] The phase III 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] Subgroup analyses of PFS according to stratification factors and demographic or prognostic factors revealed consistent results in PALOMA-2[7] [6] and PALOMA-3 trial.[5,6] The primary toxicity of Palbociclib is neutropenia, which can be managed with dose interruption/reduction, resulting in a favorable safety profile and delayed deterioration of global QoL.[8,9] The safety results from all three trials were consistent, with no new safety signals identified in the phase III studies. Subsequently, Palbociclib has been granted regular approval in combination with an aromatase inhibitor (AI) for initial endocrine based treatment.[10]

Since its approval in February 2015, Palbociclib has rapidly become the standard of care in the treatment of HR+/HER2- MBC in women, commercially available multi-nationally. Palbociclib has been prescribed for more than 100,000 patients. Long-term pooled safety analyses of three randomized phase II and III studies demonstrated no evidence of specific cumulative or delayed toxicities with Palbociclib plus endocrine therapy.[11] Recent real-world data have demonstrated that Palbociclib is effective in HR+/HER2– MBC patients

in the routine clinical practice setting.[12-15] It is important to better understand a treatment's benefits and risks in a real world setting as published real-world studies to date have limitations including small cohorts, short duration of follow-up, inconsistent definitions of outcomes, and lack of a comparator.

Electronic health record (EHR) data is collected as part of the routine clinical practice and enables quick access to richer health information (as compared to medical or pharmacy claims data) in a timely manner (as compared to primary data collection) in a relatively large population. The Flatiron Health database (https://flatiron.com/real-world-evidence/) is a longitudinal, demographically and geographically diverse database derived from electronic health record (EHR) data. The database includes data from over 265 cancer clinics (~800 sites of care) representing more than 2 million active U.S. cancer patients available for analysis. In the current study, a novel non-interventional (NI) study approach will be taken to utilize Flatiron Health database to understand patient characteristics, treatment patterns and effectiveness of Palbociclib + AI at initial endocrine based therapy in MBC patients.

The current protocol is not designed as a PASS per CT34 Post-Authorization Safety Studies (PASS) and the study is not a commitment or requirement to any regulatory authority.

8. RESEARCH QUESTION AND OBJECTIVES

This study aims to assess treatment patterns and real-world effectiveness in HR+/HER2- MBC patients initiating Palbociclib + AI as initial endocrine based therapy during the period February/3/2015 through August/31/2018 (or 3 months prior to study cut-off date) in the US real-world clinical practice setting.

Primary objectives

- To describe demographic and clinical characteristics of metastatic/advanced (MBC) patients who were treated with Palbociclib + an aromatase inhibitor (AI) as initial endocrine based therapy.

- To describe treatment patterns of Palbociclib + AI as initial endocrine based therapy for MBC.

- To examine effectiveness of Palbociclib + AI as initial endocrine based therapy for MBC, including real world progression free survival (rwPFS), overall survival (OS), and real-world tumor response (rwTR).

Secondary objectives

- To examine effectiveness of Palbociclib + AI as initial endocrine based therapy for MBC by subgroups such as age, ECOG performance, metastatic status, menopausal status, and prior therapy.

- To examine the time from Palbociclib + AI initiation to the next line of anti-cancer treatment and time to first use of chemotherapy.

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9. RESEARCH METHODS

9.1. Study Design

A retrospective cohort study of treatment patterns and effectiveness of Palbociclib + AI as initial endocrine based therapy during the period February/3/2015 through August/31/2018 (or 3 months prior to study cut-off date) for MBC will be conducted utilizing secondary de-identified Flatiron Healthcare Analytic data in the United States. This study design is selected to meet the study objectives with consideration of feasibility and availability and validity of exiting database.

- **Index date:** the date of first prescription for + AI between February 3, 2015 and August 31, 2018 (or 3 months prior to study cut-off date).

- **Observation period**: February 3, 2015 – study cut-off date.

- **Follow-up:** Patients will be followed from the index date to the end of the study (study cut-off date) or death, whichever came first.

  - **Primary endpoints**

    - RwPFS.

  - **Secondary endpoints**

    - OS.

    - RwTR.

    - Response rate.

    - Real-world duration of treatment (rwDOT).

    - Time from index date to next line of anti-cancer therapy and time to first use of chemotherapy.

9.2. Setting

This study uses secondary de-identified Flatiron Healthcare Analytic data that involve patients who have been diagnosed with MBC in the United States.

9.2.1. Inclusion Criteria

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

1. Female sex.
2. At least 18 years old at MBC diagnosis.
3. Diagnosis of MBC at any point in patient history.
    a. ICD-9 (174.x, 175.x) or ICD-10 (C50.xx) diagnosis of BC.
    b. Confirmation of metastatic disease.
    c. At least 2 document clinical visits.
    d. Evidence of stage IV or recurrent MBC with a metastatic diagnosis date on or after 2011, as confirmed by unstructured clinical documents.
4. HR+/HER2-.
    a. HR+: ER+ or PR+ test before or up to 60 days after MBC diagnosis.
    b. HER2-: any HER2 negative test and the absence of a positive test (IHC positive 3+, FISH positive/amplified, Positive NOS) before or up to 60 days after MBC diagnosis.
5. Palbociclib + AI or letrozole alone as initial endocrine based therapy (ie, first line therapy) for MBC during the period from February/2015 through August/31/2018 (or 3 months prior to study cut-off date) to allow for a possible minimum follow-up time of 90 days until the study cut-off date. AI was administered within (±) 28 days of Palbociclib index date.

9.2.2. Exclusion Criteria

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

1. Evidence of prior treatment with other CDK4/6I (Ribociclib or Abemaciclib), AI (Letrozole, Exemestane, and Anastrazole), Tamoxifen, Raloxifene, Toremifene, or Fulvestrant for MBC.
2. First structured activity greater than 90 days after MBC diagnostic date.
3. Treatment with a CDK4/6 inhibitor as part of a clinical trial.

9.2.3. Study Cohorts

Eligible MBC patients will be assigned into the following cohorts:

Cohort 1: Patients who were treated with Palbociclib + AI as the initial endocrine based therapy to be analyzed for the primary and secondary objectives.

Cohort 2: Patients who were treated with Palbociclib + Letrozole to be analyzed for the primary and secondary objectives CCI

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9.3. Variables

All variables are assessed or defined by Flatiron using business rules before and after Palbociclib + AI initiation.

Table 1. List of Variables

Variable	Operational definition
Demographic characteristics	
Age	Age at MBC diagnosis, years
Age category	<50, 50-64, 65 –74, ≥75 years
Gender	Female
Race	White, Black, Asian, other, unknown
Region of residence	Based on state where the patient resides: Northeast, Midwest, South, West
Practice type	Academic, community
Insurance type	Commercial, Medicare, Medicaid
Menopause status	Pre-/peri-menopausal, postmenopausal, Unknown based on patients age at diagnosis and/or treatment
Duration of follow-up	Months from index date to the end of the study or death, whichever came first
Clinical characteristics	
Type of MBC	De novo MBC (newly diagnosed): Stage 4 at initial BC diagnosis Recurrent MBC: Stages 0-3 at initial BC diagnosis
ECOG performance score	ECOG performance at index date, 0, 1,2,3,4
Stage at initial BC diagnosis	Stage I, II, III, IV, unknown/ undocumented
Time from initial BC diagnosis to first MBC diagnosis	Months from the date of initial BC diagnosis to the date of metastatic diagnosis
ER status	Positive, negative or unknown
PR status	Positive, negative or unknown
HER2 status	Positive, negative or unknown
BRAC status	BRAC 1 and BRAC 2: positive, negative, unknown/unassessed
Organ-level metastatic sites	Number of sites; Sites of metastases (bone, lung, liver, brain, distant lymph nodes, other) Visceral vs. non-visceral, bone only
De novo metastatic	Yes or no
Disease Free Interval (DFI)	Months from the end of adjuvant/neo-adjuvant therapy to the date of disease recurrence <=12 months, 13-24 months, 25-36 months >36 months Unknown
Prior neo/adjuvant therapies	Chemotherapy Hormonal therapy Unknown See Table 2 for detail
Prior chemotherapy at MBC setting	Chemotherapy (See Table 2 for detail) Unknown
Modified Charlson comorbidity index (CCI)	Include Myocardial infarction, Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Dementia, Chronic pulmonary disease, Rheumatologic disease, Peptic ulcer disease, liver disease, diabetes, Hemiplegia or paraplegia, renal diseases/impairment, and AIDS/HIV

Longitudinal treatment patterns	
Lines of therapy	Lines of therapy in the metastatic setting are assigned by Flatiron to evaluate systemic treatment on or after the MBC date
Initial prescribed dose	Palbociclib: 125mg, 100mg, 75mg using
Dose adjustment	Dose strength other than initial/previous prescription
Type of the first dose change	Dose reduction 125mg to 100mg, 125mg to 75mg, 100mg to 75mg Dose increase 75mg to 100mg, 100mg to 125mg, 75 mg to 125 mg
Time to the first dose change	Days from index date to first dose change
Number of dose adjustment	Number of dose reduction and number of dose increase over the calendar time (quarter since February 2015) and over treatment cycle since index date
Reasons for dose adjustment	As categorized by Flatiron
Reasons for discontinuation	Disease progress, toxicity, financial, patient request, other
Duration of treatment	Days from index prescription order date to end of treatment
Combination endocrine partner	Letrozole, Anastrozole, Exemestane
Concomitant LHRH Agonists	Goserelin (Zoladex), Histrelin (Vantas), Leuprolide (Eligard, Lupron), Triptorelin (Trelstar)
Other concomitant anti-cancer therapies	Chemotherapy (See Table 2 for detail)
Effectiveness outcomes	
Real-world PFS (rwPFS)	Months from index date to death or disease progression (growth or worsening in the disease concluded by the treating clinician based on radiology, laboratory evidence, pathology, or clinical assessment) whichever came first. If patients did not die or have disease progression, they were censored at the date of initiation of next line of therapy for patients with two or more lines of therapy or their last visit date during the study period for patients with only one line of therapy
Overall survival (OS)	Months from index date to the date of death. Patients who did not die period are censored at the time of data cut-off
Real-world tumor responses (rwTR)	Real-world tumor responses are assessed based on treating clinician's assessment of radiological evidence for change in burden of disease over the course of treatment: • Complete response: complete resolution of all visible disease. • Partial response: partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease. • Stable disease: no change in overall size of visible disease; also included cases where some lesions increased in size and some lesions decreased in size. • Progressive disease: an increase in visible disease and/or presence of any new lesions; included cases where the clinician indicated progressive disease.
Response rate	Complete response or partial response divided by the number of patients with at least one tumor assessment while on the index treatment

Real-world duration of treatment (rwDOT)	Months from index treatment initiation to end of the treatment
Time to next line of anti-cancer therapy	Months from index treatment initiation to next line of anti-cancer therapy or death from any cause, whichever occurred first
Time to chemotherapy	Months from index treatment initiation to first use of chemotherapy or death from any cause, whichever occurred first

Table 2. List of Medications for the Treatment of HR+/HER2- Metastatic Breast Cancer

Drug Name	Brand Name	Type of therapy	Code
Anastrozole	Arimidex	Endocrine	S0170
Exemestane	Aromasin	Endocrine	S0156
Fulvesterant	Faslodex	Endocrine	J9395
Letrozole	Femara	Endocrine	N/A
Megestrol acetate	Megace	Endocrine	S0179
Raloxifene	Evista	Endocrine	N/A
Tamoxifen	Nolvadex	Endocrine	G8376, G8380, G8381, S0187
Toremifene	Fareston	Endocrine	N/A
Everolimus	Afinitor	Target therapy	J7527, J8561
Palbociclib	Ibrance	Target therapy	N/A
Ribociclib	Kisqali	Target therapy	N/A
Abemaciclib	Verzenio	Target therapy	N/A
Capecitabine	Xeloda	Chemotherapy	J8520, J8521
Cyclophosphamide	Cytoxan	Chemotherapy	• C9420 - cyclophosphamide (2) *(HCPCS Procedure Drug).* • C9421 - cyclophosphamide (2) *(HCPCS Procedure Drug).* • J8530 - Cyclophosphamide oral 25 mg (2) *(HCPCS Procedure Drug).* • J9070 - Cyclophosphamide 100 mg inj (2) *(HCPCS Procedure Drug).* • J9080 - Cyclophosphamide

Drug Name	Brand Name	Type of therapy	Code
			200 mg inj (2) *(HCPCS Procedure Drug)*. • J9090 - Cyclophosphamide 500 mg inj (2) *(HCPCS Procedure Drug)*. • J9091 - Cyclophosphamide 1.0 grm inj (2) *(HCPCS Procedure Drug)*. • J9092 - Cyclophosphamide 2.0 grm inj (2) *(HCPCS Procedure Drug)*. • J9093 - Cyclophosphamide lyophilized (2) *(HCPCS Procedure Drug)*. • J9094 - Cyclophosphamide lyophilized (2) *(HCPCS Procedure Drug)*. • J9095 - Cyclophosphamide lyophilized (2) *(HCPCS Procedure Drug)*. • J9096 - Cyclophosphamide lyophilized (2) *(HCPCS Procedure Drug)*. • J9097 - Cyclophosphamide lyophilized (2) *(HCPCS Procedure Drug)*.
Nab-paclitaxel	Abraxane	Chemotherapy	No code specific to Abraxane
Paclitaxel	Taxol	Chemotherapy	• C9127 - paclitaxel (2) *(HCPCS Procedure Drug)*. • C9431 - paclitaxel (2) *(HCPCS Procedure Drug)*.

Drug Name	Brand Name	Type of therapy	Code
			• I - PACLITAXEL NO STRENGTH *(Uncoded Product Identifier).* • J9264 - Paclitaxel protein bound (2) *(HCPCS Procedure Drug).* • J9265 - Paclitaxel injection (2) *(HCPCS Procedure Drug).* • J9267 - Paclitaxel injection (2) *(HCPCS Procedure Drug).*
Doxorubicin	Taxotere	Chemotherapy	• C9415 - doxorubicin (2) *(HCPCS Procedure Drug).* • J9000 - Doxorubicin hcl injection (2) *(HCPCS Procedure Drug).* • J9001 - Doxorubicin hcl liposome inj (2) *(HCPCS Procedure Drug).* • Q2050 - Doxorubicin inj 10mg (2) *(HCPCS Procedure Drug).*
Carboplatin	Paraplatin	Chemotherapy	• C9418 - cisplatin (2) *(HCPCS Procedure Drug).* • J9060 - Cisplatin 10 mg injection (2) *(HCPCS Procedure Drug).* • J9062 - Cisplatin 50 mg injection (2) *(HCPCS Procedure Drug).*
Eribulin	Halaven	Chemotherapy	• C9280 - Injection, eribulin mesylate (2) *(HCPCS Procedure Drug).* • J9179 - Eribulin mesylate injection (2) *(HCPCS Procedure Drug).*
Gemcitabine	Gemzar	Chemotherapy	J9201
Ixabepilone	Ixempra	Chemotherapy	J9207

Drug Name	Brand Name	Type of therapy	Code
5-fluorouracil	Adrucil	Chemotherapy	J9190
Epirubicin	Pharmorubicin	Chemotherapy	J9178
Vinorelabine	Navlabine	Chemotherapy	J9390
Methotrexate		Chemotherapy	J8610, J9250, J9260,
Mitomycin		Chemotherapy	J9280
Mitoxantrone	Novantrone	Chemotherapy	J9293

9.4. Data Source

Flatiron Health Database (https://flatiron.com/real-world-evidence/).

This retrospective observational study utilized Flatiron Health's longitudinal, demographically and geographically diverse database derived from electronic health record (EHR) data from over 265 cancer clinics (~800 sites of care) including more than 2 million active US cancer patients available for analysis. Across the clinics in the Flatiron Health Network, data become available in near real time after each clinical encounter and contribute to Flatiron's continuously aggregating centralized data set. The patient-level data in the EHRs includes structured data (ie, data points that are organized in a predefined manner, such as dropdown fields that reside in an EHR to capture a patient's gender or date of birth or laboratory data), unstructured data collected via expert human chart abstraction of physician's notes and other free text fields couple with quality controlled natural language processing and business rules technology, and other unstructured documents (ie, information from a portable document format [PDF] laboratory reports or narratives from synoptic reports). Flatiron integrates the structured EHR data with quality controlled curated data from unstructured EHR data into a single data model, where all data are certified HIPAA-compliant with all de-identified patients being assigned a longitudinally stable identifier. Details of de-identification procedure and data management are outline in the Flatiron's parent database protocol (NEIRB#15 159, "The Flatiron Health Analytic Database"). CCI [redacted] CCI [redacted] The data used in this analysis already exist within this model, stored in an electronic database.

All data, code to create the MBC dataset, and other technical artifacts are version-controlled and managed within a Flatiron repository. These artifacts are stored and backed up on Flatiron's servers for at least 7 years. All data within the dataset can be traced back to the original source data or documents within the EHR, and appropriate change management and provenance best practices are maintained by Flatiron in the event of a regulatory audit.

Institutional Review Board approval of the study protocol was obtained prior to study conduct, and included a waiver of informed consent. Data provided to third parties were de-identified and provisions were in place to prevent re-identification in order to protect patients' confidentiality.

The data cut-off for this study is November 30, 2018 (or latest Flatiron data cut-off date).

9.5. Study Size

Based on an initial feasibility assessment using Flatiron Health Analytic Database between February 2015 – November 2018, there are 1,367 HR+/HER2- MBC patients who received Palbociclib + AI (including 1,221 Pablociclib + Letrozole, 70 Palbociclib + Anastrozole, and 76 Palbociclib + Exemestane) **and 627 patients who received Letrozole monotherapy** in the database. All eligible patients will be included for descriptive analyses.

9.6. Data Management

Flatiron Health Database (https://flatiron.com/real-world-evidence/) collects data through a HIPAA-compliant process that results in de-identified patient data as described above. De-identified data are prepared by Flatiron and transferred securely to Pfizer in a standard flat file format. Once on Pfizer servers, Pfizer staff perform quality assurance on the data, checking that the metadata align with the data dictionary from Flatiron Health, that the number of records equals that expected from the vendor and that the data types and controlled vocabularies are correct in a semi-automated process. The data are then loaded into a secure Pfizer server. Pfizer servers are backed up nightly, and have failover and off-site redundancy. Access to data is limited only to Pfizer colleagues and is monitored with all end user activity is logged. Pfizer maintains copies of all EHR or other real world data in accordance with the FDA's July 2018 Industry Guidance on Use of Electronic Health Record Data in Clinical Investigations (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM501068.pdf), though Pfizer maintains its data in excess of the guidance – for a minimum of 7 years.

9.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As described above, Flatiron Health Database collects data through a HIPAA-compliant process that results in de-identified patient data.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Flatiron Health has agreed to keep all study-related records, including electronic health records, data curated by Flatiron from unstructured fields within those records, rationale for a curated data point, query code and the dataset provided under this protocol from their larger MBC registry. The records should be retained by Flatiron according to local regulations or as specified in the statement of work, whichever is longer. Flatiron must ensure that the records continue to be stored securely for so long as they are retained.

If Flatiron becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 7 years after completion or discontinuation of the study, as expressly agreed to within the statement of work by Flatiron and Pfizer. Pfizer will retain all analysis datasets, code and other artefacts generated over the course of

executing this protocol for at least 15 years or longer if required by applicable local regulations.

Flatiron must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

The primary and secondary objectives of the study are to describe patient characteristics, real-word treatment patterns and effectiveness of Palbociclib + AI as initial endocrine based therapy for metastatic breast cancer.

Descriptive analyses: For categorical variables (eg, region, race, and stage at initial diagnosis), data will include the frequency (number of cases) and percentage (%) of total patients observed in each category; for continuous variables (eg, age and time from initial breast cancer diagnosis to metastatic diagnosis), variables will be presented as the mean, standard deviation (SD), median, 25^{th} and 75^{th} percentiles and ranges (minimum and maximum) in some cases. The calculation of percentages will always include the missing category in the case of missing values. Continuous variables may be categorized into intervals, with the distribution of patients (N, %) provided.

Kaplan-Meier curves and landmark analyses will be performed to estimate real-world progression-free survival, overall survival, and time on treatment, time to next line of anti-cancer therapy, and time to first use of chemotherapy. Specifically, landmark time points are 3, 6, 12, 18, 24, 30, and 36 months for rwPFS and rwTR, 0.5, 1, 1.5, 2, 2.5, and 3 years for overall survival, and 3, 6, 12, 18, 24, 30, and 36 months for Time on Treatment with Palbociclib + AI and time to next ant-cancer therapy and to first use of chemotherapy. Ninety-five percent (95%) confidence intervals on the median rwPFS, overall survival, and treatment time will be reported.

The maximum real-world tumor response will be computed for each patient with at least one on-Palbociclib + AI treatment tumor assessment. If a patient has a maximum tumor response of a CR or PR, then the patient will be considered to be a responder. Response rate will be computed using the number of patients with a CR or PR as the numerator and the number of patients with at least 1 on-treatment tumor assessment as the denominator.

Subgroup analyses will be conducted according to age, ECOG performance (0, 1, ≥2), de novo metastatic, visceral, non-visceral, bone only, disease sites (1, 2, ≥3), menopausal status, prior endocrine therapy, prior chemotherapy, prior surgery, prior radiation therapy as appropriate based on availabilities of the data and sample sizes.

The following sensitivity analyses will be performed as appropriate:

1. A subset of patients receiving Palbociclib+AI in the first-line metastatic setting with at least three prescriptions for Palbociclib will be included.

2. Patients were followed for at least 6 months.

Detailed methodology for summary and statistical analyses of data collected in this study for the primary and secondary objectives is documented herein, following the requirements of the Statistical Analysis Plan (SAP) template; therefore a separate SAP document will not be necessary for these analyses.

9.8. Quality Control

This is a retrospective study, so issues of quality control at study sites, eg, data clarification queries, do not apply. Analyses are programmed according the specifications in the protocol's SAP and all code and other technical artifacts are documented and stored following established programming practices on Pfizer servers and in Pfizer's Global Document Management System. Quality control (QC) will follow the Flatiron's standard procedure for quality control and assurance as described in Flatiron Health Analytic Database Parent Protocol. QC for structured and unstructured data is conducted prior to delivery of each dataset. For each data model, Flatiron generates and continually maintains a set of quality standards and versioned business rules. These QC standards cover themes such as demographics, biomarkers, treatment, therapy shares, treatment length/dosage, lines of therapy, real world recurrence, and real world progression free survival. They have a team of 900 expert nurse and physician abstractors that co-create and version rules, and also to create QC that includes both medical considerations (eg, what are expected based on the literature and clinical practice) and data considerations (eg, stability from prior months). Missingness of death data is a major confounding factor for many real-world oncology analyses. For survival data, Flatiron Health utilizes four resources, including the National Death Index, US Social Security Death Index, obituaries and commercial death data published from a vendor to identify when patients have died (https://onlinelibrary.wiley.com/doi/full/10.1111/1475-6773.12872). In a study of advanced non-small cell lung cancer patients, sensitivity increased from 66% from Flatiron's HER-based registry alone to over 91% from the composite of the four sources.

QC will be performed for the results of the study, including reviewing and double checking for correct data, consistency, spelling, grammar and structure. It is also reviewed to ensure that it conforms to Flatiron's data dictionary, has internal consistency (eg, that date of diagnosis occurs after date of birth) and meets the study objectives. The final review of the findings and content will be conducted in a summary presentation.

9.9. Limitations of the Research Methods

The proposed study may have the following limitations.

One of the main challenges of EHR data is the potential for missing, inaccurate or incomplete data. For example, EHR contains only that a physician prescribed a drug but not whether it was filled/refilled. The quality of information extracted from the EHR depends on the quality of information entered the EHR by the clinician. Feeds of EHR data may be updated only every 3-6 months, with some vendors providing more rapid updates. Data quality, missingness and other challenges are mitigated with Flatiron's semi-automated enhanced curation and quality control, though these challenges are not fully obviated by these expert biocurators, rules and processes.

The patient populations in the Flatiron database may not be reflective of the general population nationally. Some skewing in the data is possible if differences exist between patients in this study cohort and general patient population. Thus, the results of this study will be unprojected (ie, analyses will be based on the sample collected and not projected to the national level).

Due to the nature of the data employed in this study, it is not feasible to make an assessment of causality between medical events recorded and the medicinal products at an individual case level. As a result of the way this study is designed, no causal inference can be ascertained, as this is an observational study using retrospective data. Secondary data does not report the causality.

In addition, sample size may limit subgroup analyses and generalizability of the findings.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient personal data will be stored at Flatiron in *encrypted electronic* form and will be *password protected* to ensure that only authorized study staff has access. Flatiron will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, Flatiron shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the *statement of work with Flatiron* and applicable privacy laws.

10.2. Patient Consent

As this study involves de-identified data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Patient Withdrawal

Not applicable.

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

The IRB approval of this observational study with secondary data use from an existing EHR database is covered by IRB approval on Flatiron parent protocol. Data provided by Flatiron to third parties were de-identified and provisions were in place to prevent re-identification in order to protect patients' confidentiality. This study is exempt from institutional review board approval because it is retrospective, non-interventional, and will use anonymized data provide by Flatiron.

10.5. 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 follow generally accepted Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) research practices (https://www.pharmacoepi.org/resources/guidelines_08027.cfm), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (http://www.ispor.org/workpaper/practices_index.asp) and Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372/) and similar standards.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study uses existing health care databases, in which it is generally not possible to link (ie, identify a potential association between) a particular product and medical event for any individual.

In addition, this study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewers are obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the chart abstraction form and reported, within 24 hours of awareness, to Pfizer safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using NIS AEM Report Form.

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

All research staff members will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages*)" and any relevant Your Reporting Responsibilities supplemental training. This training must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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 which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.