NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Treatment patterns and clinical effectiveness outcomes of palbociclib in combination with aromatase inhibitor (AI) or fulvestrant in hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer patients: an observational study using Flatiron Electronic Health Record (EHR) database
Protocol number	A5481076
Protocol version identifier	3.0
Date of last version of protocol	22 August 2017
EU Post Authorisation Study (PAS) register number	Study not registered
Active substance	Palbociclib/PD332,991
Medicinal product	Palbociclib
Research question and objectives	The main objective is to describe patient demographics, clinical characteristics, treatment patterns and clinical effectiveness outcomes in a cohort of HR+/HER2- breast cancer patients who initiated palbociclib (Ibrance®) in combination with an AI or fulvestrant for treatment of advanced or metastatic disease, using flatiron HER database. Exploratory objectives include describing the complete blood count (CBC) monitoring patterns and comparing effectiveness outcomes between palbociclib plus an AI and AI monotherapy using a propensity score matched cohort analyses method.
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APPENDICES

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC	Advanced breast cancer
AE	Adverse event
AEM	Adverse event monitoring
AI	Aromatase inhibitors
BMI	Body Mass Index
CBC	Complete blood count
CDK	Cyclin Dependent Kinase
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
EDP	Exposure during pregnancy
EHR	Electronic Health Record
ER	Estrogen receptor
ER+	Estrogen receptor positive
FDA	Food and Drug Administration
FI	Flatiron
HER2-	Human epidermal growth factor receptor 2 negative
HR	Hazard ratio
HR+	Hormone receptor positive
IEA	International Epidemiological Association
IEC	Independent ethics committee
IRB	Institutional review board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MBC	Metastatic breast cancer
NCCN	National Comprehensive Cancer Network
NIS	Non-interventional study
PR+	Progesterone receptor positive
PV	Pharmacovigilance
SAP	Statistical analysis plan
US	United States

2. RESPONSIBLE PARTIES

STUDY TEAM

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3. ABSTRACT

Title: Treatment patterns and clinical effectiveness outcomes of palbociclib in combination with aromatase inhibitor (AI) or fulvestrant in hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer patients: an observational study using Flatiron Electronic Health Record (EHR) database

Wanning Xu, Lynn McRoy, Yao Wang, Jack Mardekian, James Harnett, Shrividya Iyer, Pfizer Inc. Version 3.0, 22 August 2017

Rationale and background: Palbociclib is the first cyclin dependent kinase (CDK)4/6 inhibitor approved in the United States (US) in combination with aromatase inhibitors (AIs) or fulvestrant for hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer (ABC or MBC). Since approval, more than 59,000 patients have been treated in the US. This study aims to describe treatment patterns and clinical effectiveness outcomes among HR+/HER2- breast cancer patients who have been treated with palbociclib in treatment of advanced or metastatic disease, using electronic health record (EHR) data from Flatiron (FI) Health Analysis Database.

Research question and objectives: The main objective is to describe patient demographics, clinical characteristics, treatment patterns, and clinical effectiveness outcomes in a cohort of HR+/HER2- breast cancer patients who initiated palbociclib (Ibrance®) in combination with an AI or fulvestrant for treatment of advanced or metastatic disease. Exploratory objectives include describing complete blood count (CBC) monitoring patterns and comparing clinical effectiveness outcomes between palbociclib plus an AI and AI monotherapy using a propensity score matched cohort analyses method stratified by line of therapy.

Study design: This is an observational study using de-identified EHR data from Flatiron Health Analytic Database.

Population: The study population includes adult patients diagnosed with breast cancer identified from FI database between 01 January 2011 and 30 June 2017 (defined as "study period") and who initiated palbociclib for treatment of advanced or metastatic disease on or after 03 February 2015.

Variables: Information on patient demographics, clinical characteristics, treatment characteristics, CBC monitoring patterns and clinical effectiveness outcomes will be identified.

Data sources: EHR data from Flatiron Health Analytic Database.

Study size: This is a descriptive study and sample size calculation is not applicable. All adult breast cancer patients identified during the study period and initiated palbociclib on or after 03 February 2015 will be included in the analysis.

Data analysis: Descriptive analyses will be conducted to describe patient demographics, clinical characteristics, treatment patterns, and clinical effectiveness outcomes overall and by line of therapy. The CBC monitoring patterns may be described depending on data sufficiency and structure. Exploratory propensity score matched analyses might be conducted to compare clinical effectiveness outcomes between treatments.

Milestones: Final dataset will be delivered by 06 October 2017. Final tables for poster presentation at San Antonio Breast Cancer Symposium (SABCS) will be completed by 08 November 2017. Final study report will be completed on 15 March 2018.

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	10 June, 2017	Substantial	3 (abstract), 6 (background), 7 (research and objectives), 8.2 (setting), 8.2.1 (inclusion criteria), 8.3 (variables), 8.5 (study size), and 8.7 (data analysis)	Including patients who initiated palbociclib treatment regardless of gender and combination drugs.	This is a pure description of an existing patient population who initiated palbociclib treatment in the real-world practice setting based on secondary data in structured format.
2	15 August, 2017	Substantial	3 (abstract), 6 (background), 7 (research and objectives), 8.3 (variables), 8.7 (data analysis), and 10. (management and reporting of adverse event/adverse reactions)	Including clinical effectiveness outcomes in study endpoints and revising the AE reporting language due to human review of patient-level unstructured data. Adding an exploratory objective to compare between palbociclib plus an AI and AI monotherapy using propensity score matched analyses.	Clinical effectiveness outcomes are added to main study objectives due to the data availability. As clinical outcomes will be collected through human review of patient-level unstructured data, AE reporting to Pfizer is required. Additional exploratory objective to compare to AI monotherapy are added to generate data to respond to an EU regulatory request.

5. MILESTONES

Milestone	Planned date
Start of structured data collection	10 May 2017
Tables for Abstract Submission to 2017 San Antonio Breast Cancer Symposium (SABCS)	11 June 2017
Start of unstructured data collection	21 July 2017
Final unstructured data available	06 October 2017
Final tables for poster presentation at SABCS	08 November 2017
Final study report	15 March 2018

6. RATIONALE AND BACKGROUND

Breast cancer is the most common cancer and the second highest cause of cancer deaths among women in the US. It is estimated that there will be 252,710 new cases of invasive breast cancer and 40,610 breast cancer deaths among US women in 2017 (American Cancer Society, 2017).[1] Patients with metastatic breast cancer (MBC) (stage IV) have poor survival prognosis, with a median survival time of 2–3 years after initial diagnosis of MBC (National Cancer Institute, 2017; Danwood et al, 2010) and the 5-year survival rate of 22% (as compared to 93% and 72%, respectively in stage II and III) (American Cancer Society, 2017).[1]

Approximately 80% of breast cancers are hormone receptor positive (HR+) (ie, expressing estrogen receptor [ER] and/or progesterone receptor ([PR]). Endocrine therapy is the main stream of the treatment for HR+ patients. The first-line endocrine treatment for HR+/HER2- advanced or metastatic breast cancer (ABC or MBC) typically includes aromatase inhibitors (AIs) (eg, anastrozole, letrozole, or exemestane) and estrogen receptor antagonists (eg, fulvestrant) (Cardoso et al 2012, National Comprehensive Cancer Network, 2015).

Palbociclib (PD-0332991) is an oral small-molecule inhibitor of cyclin dependent kinases 4 and 6 (CDK4/6). It has high activity in HR+ breast-cancer cell lines and is synergistic in combination with endocrine therapies (Finn et al, 2009). In February 2015, FDA granted accelerated approval of palbociclib in treating HR+/HER2- ABC or MBC in combination with letrozole as initial endocrine-based therapy in postmenopausal women based on the significantly prolonged PFS in a phase II study (PALOMA-1), where the median PFS was

20.2 months in palbociclib plus letrozole group and 10.2 months in letrozole monotherapy group (Hazard ratio [HR]=0.488) (Finn et al, 2015).[3] The clinical efficacy was confirmed in a subsequent phase III study (PALOMA-2) among 666 post-menopausal women who did not receive prior systemic therapy for ER+/HER2- ABC, with the median PFS of 24.8 months in palbociclib plus letrozole group vs. 14.5 months in placebo plus letrozole group (Finn et al, 2016)[4] and an updated label was approved in March 2017 with combination of any AI agents. In February 2016, FDA approved palbociclib in combination with fulvestrant in treating women with disease progression following endocrine therapy based on the results of a phase III study (PALOMA-3), showing the median PFS of 9.2 months in palbociclib with fulvestrant group and 3.8 months in placebo with fulvestrant group (Turner et al, 2015).[6]

Palbociclib is the first CDK4/6 inhibitor approved in the US in combination with other endocrine based therapies for treatment of HR+/HER2- MBC. Since initial approval, more than 59,000 patients have been treated in the United States (US). This study aims to describe patient demographic, clinical characteristics, treatment patterns, complete blood count (CBC) monitoring patterns and clinical effectiveness outcomes among HR+/HER2- breast cancer patients who initiated palbociclib in treatment of advanced or metastatic disease over 2 years following initial approval, using data from a real-world oncology electronic health record database. The EHR data is collected as part of the 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.

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

7. RESEARCH QUESTION AND OBJECTIVES

The main objective of this study is to describe patient demographics, clinical characteristics, treatment patterns and clinical effectiveness outcomes among a cohort of HR+/HER2- breast cancer patients who initiated palbociclib in treatment of advanced or metastatic disease.

Main research questions may include:

- To describe patient demographics, including age at initiation of palbociclib, gender, race, region, practice type, payer category, and duration of follow-up;
- To describe clinical characteristics, including disease stage at initial diagnosis, biomarker status (ER, PR, HER2, BRCA, PIK3CA, ESR1);
- ECOG performance status, Body Mass Index (BMI), sites of metastases, time from initial BC diagnosis to first diagnosis of metastatic disease, comorbidities;

- To describe the treatment patterns of palbociclib, including endocrine-based line of therapy (LOT) and regimen, initial dosage, initial dosage schedule (if data are sufficient), the dosage change, dosage schedule change (if data are sufficient), changes over calendar time in palbociclib LOT and regimens, and treatment discontinuation due to various reasons (including progression, toxic effect of therapy, disease-related symptoms not due to therapy, completed treatment, financial reason, patient request, other, and unknown);

- To describe other systemic treatment regimens (chemotherapy, other endocrine therapies) in metastatic setting.

- To describe clinical effectiveness outcomes of palbociclib combination therapy (with an AI or fulvestrant) in female patients, including but not limited to the number and proportion of patients who are progression-free at multiple intervals (eg, 12, 18, 24 months post initiation of palbociclib combination therapy), objective response rate (ORR), the number and proportion of patients alive 1 or 2 years post initiation of palbociclib combination therapy (if data is sufficient) for all patients and subgroups stratified by line of therapy (1^{st} and 2^{nd} or later) .

Exploratory research questions may include but not limited to:

- To describe the CBC monitoring patterns, including the number of patients with different number of CBC assessments over treatment cycle (if data are sufficient).

- To evaluate time to progression (TTP)/progression free survival (PFS) associated with palbociclib combination therapy (with an AI or fulvestrant) in female patients, overall and stratified by line of therapy (if data are sufficient).

- To compare clinical effectiveness outcomes between palbociclib plus aromatase inhibitor and aromatase inhibitor monotherapy using a propensity score matched cohort analyses method, stratified by line of therapy (if data is sufficient).

8. RESARCH METHODS

8.1. Study design

This is an observational study using de-identified EHR data from Flatiron Health Analytic Database.

8.2. Setting

The study population includes adult patients diagnosed with HR+/HER2- breast cancer identified from Flatiron Health Analytic Database between 01 January 2011 and 30 June 2017 (referred to as “study period”) and who initiated palbociclib treatment on or after 03 February 2015.

8.2.1. Inclusion Criteria

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

1. Female or male.
2. 18 years or older.
3. ICD-9 (174.x, 175.x) or ICD-10 (C50.xx) diagnosis of breast cancer.
4. Pathology consistent with breast cancer.
5. At least two documented clinical visits on or after 01 January 2011.
6. Initiation of palbociclib (index event) on or after 03 February 2015 (the date of initial FDA approval) and prior to 30 June 2017 (data cut-off date).

8.2.2. Exclusion Criteria

None

8.3. Variables

Key variables include:

- **Patient demographics**
  - Age at initiation of palbociclib (years);
  - Gender (Female, Male)
  - Race/Ethnicity (White, Asian, Black or African American, Hispanic or Latino, Other);
  - Region (Northeast, Midwest, South, West);
  - Practice type (Community, Academic);
  - Payer category (Medicaid, Medicare, Commercial Health Plan, Workers Compensation, Other Government Program, Patient Assistance Program, Self-pay, Other Payer/Type Unknown);
  - Duration of follow-up (months) since initiation of palbociclib.
- **Clinical characteristics**
  - Stage at initial breast cancer diagnosis (0, I, II, III, IV);

- Biomarker testing results (Positive, Negative, Not Documented/Unknown/Indeterminate) at or prior to initiation of palbociclib, whichever the latest.
    - ER;
    - PR;
    - HER2;
    - BRCA;
    - PIK3CA;
    - ESR1.
- Sites of metastases (bone, lung, liver, brain, other CNS, distant lymph nodes; date of first documentation for a given site)
- ECOG Performance Status (0, 1, 2, 3, 4) at initiation of palbociclib in combination with AIs or fulvestrant;
- Body Mass Index (BMI) (Kg/m2) at initiation of palbociclib in combination with AIs or fulvestrant;
- Time from initial BC diagnosis to first diagnosis of metastatic disease (months).
- Comorbidities (documented history [yes/no] up to the time of palbociclib initiation for the following comorbidities: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, moderate to severe liver disease, diabetes end organ disease, diabetes no organ damage, hemiplegia, moderate to severe renal disease, AIDS. Depending on data availability, the following comorbidities may also be collected: long QT syndrome/QT prolongation, bradyarrhythmias, hypertension).

- **Palbociclib treatment patterns**:
    - Endocrine-based lines of therapy (1^{st}, 2^{nd}, 3^{rd}, 4^{th} or above): defined as the 1^{st}, 2^{nd}, 3^{rd} or 4^{th} endocrine-based therapy used in metastatic setting. Chemotherapy initiated in metastatic setting is excluded from the line of therapy.
    - Palbociclib containing regimen (ie, in combination with letrozole, anastrozole, exemestane, fulvestrant, other endocrine therapies, or palbociclib alone);
    - Initial dosage (125mg, 100mg, 75mg);

- Initial dosage schedule (3 weeks on/1 week off, other) (if data are sufficient);
- Number of dose reduction (0, 1, ≥2);
- Type of the first dose reduction (125mg to 100mg, 125mg to 75mg, 100mg to 75mg) or dose increase;
- Time to the first dose reduction (days);
- Dosage schedule change (ie, switch from 3 weeks on/1 week off to other dosage schedule) and reason (if data are sufficient);
- Distribution of the endocrine-based line of therapy at initiation of palbociclib in combination with an AI an fulvestrant, respectively, over the calendar time (by quarter since February 2015);
- Distribution of palbociclib regimens (ie, combination with an AI or fulvestrant) at initiation of palbociclib over the calendar time (by quarter since February 2015).
- Number and frequency of discontinuation due to progression, toxic effect of therapy, disease-related symptoms not due to therapy, completed treatment, financial reason, patient request, other, and unknown.

- **Other systemic treatments (Appendix 1) in metastatic setting**
  - Chemotherapy regimens received before the initiation of palbociclib as the first endocrine-based therapy in treatment of metastatic disease.
  - Systemic endocrine/target therapy regimens other than palbociclib in treatment of metastatic disease

- **CBC monitoring patterns (if data are sufficient)**
  - Number of CBC assessments in the first two, four and six treatment cycles, respectively.

- **Clinical effectiveness outcomes**
  - Progression or death at specific time points (eg, 12, 18 and 24 months post initiation of palbociclib treatment)
  - Response rates
  - Overall survival at various time points (eg, 12,18 and 24 months) post initiation of palbociclib treatment

8.4. Data Sources

Flatiron Health network covers more than 255 community-based cancer clinics and 3 academic cancer centers, over 2330 clinicians, and 1.1 million active cancer patients. The Flatiron EHRs include the entire patient chart of all patients treated in the Flatiron network.

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. Flatiron accesses both 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) as well as unstructured data (ie, information that is not organized in a preexisting data model, such as free text from a physician note or a portable document format [PDF] laboratory report). The data used in this study include both structured and unstructured data in an electronic database.

8.5. Study Size

This is a descriptive study and sample size and power calculations are not applicable. All eligible breast cancer patients during the study period who initiated palbociclib on or after 03 February 2015 will be included in the analysis. According to a preliminary feasibility assessment, the number of eligible patients who were treated with palbociclib as the first endocrine-based therapy in metastatic setting is over 500 patients, and the number of patients with disease progression who were treated with palbociclib in a later line setting is over 500 patients.

8.6. Data Management

De-identified data are prepared by Flatiron and transferred securely to Pfizer in a standard flat file format. 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"). All data are stored and backed up on Flatiron's servers for at least 7 years.

8.7. Data Analysis

The main objective of this study is to describe patient demographics, clinical characteristics, treatment patterns and clinical effectiveness outcomes among a cohort of HR+ HER2- advanced or metastatic breast cancer patients who initiated palbociclib. Depending on data sufficiency, the CBC monitoring pattern may also be described. All analyses will be descriptive in nature and no statistical tests of hypotheses will be performed. Other systemic treatments (chemotherapy, other endocrine therapy) in metastatic setting may also be described in a subgroup of patients who have at least 6 months follow-up after initiation of palbociclib.

Patient demographics, clinical characteristics and/or treatment patterns will be presented for all patients and will be explored by line of therapy (provided data are sufficient). Descriptive statistics will be reported for continuous variables (eg, age, time from initial breast cancer diagnosis to metastatic diagnosis) using the mean, median, 25th and 75th quantiles, minimum, maximum, and standard deviation. Categorical variables (eg, region, stage at

initial diagnosis) will be reported using frequencies and proportions. The calculation of percentages will always include the missing category in the case of missing values. Counts of missing observations will thus be included in the denominator and presented as a separate category. Kaplan-Meier figures will be generated for "time to" variables and related statistics will be reported.

Exploratory propensity matched cohort comparison will be conducted between palbociclib plus aromatase inhibitor combination and aromatase inhibitor treatment monotherapy using Kaplan Meier analyses, stratified by line of treatment (eg, 1st line, 2nd or later endocrine based therapy). The main variables used for propensity score matching will be age, ECOG, days since diagnoses, line of therapy, number of metastatic sites and presence of visceral metastases.

8.8. Quality Control

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. These QC standards cover themes such as demographics, biomarkers, treatment, therapy shares, and treatment length/dosage, and include both medical considerations (eg, what are expected based on the literature and clinical practice) and data considerations (eg, stability from prior months). Issues identified are methodically logged, prioritized, investigated and resolved. Substantive issues are discussed by the team and a mitigation plan is developed. Any quality concerns and the approaches taken to rectify them will be communicated to the sponsor. All data undergo statistical review prior to locking the data. Statistical review includes: error log search, warning evaluation, logic and critical steps and macro usage. Queries generated are forwarded to the medical lead of the project and resolved prior to the data being locked.

8.9. Limitations of the Research Methods

One of the main challenges of EHR data is the potential for missing, inaccurate or incomplete data. Eg, EHR contains only that a physician prescribed a drug but not whether or not it was filled/refilled. In addition, the quality of information extracted from the EHR depends on the quality of information entered into the EHR by the clinician. Finally, 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 (refer to Flatiron parent protocol).

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where

required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

Informed consent is not required for this study as it is the secondary use of the existing health records and the data are de-identified. There will be no direct involvement of patients and patients will receive no direct benefit from participating in the study.

9.2. Patient Withdrawal

Not applicable.

9.3. 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. There are no known risks to the patients beyond the potential of loss of confidentiality; all precautions will be maintained to protect patient confidentiality and PHI as outlined in the parent protocol, NEIRB#15-159.

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (eg, recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

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 research practices described in Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study uses existing health care databases, in which it is generally not possible to link (i.e., 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 reviewer is 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 the 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.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study are not part of any planned regulatory submission. The results of this study may be submitted for abstracts and publications. The final output will be filed in Pfizer's Global Document Management System (GDMS) upon final study completion.

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 which 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.

12. REFERENCES

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2. Dawood S, Broglio K, Ensor J, et al. Survival differences among women with de novo stage IV and relapsed breast cancer. Ann Oncol 2010;21(11):2169-74.
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5. Flatiron Health Data, New York, NY (28 February 2017).
6. Turner NC, Ro J, André F, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015 Jul 16;373(3):209-19.

13. LIST OF TABLES

NONE

14. LIST OF FIGURES

NONE

15. APPENDIX

Appendix 1. List of Medications For The Treatment Of HR+/HER2- Metastatic Breast Cancer

Drug Name	Brand Name	HCPCS Code
Endocrine therapy		
Anastrozole	Arimidex	S0170
Exemestane	Aromasin	S0156
Fulvesterant	Faslodex	J9395
Letrozole	Femara	N/A
Megestrol acetate	Megace	S0179
Raloxifene	Evista	N/A
Tamoxifen	Nolvadex	G8376, G8380, G8381, S0187
Toremifene	Fareston	N/A
Palbociclib	Ibrance	N/A
Target therapy		
Everolimus	Afinitor	J7527, J8561
Chemotherapy		
Capecitabine	Xeloda	J8520, J8521
Cyclophosphamide	Cytoxan	• 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 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	No code specific to Abraxane
Paclitaxel	Taxol	• C9127 - paclitaxel (2) *(HCPCS Procedure Drug)* • C9431 - paclitaxel (2) *(HCPCS Procedure Drug)* • 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	• 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	• 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	• C9280 - Injection, eribulin mesylate (2) *(HCPCS Procedure Drug)* • J9179 - Eribulin mesylate injection (2) *(HCPCS Procedure Drug)*
Gemcitabine	Gemzar	J9201
Ixabepilone	Ixempra	J9207
5-fluorouracil	Adrucil	J9190
Epirubicin	Pharmorubicin	J9178
Vinorelabine	Navlabine	J9390
Methotrexate		J8610, J9250, J9260,
Mitomycin		J9280
Mitoxantrone	Novantrone	J9293