Study Information

Title	Real-World Treatment Patterns and Outcomes in Postmenopausal, Hormone-Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative, Metastatic Breast Cancer Patients Treated with Palbociclib Plus an Letrozole as Initial Endocrine Therapy at Community Oncology Practices in the U.S.
Protocol number	A5481123
Protocol version identifier	1.0
Date	20 November 2018
Active substance	Palbociclib/PD332,991
Medicinal product	Palbociclib
Research question and objectives	**Objectives** Among postmenopausal women receiving palbociclib plus letrozole (palbociclib+LET) as initial endocrine therapy for hormone-receptor positive, human epidermal growth factor receptor 2 negative, advanced/metastatic breast cancer: 1. Describe the demographic and clinical characteristics of patients at the initiation of treatment. 2. Describe the frequency of laboratory monitoring for hematologic and cardiovascular toxicities during treatment. 3. Describe treatment patterns in terms of palbociclib+LET dosing, cycles received, and post-discontinuation treatment regimens. 4. Describe clinical outcomes in terms of objective disease response rates and progression-free survival during treatment.

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AEM	Adverse event monitoring
AI	Aromatase inhibitor
CBC	Complete blood count
CBR	Clinical benefit rate
CR	Complete response
CRF	Case report form
DOT	Duration of treatment
ECOG-PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic case report form
EMR	Electronic medical record
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HR	Hormone receptor
HR	Hazard ratio
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LET	Letrozole
MBC	Metastatic breast cancer
NE	Not evaluated
NIS	Non-interventional study
OPEN	Oncology Provider Extended Network
ORR	Objective response rate
PD	Progressive disease
PFS	Progression-free survival
PHI	Protected health information
PR	Partial response
PR	Progesterone receptor
RCT	Randomized controlled trial
SAP	Statistical analysis plan
SD	Stable disease

2. RESPONSIBLE PARTIES

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3. ABSTRACT

Title: Real-World Treatment Patterns and Outcomes Postmenopausal, Hormone-Receptor Positive (HR-positive), Human Epidermal Growth Factor Receptor 2 Negative (HER2-Negative), Metastatic Breast Cancer (MBC) Patients Treated with Palbociclib Plus Letrozole (Palbociclib+LET) as Initial Endocrine Therapy at Community Oncology Practices in the U.S.

Rationale and Background: Real-world research describing the demographic and clinical profile of patients, treatment patterns, and clinical benefit of palbociclib+LET as initial endocrine therapy for postmenopausal, HR-positive, HER2-negative MBC has been limited by small patient cohorts and short durations of follow-up. Similarly little is known regarding the profile of patients being prescribed newer agents such as ribociclib or what drives the continued use of aromatase inhibitor (AI) monotherapy as initial endocrine therapy for MBC with the availability of the cyclin-dependent kinase (CDK) 4/6 agents.

Research Question and Objectives: This study aims to describe demographics, clinical characteristics, toxicity monitoring, treatment patterns and clinical outcomes across a geographically diverse, representative cohort of MBC patients receiving palbociclib+LET according to its labeled indication at U.S. community oncology practices.

Objectives

Among postmenopausal women receiving palbociclib+LET as initial endocrine therapy for HR-positive, HER2-negative, MBC:

1. Describe demographic and clinical characteristics of patients at the initiation of treatment.

2. Describe the frequency of laboratory monitoring for hematologic and cardiovascular toxicities during treatment.

3. Describe treatment patterns in terms of palbociclib+LET dosing, cycles received, and post-discontinuation treatment regimens.

4. Describe clinical outcomes in terms of objective response rates (ORR), progression-free survival (PFS) during treatment and survival.

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Study Design: This will be a retrospective, observational study with all data used having been collected as a routine part of clinical care. Providers will identify patients meeting the study selection criteria. Providers will be recruited to participate from the Cardinal Health Oncology Provider Extended Network, a community of over 7,000 clinical personnel treating cancer patients in the U.S. Providers who indicated treating patients of interest during a prior feasibility assessment will be asked to participate in the research. Providers will abstract data from his/her patients' medical records into an electronic case report form. Cardinal Health will conduct data verification via telephone and electronic follow-up with providers.

Population: The study will include adult female patients with HR-positive/HER2-negative MBC who were treated with palbociclib+LET as initial endocrine therapy on or after 03 February 2015. Providers will randomly select cases beginning with the earliest palbociclib+LET treated patient at least 3 months following the providers' first use of palbociclib.

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Variables: Patient demographics, clinical characteristics, treatments, complete blood count (CBC)/cardiac toxicity monitoring patterns, and clinical outcomes will be collected and analyzed.

Data Source: All data will be collected by the patients' treating physician and entered into the eCRF.

Study Size: This is a descriptive study and sample size calculation is not applicable. The target sample size of female, adult, HR-positive, HER2-negative MBC patients receiving initial endocrine therapy with palbociclib+LET is 200.

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Data Analysis: Descriptive analysis will be conducted to describe patient demographics, clinical characteristics, treatment and monitoring patterns, and clinical outcomes. For PFS and other time to event analyses, Kaplan-Meier methods will be used estimate the time to event accounting for right-censoring.

Milestones:

- Start of data collection: Q1 2019.
- Final study report: Q2 2019.

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason

5. MILESTONES

Milestone	Planned date
Project kickoff	30 May 2018
Study protocol development	Q3-Q4 2018
Study protocol finalization/approval	Q4 2018
Statistical analysis plan (SAP) & table shells	Q3-Q4 2018
SAP & table shells finalization/approval	Q4 2018
Case report form (CRF) development	Q4 2018
CRF finalization/approval	Q4 2018
Institutional review board preparation/submission/approval	Q4 2018
Electronic CRF (eCRF) programming & testing	Q4 2018
eCRF pre-test (n=4)	Q4 2018
Recruitment & data collection – Phase 1	Q1 2019
Interim report	Q1 2019
Recruitment & data collection – Phase 2	Q2 2019
Final results	Q2 2019
Final study report	Q2 2019

6. RATIONALE AND BACKGROUND

Palbociclib is approved for the treatment of HR-positive, HER2-negative MBC in combination with an AI as initial endocrine based therapy in postmenopausal women or in combination with fulvestrant in women with disease progression following endocrine therapy.[1] Approval was based on the randomized phase II PALOMA-1 trial, which demonstrated that the addition of palbociclib to letrozole significantly improved PFS in patients with advanced estrogen receptor positive (ER-positive)/HER2-negaive MBC (median PFS, 20.2 months vs. 10.2 months; hazard ratio [HR]=0.448; *P*=0.0004).[2] Palbociclib in combination with fulvestrant was approved one year later (February 2016) in pre- or postmenopausal women with disease progression following endocrine therapy based on results from the PALOMA-3 randomized controlled trial (RCT).[3] In the phase III RCT, PALOMA-2, the findings of PALOMA-1 were confirmed. The median PFS estimate in the palbociclib+LET arm was 24.8 months compared to 14.5 months in the placebo plus letrozole arm (HR=0.58; P<0.001).[4]

Since the initial approval of palbociclib in February 2015, real-world observational studies have described treatment patterns, dose modifications, and tolerability using multiple distinct retrospective databases.[5-8] Estimates of the clinical benefit (partial response or better as reported by the treating provider) of palbociclib+LET presented in early 2018 were markedly similar ranging from 79.5% to 83.5%.[6,8] Landmark PFS analysis varied between the two studies ranging from 80.0% to 96.7% at 6 months, 67.1% to 84.1% at 12 months, and 54.7% to 69.3% at 18 months.[6,8] A 24-month estimate was available from one study (reported the higher estimates at each of the 6-, 12-, and 18-month interval previously referenced), which found 64.3% of patients were progression-free at 24 months. With an additional year of real-world experience accrued since the time of data collection for these studies, more precise estimates of disease response and PFS are available.

The prior research was not statistically powered to compare outcomes between palbociclib-treated patients to those who received LET monotherapy. A large proportion of female HR-positive/HER2-negative MBC continue to be prescribed AI monotherapy in lieu of the results of the PALOMA trials.[9] Moreover, recently published research indicates a higher rate of discontinuation (45.8% vs. 34.5%) for women prescribed AI-monotherapy.[9] The differences in the demographic and clinical disease characteristics of women receiving first-line treatment with LET versus those prescribed palbociclib+LET have not been explored nor have clinical outcomes between them been compared. Additionally, since the completion of the previously described real-world research ribociclib was approved in same indication as palbociclib in March of 2017 (in combination with an AI as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive/HER2-negative MBC).[10] No real-world data on clinical characteristics, treatment patterns (including dose reductions and rates of discontinuation), or early estimates of rates of progression have been explored in a real-world cohort of ribociclib+AI treated patients. Further exploration of treatment patterns and clinical outcomes in terms of rates of progression, which patients receive LET or ribociclib+AI, and the outcomes of this treatment is needed to understand the types of patients most likely to benefit from palbociclib+LET in the indicated population.

7. RESEARCH QUESTION AND OBJECTIVES

The main objective of this study is to describe patient demographics, clinical characteristics, toxicity monitoring, treatment patterns and clinical outcomes among postmenopausal, female, HR-positive, HER2-negative, MBC patients receiving palbociclib+LET as initial endocrine therapy. Demographic and clinical characteristics and outcomes will be presented overall, and among groups for the following three planned primary grouping variables:

1. Visceral vs. non-visceral at the initiation of initial endocrine therapy for MBC.

2. Received prior neo/adjuvant endocrine therapy versus no prior neo/adjuvant therapy.

3. De novo metastatic disease versus ≤12 months disease free interval since prior neo/adjuvant treatment versus >12 months disease free interval since prior neo/adjuvant treatment.

7.1. Objectives

Among MBC patients receiving palbociclib+LET according to its labeled indication as initial endocrine therapy for MBC the research objectives are to:

1. Describe the demographic and clinical characteristics of patients at the initiation of treatment:

    a. Demographic characteristics will include age, race/ethnicity, body mass index, insurance status, state of residence at the date of MBC diagnosis and palbociclib initiation. Employment status will be assessed to the extent documented in the record. Overall duration of follow-up (months) from the initiation of palbociclib+LET will be presented.

    b. Clinical characteristics will include year of breast cancer and MBC diagnosis, stage of initial diagnosis, menopausal status, number and sites of distant metastasis at MBC diagnosis and palbociclib initiation, verification of HER2 and ER/progesterone receptor (PR) status, histology, menopausal status at palbociclib+LET initiation, performance status and comorbid disease burden, including cardiovascular-related comorbidities (at MBC diagnosis and at palbociclib initiation), and modalities of treatment received in the neoadjuvant or adjuvant setting (chemotherapy, hormone therapy, surgery, radiation therapy).

2. Describe the frequency of laboratory monitoring for hematologic and cardiovascular toxicities during treatment:

    a. Note that CBC monitoring and cardiac function monitoring will be assessed, but lab results/values will not be assessed under this objective.

b. Evaluate the extent of laboratory monitoring using CBC per cycle:

   i. The frequency of assessment of CBC with or without differential will be evaluated during the initial endocrine-based therapy for MBC.

c. Assess the frequency of cardiac toxicity monitoring using electrocardiogram, liver function panels, and electrolytes:

   i. The frequency of assessment of cardiac monitoring by each method will be evaluated during the initial endocrine-based therapy for MBC.

3. Describe treatment patterns in terms of palbociclib+LET dosing, cycles received, and post-discontinuation treatment regimens:

   a. Palbociclib dosing will include description of the starting dose, dose adjustment, discontinuation, and time to dose adjustment for palbociclib.

   b. Duration of palbociclib in terms of the number of cycles completed prior to the discontinuation of initial treatment for MBC.

   c. Treatment patterns includes the distribution of regimens administered, by line, from MBC diagnosis through the end of the medical record.

   d. Treatment patterns also includes the sequence of treatments across lines, from MBC diagnosis through the end of the medical record.

4. Describe clinical outcomes in terms of objective disease response rates and progression-free survival during treatment:

   a. Describe the rate of objective disease response during initial endocrine-based therapy:

      i. Tumor response will be classified per provider report for each regimen received during MBC treatment.

      ii. Tumor response will be classified under a primary response classification as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and unknown/not evaluated (NE).

      iii. Tumor response will be classified under a secondary response classification as matching the primary classification, but patients with NE responses classifiable as Other Favorable or Other Unfavorable so classified.

   b. Describe progression-free survival and/or time to progression from the initiation of initial endocrine-based therapy:

      i. Landmark PFS and/or rate of progression at 3, 6, 12, 18, and 24 months.

      ii. Proportion alive at 6, 12 and 24 months.

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8. RESEARCH METHODS

8.1. Study Design

The current study will be conducted as a retrospective observational cohort study using a chart review methodology. Providers in the Cardinal Health Oncology Provider Extended Network (OPEN) will be recruited to participate in the patient identification and data abstraction for this research study. All study data are secondary data and will have been collected retrospectively from existing clinical data originally collected as part of routine care.

Patient eligibility will be confirmed by the treating physician. Providers will abstract the patient level data necessary to achieve the research objectives into an electronic case report form (eCRF). Providers may complete a maximum of 20 eCRFs; verification of submitted data will be performed by Cardinal Health Clinical Research Operations via clinical data quality review of submitted eCRFs (further description of data verification processes are provided in Section 8.8). In order to achieve the research objectives related to the estimation of a 24-month PFS, providers will be asked to select consecutive patients starting with the earliest patient treated with palbociclib+LET meeting all the study eligibility requirements (See Section 7.2). In addition, providers will be asked to consider the "earliest" palbociclib+LET treated patient as the first patient treated 60 days after the first instance they prescribed palbociclib+LET in clinical practice outside of a clinical trial. In total up to 200 patients treated with palbociclib+LET per labeled indication will be identified.

8.2. Setting

Providers from OPEN will identify patients meeting the study selection criteria. OPEN is a community of over 7,000 oncologists, hematologists and urologists providing care to cancer patients geographically distributed across the U.S. and practicing in both community and academic research settings. OPEN community members include medical doctors, nurse practitioners, pharmacists and other individuals providing care to cancer patients. Community members are not limited to any specific group purchasing organization or any other membership requirements. Community members are included in OPEN if they and their practice utilizes Cardinal Health's proprietary Point-of-Care claims remittance software for practice management purposes or if they have participated in Cardinal Health sponsored research activities. Providers within the OPEN database are evenly distributed between regions (Northeast, Midwest, South and West regions) across different size practices (small, medium or large practice) and years of experience in providing cancer care.

To be eligible for participation in this research study, a physician must have treated or be treating two or more HR-positive/HER2-negatie MBC patients who meet the eligibility criteria for the study. Providers who responded to the initial feasibility survey will be the first set of physicians asked to participate in the research. Should further recruitment be required to achieve the desired sample size Cardinal Health will recruit from its entire database of providers.

Providers will be allowed to complete up to 20 eCRFs. Providers will be asked to indicate the number of patients considered eligible for the research but for whom records were not entered. No data for the patients not entered into the eCRF will be collected. Providers must also be able to participate in the research monitored by a central Institutional Review Board (IRB). No site specific IRB approval will be sought and providers requiring this approval will not be eligible.

After IRB approval of the research protocol, the eCRF will be pre-tested with 4 providers; data collected as part of the pre-test will not be used in the final analytical dataset. After testing and revisions (if necessary), providers who completed a feasibility assessment for the research will be contacted and asked to participate in the research. Data collection will be conducted over the course of 4-weeks. Providers are compensated at fair market value for each completed and verified eCRF assuming a rate of payment based on one hour of data collection (see Section 8.6.1).

8.2.1. Inclusion Criteria

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

1. Diagnosed with locoregional recurrent or metastatic female breast cancer.

2. Pathologically confirmed HR-positive/HER2-negative diagnosis.

3. Received treatment with palbociclib in combination with letrozole as initial endocrine-based therapy for advanced/metastatic breast cancer:

    a. Initiated treatment with palbociclib at least 3 months following the provider's first use of palbociclib following its FDA approval.

    b. At least 1 month of follow-up (at least one visit with the provider) after initiation of palbociclib.

4. Postmenopausal (or receiving surgical or medical treatment to induce menopause) at the time of initiation of palbociclib.

5. ≥18 year old at initiation of palbociclib.

8.2.2. Exclusion Criteria

No exclusion criteria will be imposed for the selection of patients.[i]

8.3. Variables

For purposes of this study, a regimen will be defined as one or more anti-cancer agents given in combination, over a period of time. Providers will be informed as to the definition of a regimen *but will make the determination themselves as to what constituted a line of therapy in the advanced/metastatic setting*. However, re-assignment of the lines of therapy in the metastatic setting may occur during data analysis based on the dates regimens were initiated and discontinued and the rationale for that discontinuation. For example a patient treated with palbociclib+LET who discontinued palbociclib but continued with LET may be indicated as a single line by the provider but the use of LET monotherapy may be recoded as a subsequent line of therapy during the analysis phase. All dates of initiation and discontinuation of individual agents when received in combination will be abstracted by the patient's treating physician.

Additionally, disease progression is taken to have occurred when a pathology report or radiological scan note indicates disease progression and/or there is a physician progress note consistent with that determination. Providers will be informed of these criteria and indicate the date of disease progression as recorded in the patient charts during initial endocrine therapy for MBC following that guidance.

The table below describes data elements to be abstracted by the provider ("Abstracted Data Points") and independent/exposure variables calculated from the abstracted data ("Calculated Variables").

Variable	Operational definition
Patient demographics	**Abstracted Data Points:** Year of birth, payer, state of residence, ethnicity, weight, height, ER status, PR status, HER2 status, family history of breast cancer. **Calculated Variables:** age at advanced/metastatic diagnosis, age at initiation of endocrine-based therapy, body mass index.
Clinical characteristics	**Abstracted Data Elements:** date of initial breast cancer diagnosis, date of diagnosis of advanced/metastatic disease, AJCC stage, node status, menopause status, ECOG-PS (@ treatment for advanced/metastatic disease), sites of metastatic disease (@ initiation of treatment for advanced/metastatic disease), comorbidities (@ initiation of treatment for advanced/metastatic disease. **Calculated Variables:** time to advanced/metastatic disease, Charlson comorbidity index.

[i] Participation in any interventional clinical trials following the diagnosis of metastatic or locoregionally advanced breast cancer will be flagged for further evaluation.

Variable	Operational definition
Neo/adjuvant treatment history	**Abstracted Data Elements:** chemotherapy/hormonal therapy regimens received, date of discontinuation of adjuvant treatment, type of surgery, receipt of radiotherapy. **Calculated Variables:** disease free interval (time from discontinuation of adjuvant therapy to diagnosis of advanced/metastatic disease).
Initial endocrine-based therapy treatment characteristics	**Abstracted Data Elements:** Drug and/or combination endocrine partner, date of initiation, date of discontinuation, total number of cycles received, dose at initiation, dose reductions, dose increases, rationale for dose increase/decrease, treatment interruptions (eg, drug holiday), rationale for treatment discontinuation (eg, progression, toxicity, patient choice). **Calculated Variables:** duration of treatment (DOT) with initial endocrine-based therapy.
Initial endocrine-based therapy laboratory monitoring	**Abstracted Data Elements:** Frequency of CBC monitoring, dates of CBC monitoring during first 6 cycles of therapy, dates of cardiac monitoring using electrolyte panel, liver function panel, electrocardiogram. **Calculated Variables:** None.
Clinical outcomes during initial endocrine-based therapy	**Abstracted Data Elements:** provider assessed response to therapy (CR, PR, SD, PD), date of best initial response (CR, PR, SD), date of disease progression, stable disease lasting >24 weeks, favorable/unfavorable response (if stable), development of new measurable target lesions since initiation of endocrine-based therapy. **Calculated Variables:** visceral disease at initiation of endocrine-based therapy, duration of stable disease, ORR (CR+PR+SD lasting greater than 24 weeks).
Advanced/metastatic treatment patterns following discontinuation of initial endocrine-based therapy	**Abstracted Data Elements:** drug regimens received post discontinuation of initial endocrine-based therapy (chemotherapy, switch to alternative endocrine), date of initiation and discontinuation of treatment regimens received. **Calculated Variables:** total lines of therapy received in the metastatic setting.
Status at last follow-up	**Abstracted Data Elements:** date of last follow-up, receipt of hospice care, receipt of palliative care, date of death (if deceased), cause of death. **Calculated Variables:** None.

8.4. Data Sources

Providers will complete data abstraction into the eCRF using all structured and unstructured data, including laboratory, pathology, and radiology files from the selected patients' electronic health records.

8.5. Study Size

To ensure sufficient patients treated with palbociclib+LET could be identified a feasibility assessment was conducted. A random sample of providers in the OPEN database were queried in March 2018 to determine the number of potential patients' eligible for the research. Among the 51 physicians who responded, 44 (86%) reported treating a total of 804 HR-positive/HER2-negative MBC patients with palbociclib+LET in the past year. Among those 804 patients treated with palbociclib combination therapy in the past year, 126 achieved CR, 340 achieved PR, 232 achieved SD, 95 achieved PD, and 11 were missing response documentation. Based on the results of this query, it is estimated that Cardinal Health through OPEN will be able to identify 200 patients treated with palbociclib+LET, CCI for the study cohort.

8.6. Data Management

All study data will be entered into the eCRF. The eCRF is designed to allow providers to efficiently move through the patient chart or electronic medical record (EMR) based on the journey of the patient through the course of their disease. The eCRF conforms to the rules and regulations of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 governing the abstraction and storage of protected health information (PHI). No protected health information will be collected in the course of the chart review or stored in the eCRF.

Physicians will be compensated through an honoraria payment for each completed and validated eCRF. The eCRF is anticipated to take up to 45 minutes per patient to complete, and the rate of payment to providers for participation in this study is $300/completed and validated eCRF. Participating physicians will be asked to complete the chart review individually, meaning that site research staff or supportive staff will not complete any data abstraction.

Cardinal Health will be responsible for the programming, testing, and hosting of data from submitted eCRFs. Providers will access the eCRF through a secure web-based portal, including during the field testing procedures, with all data stored on encrypted, password protected and HIPAA compliant servers housed within the Cardinal Health electronic data storage infrastructure. Cardinal Health will perform extensive testing of the eCRF to ensure functionality across web-based user environments, looping logic to ensure proper alignment of data-related fields (required responses to certain fields prior to entering data into subsequent field), and other programmatic checks to ensure the reduction of the input of erroneous data (such as specifying maximums for year of birth or initiation of first-line treatment within the dates of the enrollment period). In addition, the eCRF will be field-tested among 4 providers to ensure its functionality, the correct interpretation of the questions in relation to the data points of interest, and the length of time required for

completion for a single patient. The pre-test results will be reviewed by Pfizer with Cardinal Health staff; however, Pfizer will not have access to the individual data collected. Any changes made to the eCRF document as a result of the pre-test will require the resubmission of the eCRF and study protocol to the IRB.

8.6.1. Case Report Forms (CRFs)/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. Cardinal Health shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

Cardinal Health has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by an authorized staff member of Cardinal Health to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at Cardinal Health and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

8.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Cardinal Health agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by Cardinal Heath according to local regulations or as specified in the vendor study contract whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If Cardinal Health 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, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

8.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Beyond the variables described in Section 8.3, non time-to-event clinical outcomes of interest include the ORR and clinical benefit rate (CBR) (CR+PR+SD lasting >24 weeks). The ORR and CBR will be evaluated according the provider assessed response to therapy. Additionally, providers will also enter the data of disease progression into the eCRF (or discontinuation due to toxicity or other rationale) as reported in the patient charts. PFS and/or time to progression will be assessed at 6-, 12-, 18-, and 24-month following the initiation of therapy (survival rates will also be reported separately).

All categorical or numeric non time-to-event variables collected from the chart data abstraction or calculated from said data will analyzed using descriptive statistical techniques. For numeric variables, the mean, standard deviation, median, and minimum/maximum will be calculated as appropriate. For categorical variables, frequencies and percentages will be provided. The number of missing or unknown observations will be described for both categorical and numeric variables. The 95% confidence internals will be provided as a measure of estimated precision when appropriate. Comparisons of categorical variable will be made using Chi-square tests (or Fisher exact test) while the student's T-test (or Wilcoxon rank-sum test), F-test or other non-parametric equivalent test will be used to compare values for numeric variables. Statistical significance will be determined using a two-sided α=0.05. For univariate comparisons of proportions, any analysis resulting in less than 5 individuals in any cell will not be performed. Similarly, the minimum number of patients to conduct an analysis comparing means of some continuous variable is 30 patients.

Survival analysis, also called time to event analysis, will be used in the current research to describe duration of stable disease, time to disease progression, and PFS. This method of analysis is employed when non-informative right-censoring of observed time-to-event occurs, as is the case for this study since not all patients will have progressed by the end of the study period, the Kaplan-Meier method (product limit estimator) will be used to generate median estimates of time to events if median time is reached within the population and survival curves will also be generated. In addition to calculating the median survival estimate, the life-table method will be used to estimate progression free rates and PFS at 6-, 12-, 18-, and 24-month following initiation of endocrine-based therapy in the metastatic setting.

8.8. Quality Control

During data collection, Cardinal Health's clinical research staff will review all submitted eCRFs for quality control. Cardinal Health's clinical research team will inspect each submitted eCRF for implausible dates (ie, date of death prior to last date of treatment), non-standard treatments, lab and radiology results which are inconsistent with known clinical parameters, or other clinical data which is inconsistent with known standards and outcomes. Should these items be discovered, Cardinal Health's clinical research team will contact the provider submitting the eCRF for data verification. All providers are informed in their contractual agreement that follow-up with clinical staff at Cardinal Health may be required. Participating providers are asked to create a 4-digit unique identifier code per patient which is provided to Cardinal Health through the eCRF and used for identifying the patient record for verification between Cardinal Health and the provider.

In addition to review of the submitted data by the clinical research team, the study statistician will conduct an analysis of submitted data to identify any data points which are inconsistent (outliers) with the study population average. This analysis will include a descriptive analysis of the provider characteristics, demographics, baseline clinical and disease characteristics, and characteristics of treatment patterns (eg, DOT). Data points flagged as outliers will be delivered to the clinical research team who will contact providers to validate data as previously described.

8.9. Limitations of the Research Methods

The key limitation of this research and research of this nature involving retrospective medical chart review abstraction by a patient's treating providers is the reliance on the provider to accurately complete the eCRF. In order to ensure clarity and consistency in reporting, the eCRF will be internally and externally pre-tested. In addition, clinical data quality review will be conducted for each eCRF and invalid or outlier data will be flagged for further review with the treating clinician by Cardinal Health clinical research staff.

Several other limitations impact the external generalizability the results of this retrospective cohort study. Given that providers abstract data on selected patients there is an opportunity for the following to occur: (1) provider selection bias; (2) patient selection bias; (3) and information bias, related to the availability and quality of data contained within the patient charts.

In terms of the representativeness of the provider cohort by imposing a maximum number of eCRFs which can be completed this bias is reduced. With a maximum of 20 eCRFs, the minimum number of providers participating is 30. While the number of providers to be recruited is not specified, not all providers will submit the maximum number of patients. In past research of this nature, the median number of eCRFs submitted per provider is 10. Based on this assessment, the expected number of providers participating is 60. Providers invited to participate but not participating in the research will not be described.

In this study, the magnitude of a patient selection bias will be assessed by quantifying the number of potentially eligible patients and the number of patients submitted for inclusion by the provider. To address this potential bias, providers may only contribute a maximum of 20 patient eCRFs, of which, no more than 10 eCRFs may be submitted for any single treatment group. Differences between providers submitting fewer than 5 versus more than 5 eCRFs may be explored to assess systematic differences and address the potential selection bias.

In regard to information bias, while providers are asked to consult all available patient records certain elements such as the pharmacy dispensing record, data may not be available directly making it possible that items such as dates of initiation and discontinuation of treatment would be less accurate compared to data obtained from an administrative claims database. Similarly, data points such as date of death will be determined based on patient records; providers are not asked to verify date of death based on the Social Security Administration or commercial entities which collect detailed death data. In all these examples, the data are assumed to be missing at random and inspection of data elements will be used to confirm this hypothesis.

There is also a risk of incomplete data as a result of variable patient follow-up with a single provider. Patients may have initiated care at another provider and transitioned to the provider or practice completing the data abstraction. Patients may also have received care from another provider within the practice at multiple points during the course of their disease management and treatment. Thus, data elements from the prior period may not be captured in the participating physician's EMR or clinical notes and providers abstracting the data may misinterpret the intent of the treating provider's notes. In this study, it is required that the patient submitted for study inclusion has been managed and or seen by the provider submitting the data or at the providers practice in order to minimize these potential biases.

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9. PROTECTION OF HUMAN SUBJECTS

All study materials, including the research protocol and paper-version of the eCRF, will be reviewed by a central IRB prior to any data abstraction including field-testing of the eCRF. Providers are required to be able to participate in research monitored by a central IRB. At all times, patients' PHI will be kept confidential in accordance with HIPAA. The eCRF will not capture any data related to the patients' name, full date of birth, social security number, health insurance plan number, medical record number, or other such PHI although PHI related to dates of treatment or clinical events will be collected. A waiver for obtaining informed consent from the provider or patient is sought for this research given the minimal risk imposed by the data elements to be collected.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology (ISPE) 2008, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines,[12] and with the ethical principles laid down in the Declaration of Helsinki.

9.1. 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.

The personal data will be stored at the study site in encrypted form and will be password protected to ensure that only authorized study staff have access. Cardinal Health 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, the study site 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, patient names will be removed and will be replaced by a single, specific, numerical code based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

9.2. Patient Consent

As this study involves anonymized structured or unstructured 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.

9.3. Patient Withdrawal

Not applicable.

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

The study will be submitted to a centralized independent IRB in the U.S. for approval of the methodological approach and for obtaining a waiver of informed consent. An exemption will be sought on the basis that the study will collect only secondary data, no PHI will be collected and all data will be de-identified.

9.5. 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 research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the ISPE, Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, and with the ethical principles laid down in the Declaration of Helsinki.

10. MANAGEMENT AND REPORTING OF ADVANCE EVENTS/ADVANCE REACTIONS

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 (AEs) 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 CRF 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 AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement “A 35-year-old female...” or “An elderly male...” Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

These trainings 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.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

11. 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.

12. REFERENCES

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13. LIST OF TABLES

None.

14. LIST OF FIGURES

None.

15. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

16. ANNEX 2. ADDITIONAL INFORMATION

Not applicable.