Study information

Title	Treatment Patterns And Clinical Outcomes Among Patients With Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer (mBC) Receiving Palbociclib in Combination with Fulvestrant (PB+FUL) In The US Community Oncology Setting
Protocol number	A5481128
Protocol version identifier	Version 2
Date	August 30, 2021
Active substance	Palbociclib (IBRANCE®; PD 0332991)
Medicinal product	Palbociclib
Research question and objectives	The following primary and secondary objectives will be assessed among all study-eligible patients who initiated first-line PB+FUL in the metastatic setting: **Primary Objectives** 1. Describe baseline patient demographic and clinical characteristics, as well as provider- and clinic-level characteristics 2. Describe treatment patterns including number of complete cycles, post-discontinuation treatment regimens and treatment initiation by quarter **Secondary Objectives** 3. Evaluate, from initiation of index treatment: o Time to chemotherapy o Reasons for treatment discontinuation o Real-world duration of therapy (rwDOT) o Time to next treatment (TTNT) o Provider-documented progression

	○ Real-world time to progression (rwTTP) ○ Real-world progression-free survival (rwPFS) ○ Overall survival (OS) CCI [redacted]
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse events
AEM	Adverse event monitoring
BC	Breast cancer
BMI	Body mass index
BOR	Best overall response
BRCA	Breast cancer gene
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CDK	Cyclin-dependent kinase
CRF	Case report form
DCT	Data collection tool
eCRF	Electronic case report form
ECOG	Eastern Cooperative Oncology Group
EHR	Electronic healthcare record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESR1	Estrogen receptor 1 gene
FDA	Food and Drug Administration
FUL	Fulvestrant
CCI	[redacted]

GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HEOR	Health Economics Outcomes Research
HER2-	Human epidermal growth factor receptor 2 negative
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health
HR	Hazard ratio
HR+	Hormone-receptor positive
ICD	International Classification of Diseases
ICMJE	International Committee of Medical Journal Editors
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IPTW	Inverse probability of treatment weighting
IRB	Institutional review board
iKM	iKnowMed
LADMF	Limited Access Death Master File
LHRH	Luteinizing hormone-releasing hormone
LOT	Line of therapy
mBC	Metastatic breast cancer
MRN	Medical record number
NCCN	National Comprehensive Cancer Network
NDI	National Death Index

NGS	Next generation sequencing
NIS	Non-interventional study
OS	Overall survival
PASS	Post-Authorization Safety Study
PB+FUL	Palbociclib combination therapy with fulvestrant cohort
PFS	Progression-free survival
QC	Quality control
RECIST	Response Evaluation Criteria In Solid Tumors
rwDOT	Real-world duration of therapy
rwPFS	Real-world progression-free survival
rwTTP	Real-world time to progression
SAP	Statistical analysis plan
SAS	Statistical analysis software
SD	Standard deviation
SEER	Surveillance Epidemiology and End Results
TNM	Tumor, Node, Metastasis
TTNT	Time to next treatment
US	United States
USON	US Oncology Network

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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PPD, MPH	Sr. Research Manager	PPD	PPD, PPD
PPD, DrPH	Sr. Director, PPD	Pfizer, Inc.	PPD, PPD

3. ABSTRACT

Title: Treatment Patterns And Clinical Outcomes Among Patients With Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer (mBC) Receiving Palbociclib in Combination with Fulvestrant (PB+FUL) In the US Community Oncology Setting

Protocol date/version: August 30, 2021/ Version 2

Primary protocol authors: PPD , MPH, PPD

Rationale and background: Palbociclib is approved in the United States (US) for the treatment of adult patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer (mBC) in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men; or fulvestrant in patients with disease progression on prior endocrine therapy. While recent real-world studies have evaluated palbociclib in combination with aromatase inhibitors, limited evidence currently exists to describe the real-world treatment patterns and outcomes of PB+FUL. By leveraging a community-based, cancer-specific electronic healthcare record for this study, we aim to provide new insights into the patients with mBC who received PB+FUL within the context of a large community oncology network and outside of an academic or clinical trial setting in the US.

Research question and objectives:
The following primary and secondary objectives will be assessed among all study-eligible patients who initiated first-line PB+FUL in the metastatic setting:

Primary Objectives

1. Describe baseline patient demographic and clinical characteristics, as well as provider- and clinic-level characteristics
2. Describe treatment patterns including number of complete cycles, post-discontinuation treatment regimens and treatment initiation by quarter

Secondary Objectives

3. Evaluate, from initiation of index treatment:
    - Time to chemotherapy
    - Reasons for treatment discontinuation
    - Real-world duration of therapy (rwDOT)
    - Time to next treatment (TTNT)
    - Provider-documented progression

- Real-world time to progression (rwTTP)
- Real-world progression-free survival (rwPFS)
- Overall survival (OS)

Study design: The is a retrospective observational cohort study to examine patient and practice-level characteristics, treatment patterns and clinical outcomes among HR+/ HER2- mBC patients treated in the US Oncology Network (USON). Patients who initiated a qualifying treatment between 01 February 2016 and 31 December 2019 will be eligible for inclusion in the study. To allow of a potential minimum follow-up period of 6 months, study-eligible patients will be followed longitudinally until 30 June 2020 last patient record or date of death, whichever occurs first.

Population: The study population will consist of patients with a diagnosis of hormone receptor-positive/human epidermal growth factor receptor 2-negative mBC who initiated PB+FUL CCI

Variables: A complete list of study variables and their associated operational definition are presented in **Table 2**.

Data sources: Structured data fields within the iKnowMed (iKM) electronic healthcare record (EHR) database will provide information needed to address most research questions. These data will be supplemented by additional unstructured data collected through chart review for a subset of the study population.

Study size: A feasibility assessment from iKM identified 783 patients who met study eligibility criteria and initiated PB+FUL and CCI . The 1035 patients who initiated PB+FUL and CCI in the first- through third-line setting were selected for chart review (633 PB+FUL and CCI). During chart review, these patients' eligibility was confirmed and some patients were disqualified. The final sample size for analysis will consist of the confirmed eligible patients

who initiated first-line PB+FUL and, CCI [redacted].

Data analysis: Descriptive analyses will be conducted to evaluate demographic, clinical and treatment characteristics of the study population, stratified by pre-specified cohorts. Time-to-event outcomes will be assessed using the Kaplan-Meier method with 95% confidence intervals (CIs) and summary tables for patients who initiated first-line PB+FUL. CCI [redacted]

Milestones: Chart review was completed December 2020. Updated descriptive analyses for the primary, secondary and CCI [redacted] are expected September 2021. Primary CCI [redacted] outcomes analyses are expected January 2022. The final study report is expected February 2022.

4. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	21 September 2020	Sections 1, 2, 3, 4, 5, 6, 7, 8, 9 and 11.	- Changed eligibility criteria to solely focus on patients who received CCI or PB+FUL (removed the cohorts focused on aromatase inhibitors alone or with palbociclib). - Revised study objectives to reflect removal of cohorts focused on aromatase inhibitors alone or with palbociclib. - Revised throughout to indicate that a structured feasibility assessment was completed, including the description of the study phases and milestones. - Updated the sample size estimates based on the structured feasibility results. - Updated references in background section. - Extended the study identification and observation periods. - Updated the eligibility criteria and variables list to reflect changes made during development of the eCRF. - Updated chart review selection criteria to reflect focus on patients who received CCI or PB+FUL in the first-through third-line setting. - Updated the description of the sources of death. - Updated the eCRF and record retention sections to reflect the Pfizer protocol template.	The strategic aim of the study has shifted to focus on patients who received CCI or PB+FUL. Additionally, the protocol was updated to reflect recent changes by the study team.
2	August 30, 2021	All	- Revised objectives to focus on patients who received first-line PB+FUL, CCI - Revised the study identification to start on 01 February 2016 and updated the attrition table accordingly. - Updated the milestone timeline to reflect completion dates of activities that have concluded and the anticipated completion dates of those that remain.	The strategic aim of the study has shifted to focus on the subset of patients who received first-line PB+FUL after 01 February 2016. Some project activities have been completed and other dates have shifted. Newly available publications were cited to strengthen the Background section. The original Pfizer study leads have transitioned off the project.

			- Updated Background section with newly published literature. - Changed the Pfizer study leads. - Removed the provider -documented response to treatment (real-world response rate) endpoint.	Removed the provider -documented response to treatment (real-world response rate) endpoint given the number of patients with non-evaluated tumor assessments.

5. MILESTONES

The table below reflects actual and planned completion dates of study milestones. Note, some milestones were completed under prior versions of this protocol.

Table 1. Study milestones

Milestone	Planned/completed date
Finalization of study protocol (version 1) and submission to the Institutional Review Board (IRB)	October 2019 (complete)
Initial structured data collection	November 2019 (complete)
Updated structured data collection	July 2020 (complete)
Start of chart review	August 2020 (complete)
End of chart review	December 2020 (complete)
Primary and secondary descriptive analyses	September 2021
CCI [redacted]	[redacted]
Unadjusted outcomes analyses	December 2021
Adjusted outcomes analyses	January 2022
Final study report	February 2022

6. RATIONALE AND BACKGROUND

Breast cancer is the most common noncutaneous cancer in the United States (US), with 279,100 new cases expected in 2020.[1] Breast cancer predominantly occurs among women, with men accounting for approximately 1% of new cases.[2] Among women diagnosed with localized or regional disease, the 5-year overall survival (OS) ranges from 85%-99%.[3] In contrast, the 5-year survival rate is 27% among women diagnosed with distant disease. Annually, over 42,000 deaths associated with breast cancer are expected in the US.[1]

For patients diagnosed with recurrent or metastatic breast cancer (mBC), treatment recommendations are guided by the presence or absence of bone metastases (visceral versus non-visceral disease), as well as patients' hormone receptor and human epidermal growth factor receptor-2 status.[4] In particular, patients who are hormone receptor-positive (estrogen receptor- and/or progesterone receptor-positive) are eligible for endocrine therapies, which have more favorable toxicity profiles than cytotoxic regimens.[5] The National Comprehensive Cancer Network (NCCN) currently provides recommendations for the following endocrine therapies among postmenopausal, human epidermal growth factor receptor 2-negative patients: aromatase inhibitors (anastrozole, letrozole and exemestane), fulvestrant (a selective estrogen receptor down-regulator) and estrogen receptor down-regulators (tamoxifen and toremifene).

Up to 50% of mBC patients treated with endocrine therapy are either initially refractory or eventually become resistant to the treatment.[6-9] To prolong the clinical benefit of these treatments, endocrine therapies can be administered in combination with cyclin-dependent kinases 4/6 (CDK 4/6) inhibitors.[4,6] CDK 4/6 inhibitors disrupt the G1 and S phases of the cell cycle and reduce cellular proliferation. The NCCN currently provides category 1 recommendations for abemaciclib, palbociclib, and ribociclib to be administered in combination with either an aromatase inhibitor or fulvestrant.[4]

Palbociclib (Ibrance®) was initially granted accelerated approval in 2015 from the US Food and Drug Administration (FDA) to be administered in combination with letrozole among treatment-naïve patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer.[10] This approval was based on results from the PALOMA-1 Phase 2 study, which demonstrated improved progression-free survival (PFS) among patients who received palbociclib plus letrozole compared to those who received letrozole alone (median PFS 20.2 versus 10.2 months; hazard ratio 0.488, 95% CI 0.319-0.748; p=0.0004).[11] The PALOMA-2 trial subsequently affirmed this advantage of palbociclib plus letrozole.[12]

In 2016, the FDA approved PB+FUL for women with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced or mBC following progression on an endocrine therapy.[13] This approval was based on the PALOMA-3 double-blind, randomized Phase 3 trial of hormone receptor-positive/human epidermal growth factor receptor 2-negative mBC who had progressed on prior endocrine therapy (n=521).[14] Median PFS was

significantly longer among patients who received PB+FUL compared to those who received FUL mono (9.5 versus 4.6 months; hazard ratio 0.46, 95% CI 0.36-0.59, p<0.0001).

Further analyses of the PALOMA-3 trial evaluated the influence baseline characteristics on OS among the patient population.[15] As reported by Rugo et al. (2021), these multivariable analyses of the PALOMA-3 trial suggested that endocrine sensitivity, non-visceral disease, lack of prior chemotherapy and ECOG performance status score of 0 influenced OS among patients with advanced breast cancer who received PB+FUL. In particular, among patients who did not receive prior chemotherapy, median OS was 3.9 months (versus 29.5 months among those who received prior chemotherapy; hazard ratio [HR] 0.91 [95% confidence interval (CI) 0.63, 1.32]).

While median PFS across the overall population was 11.2 and 4.6 months among patients who received palbociclib and placebo, respectively, Rugo et al. (2021) reported among select patient subgroups.[15,16] In all subgroups analyzed, median PFS was longer among those who received fulvestrant with palbociclib compared to those who received fulvestrant with the placebo.[15] Specifically, among patients without prior chemotherapy, median PFS was 12.9 months (95% CI 11.0, 15.0) who received palbociclib and fulvestrant, compared to 5.5 months (95% CI 3.6, 7.6) among those who received fulvestrant and the placebo (HR 0.49; 95% CI 0.37, 0.65). Likewise, among patients with prior chemotherapy, median PFS was 9.5 months (95% CI 7.3, 11.3) among those who received palbociclib and fulvestrant and 3.5 months (95% 1.9, 5.4) among those who receive fulvestrant with the placebo (HR 0.53, 95% CI 0.37, 0.77). Among those who were endocrine sensitive, median PFS was 12.0 and 4.2 months among patients who received palbociclib with fulvestrant and those who received fulvestrant with the placebo, respectively (HR 0.46; 95% CI 0.36, 0.59).

There were two studies which examined the efficacy of palbociclib + fulvestrant combination within the endocrine sensitive population. In the first study, PARSIFAL, Llombart-Cussac et al. (2020) randomly assigned treatment-naive estrogen receptor positive/HER- mBC patients who were all endocrine sensitive to receive palbociclib with fulvestrant or palbociclib with letrozole.[17] Among the 486 patients included in the study, 243 received PB+FUL and 243 received palbociclib-letrozole and baseline characteristics between the groups were similar. The median PFS durations were 27.9 months and 32.8 among the PB+FUL and palbociclib-letrozole cohorts, respectively. The difference between the groups did not demonstrate statistical advantage for PB+FUL compared to palbociclib-letrozole. The three-year OS rate was 79.4% and 77.1% among the PB+FUL and palbociclib-letrozole cohorts, respectively.

In a double-blind phase II study, FLIPPER, Albanell et al. (2020) randomly assigned postmenopausal HR+/HER2- patients with all with endocrine sensitive advanced breast cancer to first-line PB+FUL or fulvestrant-placebo.[18] Among the 189 patients included in the study, 94 received PB+FUL and 95 received fulvestrant-placebo. Patients who received PB+FUL had a longer median PFS than those who received fulvestrant-placebo (31.8 versus 22.0 months, respectively; HR 0.52; 95% CI 0.39, 0.68; p=0.002). Likewise, the overall response rates were 68.3% and 42.2% among the PB+FUL and fulvestrant-placebo cohorts, respectively.

While recent real-world studies have evaluated palbociclib in combination with aromatase inhibitors, limited evidence currently exists to describe the real-world treatment patterns and outcomes of PB+FUL or FUL mono.

The objective of this retrospective, observational cohort database study is to describe the real-world demographic, clinical and treatment characteristics, as well as clinical outcomes of hormone receptor-positive/human epidermal growth factor receptor 2-negative mBC patients treated with PB+FUL. By leveraging a community-based, cancer-specific electronic healthcare record (EHR) for this study, we aim to provide new insights into the patients with mBC who received PB+FUL within the context of a large community oncology network and outside of an academic or clinical trial setting in the US.

This non-interventional study is not designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The overall objective of this study is to understand the demographic, clinical, and treatment characteristics, as well as clinical outcomes of hormone receptor-positive/human epidermal growth factor receptor 2-negative mBC patients in the US community oncology setting.

Complete study eligibility criteria and cohort definitions are presented in **Section 8.2**. If supported by the final sample size, all study results will be stratified by the subgroups defined in **Section 8.2.4**.

The following primary and secondary objectives will be assessed among all study-eligible patients who initiated first-line PB+FUL in the metastatic setting.

7.1. Primary objectives

1. Describe baseline patient demographic and clinical characteristics, as well as provider- and clinic-level characteristics
2. Describe treatment patterns including number of complete cycles, post-discontinuation treatment regimens and treatment initiation by quarter

7.2. Secondary objectives

3. Evaluate, from initiation of index treatment:
    - Time to chemotherapy
    - Reasons for treatment discontinuation
    - Real-world duration of therapy (rwDOT)
    - Time to next treatment (TTNT)
    - Provider-documented progression
    - Real-world time to progression (rwTTP)
    - Real-world progression-free survival (rwPFS)
    - Overall survival (OS)

CCI [redacted]

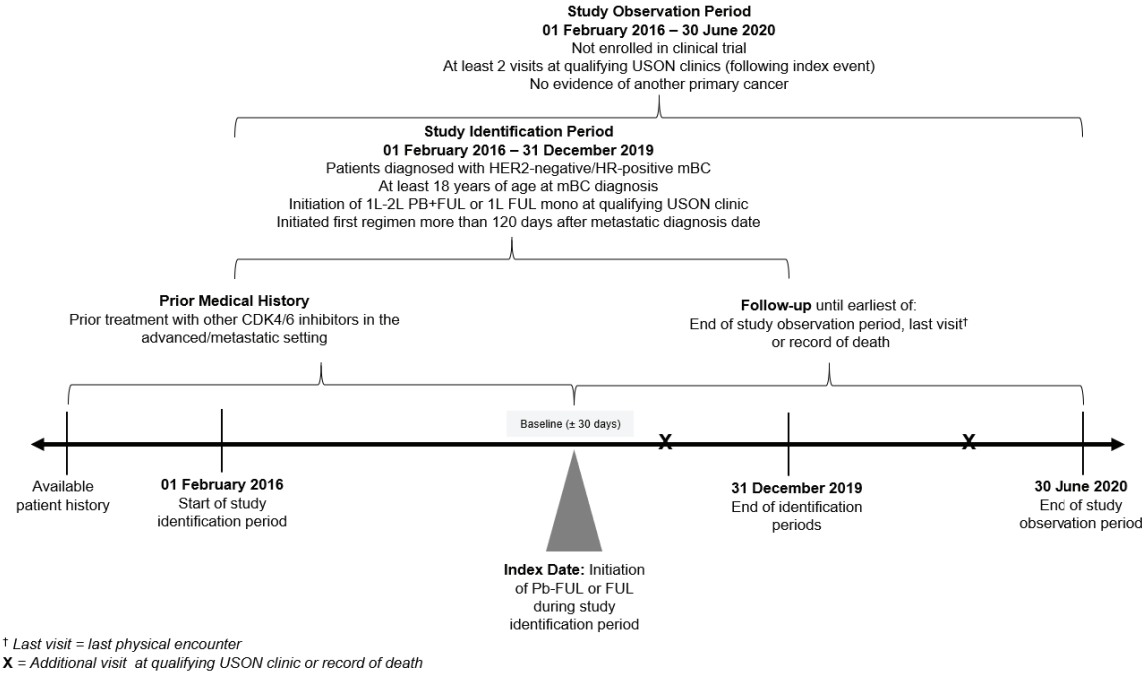
8. RESEARCH METHODS

8.1. Study design

The is a retrospective observational cohort study to examine patient and practice-level characteristics, treatment patterns and clinical outcomes among hormone receptor-positive/human epidermal growth factor receptor 2-negative mBC patients treated in the US Oncology Network (USON). Patients who initiated a qualifying treatment between 01 February 2016 and 31 December 2019 will be eligible for inclusion in the study. Complete study eligibility criteria and cohort definitions are presented in **Section 8.2**. To allow of a potential minimum follow-up period of 6 months, study-eligible patients will be followed longitudinally until 30 June 2020, last patient record or date of death, whichever occurs first.*

An overview of the study design is presented in **Figure 1**.

Figure 1. Overview of study design



* Data can be updated at a later time to extend the follow-up period through an amendment to refresh the data and revisit charts of patients who were alive at the end of the original study period. The health information available for research purposes may vary in accordance with the data rights under agreements with physician practices. Therefore, data from some practices that are part of the USON may not be available for research purposes.

A phased approach to project execution is being undertaken for this study. First, a feasibility assessment has been performed based solely on structured data to describe demographic, clinical and treatment characteristics of all patients who meet the eligibility criteria defined in **Section 8.2**. Next, chart review was performed to verify patients' eligibility and capture additional details about eligible patients. The chart review sampling method is described in **Section 8.2.4**.

Study objectives are described in **Section 7**. The primary and secondary objectives will be assessed among patients who initiated first-line PB+FUL, CCI [redacted]

A complete list of study variables and their associated operational definition are presented in **Table 2**. The clinical endpoints to be evaluated for this study include:

- Time to chemotherapy
- Reasons for treatment discontinuation
- rwDOT
- TTNT
- Provider-documented progression
- rwTTP
- rwPFS
- OS

The complete analysis plan is presented in **Section 8.7**. Descriptive analyses will be conducted to evaluate demographic, clinical and treatment characteristics of the study population, stratified by pre-specified cohorts. Time-to-event outcomes will be assessed using the Kaplan-Meier method with 95% CIs and summary tables among those who initiated first-line PB+FUL. CCI [redacted]

8.2. Setting

The study population will consist of patients with a diagnosis of hormone receptor-positive/human epidermal growth factor receptor 2-negative mBC who initiated a who initiated PB+FUL and [redacted] The USON includes 1,200 affiliated physicians operating in over 470 sites of care across states and treats approximately 1 million US cancer patients annually.[20]

Figure 1 presents a graphical depiction of the study time periods, which are as follows:

- Study observation period: 01 February 2016 – 30 June 2020.*
- Study identification period: 01 February 2016 – 31 December 2019.
- Index date: The date of initiation with PB+FUL or [redacted] during the study identification period. For PB+FUL, the date of the first administration of either drug will be used.
- Baseline: Assessment will be done for the data collected at the closest date prior to index within 30 days of index (in absolute value). Variables to be assessed at baseline are specified in **Table 2**.
- Prior medical history: Patients' available history in the iKnowMed (iKM) EHR will vary based on the length of disease and the time within the USON. The prior medical history period will end the day prior to the index date. Variables to be assessed with prior medical history are specified in **Table 2**.
- Follow-up: Patients will be followed through the end of the study observation period, date of last visit or date of death, whichever occurs first. For analysis, patients will have a potential of at least 6 months of follow-up duration; however, patients will have variable follow-up time periods, depending on their index dates and last contact dates.

8.2.1. Inclusion criteria

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

* Data can be updated at a later time to extend the follow-up period through an amendment to refresh the data and revisit charts of patients who were alive at the end of the original study period.

1) Patients with a documented diagnosis of hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive), human epidermal growth factor receptor 2-negative mBC*

2) Aged 18 years at initial recorded diagnosis of mBC

3) Initiated one of the following qualifying regimens within the USON during the study identification period:

   a) PB+FUL as first-line (for primary and secondary objectives) or CCI [redacted]

CCI [redacted]

4) Received care at a USON site(s) utilizing the full EHR capacities of iKM at the time of treatment.

5) EHR data available from the USON site(s) where the patient received treatment are accessible for research purposes.

6) During the study observation period, patients observed with at least 2 visits† after the index date.

8.2.2. Exclusion criteria

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

1) Enrollment in an interventional clinical trial during the study observation period since clinical trial participants may have clinical scenarios that deviate from the population of interest.

2) Evidence of prior treatment with CDK 4/6 inhibitors (ribociclib or abemaciclib) in the metastatic setting.

3) Receipt of treatment indicated for another primary cancer during the study observation period or history of another primary cancer within the USON iKM EHR database.

* Diagnosis of hormone receptor-positive/human epidermal growth factor receptor 2-negative breast cancer (BC) will be determined through a review of iKM's discrete diagnosis fields, which are populated during the routine course of care (International Classification of Diseases [ICD] codes will not be used). To identify patients with metastatic disease status, patients must have at least one of the following indicators: 1) receipt of a numbered LOT, 2) Stage IV disease, 3) Tumor, Node, Metastasis (TNM) staging with M value of 1, 4) record of location of metastatic disease or 5) current or prior disease status containing reference to metastatic disease.

† Visits are defined as physical encounters with the practice, detected by vital sign records. The second and third visits must be observed after the index date to demonstrate continuity of care. There is no required time span between the additional visits and the index date.

4) Initiated first treatment more than 120 days after metastatic date.

8.2.3. Cohort definitions and stratifications

Patients who meet the eligibility criteria described in **Sections 8.2.1-8.2.2** will be classified into the following cohorts described in **Section 8.1**.

As supported by the final sample size, each of the results tables and figures will be stratified to present the data for the following stratifications:

- Menopausal status (pre-, peri-, and post-menopausal) – post-menopausal only
- Metastases (visceral vs. non-visceral, bone only vs. non-bone only)
- Metastatic status (de novo versus relapsed/recurrent)
- Stage at diagnosis (I/II, III, IV or not documented)
- Number of metastatic sites (1, 2 and ≥3)
- Prior adjuvant endocrine therapy (both prior to and after metastases)
- Prior adjuvant chemotherapy (both prior to and after metastases)
- Age stratifications (e.g., 18-50, 51-69, ≥70) also <65 years and ≥65 years
- Race (White, Black, other, not documented)
- Palbociclib starting dose (75 mg, 100 mg, and 125 mg starting dose)
- Eastern Cooperative Oncology Group (ECOG) performance status score (0/1, and 2+) 90 days prior to index
- Disease-free interval from end of adjuvant treatment (< 12 months, ≥12 months)

8.2.4. Chart review selection

For an initial feasibility assessment, all patients who meet the eligibility criteria described in **Sections 8.2.1-8.2.2** were included in the interim analysis. A subset of patients (n=1035) who initiated PB+FUL and CCI in the first- through third-line setting were selected for chart review.

During the course of abstraction, patients' eligibility for the study was verified and some of these patients were found to be ineligible. Reasons for disqualification are presented.

8.3. Variables

Table 2 presents the list of variables that will be considered for this study. Most data will originate from 1 of 2 sources: the iKM EHR database (structured data) or chart review (unstructured data), although some variables may be derived from these raw data sources (e.g., age from date of birth). Derived and transformed data needed for the analysis are described and presented along with the operational definitions in the table below.

For variables that are listed as being sourced from both structured and unstructured fields, chart review is recommended and, in some cases, may be required. Specifically, many of these are variables that are available in structured fields but have been found to be more reliably and comprehensively captured through chart review of unstructured fields. Other variables require information that can only be sourced through chart review (e.g., response and progression). Data elements listed as being "not reported" will be used to determine eligibility or in calculations of derived variables.

Variables described as being captured at "baseline" will be captured at the date closest to the index date initiation within 30 days (90 days for performance status). Variables described as being captured with "prior medical history" will be sourced from patients' entire medical history within the USON prior to index treatment initiation. Other variable assessment periods are indicated below. If multiple values are available during the time period of measurement, the one closest (in absolute value) to treatment initiation will be used.

Some data elements will be captured from both iKM and chart review. Since the chart review data are expected to provide a richer source of information, if data are available from both sources for a single patient, then chart review data will supersede what is available in the structured iKM data for the final analysis.

Table 2. Study variables and operational definitions

Variable	Source(s)	Role(s) in study	Period of measurement	Operational definition
Demographic and patient characteristics				
Patient identification number	iKM structured data	Data linkage	Study observation period	Unique patient identifier that will be used to link clinical records. This information will not be disclosed to the study sponsor.
Medical record number (MRN)	iKM structured data	Data linkage	Study observation period	Unique patient identifier that will be used to link clinical records. This information will not be disclosed to the study sponsor.
Clinical trial participation	iKM structured data + chart review	Eligibility criteria	Follow-up	Patients will be confirmed as not being enrolled in interventional clinical trials (patients in only observational studies will be retained, if applicable) in the USON during the study observation period. If participation (on any trial other than observational only, if applicable) is detected, the patient will be excluded.
Other cancer diagnosis	iKM structured data + chart review	Eligibility criteria	Prior medical history + study observation period	Patients will be confirmed as having no additional primary or secondary malignancies prior to and after the index date. Patients with a secondary diagnosis or receipt of treatment indicated for another primary cancer will be excluded.
Hormone receptor status	iKM structured data + chart review	Eligibility criteria; Baseline characteristic	Prior medical history	Patients who have a documented hormone receptor-positive status, either estrogen and/or progesterone, will be included in the study. The proportions of patients who are estrogen or progesterone receptor-positive will be reported.
Human epidermal growth factor receptor 2-negative status	iKM structured data + chart review	Eligibility criteria	Prior medical history	Patients who have a documented human epidermal growth factor receptor 2-negative status will be included in the study.
Prior treatment	iKM structured data + chart review	Eligibility criteria	Prior medical history	Patients will be excluded if they have evidence of prior treatment with other CDK 4/6 inhibitors in the advanced or metastatic setting.
Additional visits	iKM structured data	Eligibility criteria	Follow-up	To capture a sample of patients with longitudinal records, patients will be required to have 2 records of either additional visits following the index date visit and/or a record of death prior to the end of the study follow-up period. Visits are defined as physical encounters with the practice, detected by vital sign records There will be no distinction made, for purposes of inclusion, between patients that have an additional USON visit and those with a record of death. There is no minimum or maximum requirement on time from index date to these qualifying events.
Sex	iKM structured data +	Baseline characteristic	Prior medical history	Patients will be categorized as: Male Female

	chart review			
Date of birth	iKM structured data	Eligibility; Data linkage; Baseline characteristic	Prior medical history	Patient's date of birth as recorded in iKM. This information will not be disclosed to the study sponsor.
Age	iKM structured data (derived)	Eligibility; Baseline characteristic	Baseline	Patient's age (in years) at the date of diagnosis, which will be calculated as the integer of [(diagnosis date – date of birth + 1) / 365.25]. Patients aged less than 18 years at the initial recorded diagnosis of mBC will be excluded from the study.
Age groups	iKM structured data (derived)	Baseline characteristic	Baseline	Multiple age categories will be created based on the continuous age data: Age (<18 years, 18-50 years, 51-70 years, ≥71 years) No information
Race	iKM structured data	Baseline characteristic	Prior medical history	Categorized as: White or Caucasian Black or African American Asian Native American Other No information The specific categories outside of White/Caucasian and Black/African American will be confirmed after reviewing sample sizes and the added value to the study with McKesson's Privacy and Compliance team.
Height	iKM structured data	Baseline characteristic	Baseline	Patient's height in meters.
Weight	iKM structured data	Baseline characteristic	Baseline	Patient's weight in kilograms.
Body mass index (BMI) at index date	iKM structured data (derived)	Baseline characteristic	Baseline	BMI = Weight (in kilograms)/(Height (in meters))^2 Based on the resulting BMI values, patients will then be categorized as underweight (BMI < 18.5), normal (BMI 18.5 – 24.9), overweight (BMI 25 – 29.9), obese (BMI ⩾ 30) or no information (missing height or weight data).
Smoking history	iKM structured data	Baseline characteristic	Baseline	Categorized as: Never smoked Current smoker Former smoker No information
Family history of cancer	Chart review	Baseline characteristic	Prior medical history	Categorized as: Yes No
Menopausal status	iKM structured data + chart review	Baseline characteristic	Baseline	Categorized as documented by physicians: Pre-menopausal Peri-menopausal Post-menopausal No information

Menopausal type	Chart review	Baseline characteristic	Prior medical history	If patients were menopausal, whether it was natural or induced and, if induced, the method (luteinizing hormone-releasing hormone [LHRH] suppression, surgical, other).
Healthcare setting and provider characteristics				
Practice location	iKM structured data (derived)	Baseline characteristic	Baseline	The US census region of the USON clinic where the patient received care at the index visit: Midwest: Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota and South Dakota Northeast: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, Pennsylvania, New Jersey and New York South: Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Washington D.C., West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma and Texas West: Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, California, Oregon and Washington State Missing clinic values will be captured in a "no information" category. Some of the regions may need to be collapsed if there are small sample sizes (e.g., South versus non-South). This determination will be confirmed after reviewing sample sizes and the added value to the study with McKesson's Privacy and Compliance team.
[redacted]	[redacted]	[redacted]	[redacted]	CCI [redacted]
Practice size	iKM structured data (derived)	Baseline characteristic	1/1/2018 – 12/31/2018	The number of patients seen at the USON clinic where the patient receive care for his/her index visit in the year 2018: <50 patients/ year 50-99 patients/year 100-149 patients/year ⩾150 patients/year
Physician BC patient volume	iKM structured data (derived)	Baseline characteristic	1/1/2018 – 12/31/2018	The number of BC patients seen by the physician who provided care for the patient's index visit in the year 2018: <10 patients/ year 11-49 patients/year > 50 patients/year
Physician specialty	iKM structured data	Baseline characteristic	Baseline	Specialty of the physician who provided care for the patient's index visit: Hematology & medical oncology Internal medicine Other

				Not documented
iKM use at practice location	iKM structured data	Eligibility criteria	Baseline	Patients who are treated at USON sites that utilize the full EHR capacities of iKM for their index visit will be eligible for participation in the study; otherwise, patients will be excluded.
Data accessibility	iKM structured data	Eligibility criteria	Baseline	Patients whose data are accessible for research purposes will be eligible for participation in the study; otherwise, patients will be excluded.
Disease characteristics				
Date of initial BC diagnosis	iKM structured data + chart review	Eligibility criteria, Baseline characteristic	Medical history prior to index	To assess BC diagnoses that occurred prior to index, patients' available medical history in iKM will searched. The completeness of this history will vary based on the length of disease and the time within the USON. Records may also be incomplete for patients with an initial BC diagnosis that occurred outside of the USON. Diagnosis of BC will be determined through a review of iKM's discrete diagnosis and histology fields, which are populated during the routine course of care (International Classification of Diseases [ICD] codes will not be used). If no initial diagnosis date is documented, the first recorded diagnosis date in iKM will be used. This date will be used in calculations, not reported separately. Patients without a recorded diagnosis of BC will be excluded from the study.
Date of mBC disease diagnosis	iKM structured data + chart review	Eligibility criteria, Baseline characteristic	Medical history prior to index	Date of first recorded diagnosis of metastatic disease within the EHR. Patients will be qualified initially based on the date identified in the structured data; this will be confirmed during chart review among patients selected for chart review. Ultimately, the primary source will be the chart if available. Patients without recorded evidence of metastatic disease will be excluded from the study. Structured data will confirm the patient as metastatic and as available, indicate the earliest associated date of any of these criteria: 1) Stage IV disease 2) Tumor, Node, Metastasis (TNM) stage with M value of 1 3) Record of location of metastatic disease 4) Current or prior disease status containing reference to metastatic disease
Time since initial BC diagnosis	iKM structured data + chart review (derived)	Baseline characteristic	Medical history prior to index	The duration of time, in weeks, between the date of BC diagnosis and presentation of metastatic disease will be calculated for each patient and summarized as the mean (± SD) and median (range) of values. The number of patients with available data will be reported.

				Date of BC diagnosis and presentation of metastatic disease will be determined as defined above.
Time since mBC diagnosis	iKM structured data + chart review (derived)	Baseline characteristic	Medical history prior to index	The duration of time, in weeks, between the index date and presentation of metastatic disease will be calculated for each patient and summarized as the mean (± SD) and median (range) of values. The number of patients with available data will be reported. Presentation of metastatic disease will be determined as defined above.
Distant metastatic site(s)	iKM structured data + chart review	Baseline characteristic	Medical history prior to index	Baseline metastatic location(s) will be identified and categorized as: Bone (single) Bone (multiple) Brain Liver (single) Liver (multiple) Lung (single) Lung (bilateral) Lung (pleural effusion) Lymph nodes (regional) Lymph nodes (distant) Ovary Other No information Note, "no information" can indicates that metastases were not documented in the chart, not necessarily that patients did not have metastases.
Endocrine sensitivity at 12 months	iKM structured data	Baseline characteristic	Baseline	Patients who experienced relapse more than 12 months of completing adjuvant endocrine therapy will be considered to be endocrine sensitive; those who relapse in less than 12 months, endocrine resistant.
Endocrine sensitivity at 24 months	iKM structured data	Baseline characteristic	Baseline	Patients who experienced relapse more than 24 months of completing adjuvant endocrine therapy will be considered to be endocrine sensitive; those who relapse in less than 24 months, endocrine resistant.
Visceral/non-visceral status	iKM structured data + chart review (derived)	Baseline characteristic	Medical history prior to index	Categorized as: <u>Visceral (asymptomatic or symptomatic*)</u> Adrenal gland Bronchus Cervix Esophagus Gastrointestinal tract Genital organ Intestinal tract Kidney Large intestine Liver Lung Mediastinum Omentum Other respiratory organ Other urinary organ Ovary Pancreas

				Pericardium Peritoneum Pleura Rectum Retroperitoneum Small intestine Spleen Non-visceral Brain Breast Cervical nodes Chest wall Eye Ipsilateral supraclavicular lymph node Leptomeninges Other parts of nervous system Skin Spinal cord Bone only Bone Bone marrow Skull Other No information The above list will be confirmed or updated after chart review is complete *Asymptomatic visceral disease will be captured by chart review for patients who have explicit documentation of symptoms in the EHR records. All others will be assumed to be asymptomatic.
Count of metastatic site(s)	iKM structured data + chart review (derived)	Baseline characteristic	Medical history prior to index	The total count of metastatic site(s) at index: No documentation 1 2 3 4+ Note, “no documentation” can indicates that metastases were not documented in the chart, not necessarily that patients did not have metastases.
Stage at diagnosis	iKM structured data	Baseline characteristic	Medical history prior to index	Categorized as: Stage 0 Stage IA Stage IB Stage IIA Stage IIB Stage IIIA Stage IIIB Stage IIIC Stage IV No information
Eastern Cooperative Oncology Group	iKM structured data	Baseline characteristic	Up to 90 days prior to index	The ECOG performance status score is a rating of a patient’s disease status, daily living activities and quality of life, with low

<table>
<tr>
<td>(ECOG) performance status</td>
<td></td>
<td></td>
<td></td>
<td>scores indicating greater functioning than high scores:
0
1
2
⩾3
No information
Karnofsky performance status is a similar measure and will be converted to ECOG using the methodology outlined below.
<table>
<tr><th>Karnofsky Performance Status</th><th>ECOG Performance Status</th><th>ECOG Performance Status Description</th></tr>
<tr><td>100</td><td>0</td><td>Fully active</td></tr>
<tr><td>80, 90</td><td>1</td><td>Restricted in physically strenuous activity</td></tr>
<tr><td>60, 70</td><td>2</td><td>Ambulatory and capable of self-care but unable to work</td></tr>
<tr><td>40, 50</td><td>3</td><td>Capable only of limited self-care</td></tr>
<tr><td>10, 20, 30</td><td>4</td><td>Completely disabled</td></tr>
<tr><td>0</td><td>5</td><td>Dead</td></tr>
</table>
</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Chart review</td>
<td>Baseline characteristic</td>
<td>6 months prior to index</td>
<td>Comorbidities documented within 6 months prior to or on the index date will be captured and summarized as:
Atrial fibrillation
Bradyarrhythmia
Cerebrovascular disease
Congestive heart failure
Chronic pulmonary disease
Connective tissue disease
Dementia
Diabetes with end organ damage
Diabetes without end organ damage
Depression
Electrolyte abnormalities
Hemiplegia
HIV/AIDS
Hyperlipidemia
Hypertension
Infection
Leukemia
Long QT syndrome (congenital)
Long QT syndrome (drug induced)
Lymphoma
Metastatic solid tumor (other than breast cancer)
Mild liver disease
Moderate to severe renal disease
Myelosuppression
Myocardial infarction
Peptic ulcer disease</td>
</tr>
</table>

				Peripheral vascular disease Tachycardia Stroke Unstable angina Venous thromboembolism (pulmonary embolism or deep vein thrombosis)
Disease histology	iKM structured data	Baseline characteristic	Baseline	Categorized as: Ductal Lobular Mixed Metaplastic Tubular Mucinous Other No information
Breast cancer gene (BRCA) 1/2 status	Chart review	Baseline characteristic	Medical history prior to index	Categorized as: Positive Negative No information
Estrogen receptor 1 gene (ESR1) status	Chart review	Baseline characteristic	Medical history prior to index	Categorized as: Positive Negative No information
Next generation sequencing (NGS) status	Chart review	Baseline characteristic	Medical history prior to index	Categorized as: Positive Negative No information
Treatment characteristics				
Prior adjuvant hormonal treatment	iKM structured data + chart review	Treatment characteristics	Medical history prior to index	The proportion of patients with prior adjuvant hormonal treatment for breast cancer prior to the index treatment.
Prior neo-adjuvant/adjuvant chemotherapy	iKM structured data + chart review	Treatment characteristics	Medical history prior to index	The proportion of patients with prior neo-adjuvant/adjuvant chemotherapy for breast cancer prior to the index treatment.
Prior metastatic hormonal treatment	iKM structured data + chart review	Treatment characteristics	Medical history prior to index	The proportion of patients with prior metastatic hormonal treatment for breast cancer prior to the index treatment.
Adjuvant treatment end dates	iKM structured data + chart review	Treatment characteristics	Medical history prior to index	Date of adjuvant treatment discontinuation.
Disease-free interval	iKM structured data + chart review (derived)	Treatment characteristics	Medical history prior to index	The duration (in weeks) between discontinuation of adjuvant therapy and the start of treatment for metastatic disease. The number of patients with available data will be reported. Findings will be summarized as the mean (± SD) and median (range) of values, along with

				the proportion of patients with a duration less than or greater than/equal to 12 months.
Surgery	Chart review	Treatment characteristics	Medical history prior to index	The proportion of patients who had surgery prior to the index treatment.
Radiotherapy	Chart review	Treatment characteristics	Medical history prior to index	The proportion of patients who received radiation prior to the index treatment.
Index treatment regimen	iKM structured data + chart review	Eligibility criteria, Treatment characteristics	Study observation period	Patients' index treatment will be categorized based on the cohort descriptions in **Section 8.1**: PB+FUL CCI [redacted]
Date of treatment initiation during the patient identification period (i.e., index date)	iKM structured data + chart review	Eligibility criteria, Treatment characteristics	Study observation period	The date of initiation with a PB+FUL or CCI [redacted] during the study identification period. If the combination regimen consists of more than one drug with drugs given on different dates, the date of the first administration of any drug will be used. Patients who did not initiate a qualifying regimen during the patient identification period will be excluded from the study.
Treatment initiation by quarter	iKM structured data + chart review (derived)	Treatment characteristics	Study observation period	The proportion of patients who initiate treatment by quarter.
Index treatment end date(s)	iKM structured data + chart review	Treatment characteristics	Study observation period	Date of final treatment for each drug or regimen. It is possible that the patient's treatment stop date is not documented if the patient dies, is lost-to follow-up or is still on-therapy. The final treatment date, death date or end of study date will be used, whichever is earliest.
Index line of therapy (LOT)	iKM structured data + chart review (derived)	Treatment characteristics	Study observation period	LOT will be assigned based on the absolute chronologic order of regimens, based treatment start and stop dates. Specifically, first-line treatment designation will be assigned to the first treatment received after metastatic diagnosis. Line of therapy will advance with each subsequent regimen.
Mean and median duration of index therapy	iKM structured data	Treatment characteristics	Study observation period	The duration (in weeks) between the start and stop of the index treatment regimen. Findings will be summarized as the mean (± SD) and median (range) of values.
Number of cycles (index treatment)	iKM structured data	Treatment characteristics	Study observation period	The number of provider-documented therapy cycles received for the index treatment. Findings will be summarized as the mean (± SD) and median (range) of values. The number of patients with available data will be reported.
Index treatment schedule (cycle length and frequency)	iKM structured data + chart review	Treatment characteristics	Study observation period	The planned frequency cycle length of the index treatment. Findings will be summarized as the mean (± SD) and median (range) of values. The number of patients with available data will be reported.

Index treatment schedule changes	Chart review	Treatment characteristics	Study observation period	Index treatment schedule changes will be captured and reported as the proportion of patients with changes.
Index palbociclib treatment starting dose	iKM structured data + chart review	Treatment characteristics	Study observation period	The actual index treatment starting palbociclib dosage received. If needed, the dose is automatically calculated with the EHR based on patient's body surface area or weight and dosage. Findings will be summarized as the mean (± SD) and median (range) for all patients within the specified cohort. The number of patients with available data will be reported.
Reasons for palbociclib initiation of less than 125 mg/day	Chart review	Treatment characteristics	Study observation period	For patients who initiated palbociclib at a dose lower than 125 mg/day, reasons will be captured and reported: Age Concomitant medications Diagnosis Due to line of therapy received ECOG performance status score Patient request Presentence of comorbidities To avoid toxicity Other
Index palbociclib treatment dose/schedule changes	Chart review (derived)	Treatment characteristics	Study observation period	Index dose/schedule changes will be captured and reported as the proportion of patients with dose changes.
Reason for palbociclib dose changes	Chart review	Treatment characteristics	Study observation period	Data for palbociclib dose change reason will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts. If available, reason patients discontinued treatment will be abstracted: Lack of response Patient preference Toxicity Other No information Reviewers will specify other reasons; these will be reported if any represent >5% of patients.
Reason for treatment discontinuation	Chart review	Treatment characteristics	Study observation period	Data for discontinuation reason will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts. If available, reason patients discontinued treatment will be abstracted: Progression Toxicity Decline in performance status Financial/insurance Completed planned treatment Death Hospice Patient preference (if other categories do not apply)

				Physician preference (if other categories do not apply) Other
Proportion of patients who advance/do not advance	iKM structured data + chart review (derived)	Treatment characteristics	Study observation period	The proportion of patients who advance and do not advance from the index treatment will be summarized as the count and percentage of the following: Patients with ongoing index treatment Patients who died following index treatment Patients who advanced to a subsequent treatment Patients who did not advance to a subsequent treatment for unknown reasons
Post-index treatment regimen	iKM structured data + chart review	Treatment characteristics	Study observation period	The regimen received by patients following discontinuation from the index treatment.
Time to chemotherapy	iKM structured data +chart review (derived)	Clinical outcomes	Study observation period	Time to chemotherapy will be defined as the interval (in weeks) between index treatment and start of chemotherapy as documented in the iKM EHR database. Patients with ongoing treatment at the study observation period will be censored on the study end date or the last visit date available in the dataset, whichever occurred first. rwDOT will be analyzed using the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients at 6, 12, 18, 24, 30, and 36 months.
Real-world duration of treatment (rwDOT)	iKM structured data + chart review (derived)	Clinical outcomes	Study observation period	rwDOT will be defined as the interval (in weeks) between the start and stop index as documented in the iKM EHR database. Patients with ongoing treatment at the study observation period will be censored on the study end date or the last visit date available in the dataset, whichever occurred first. rwDOT will be analyzed using the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients at 6, 12, 18, 24, 30, and 36 months.
Time to next treatment (TTNT)	iKM structured data +chart review (derived)	Clinical outcomes	Study observation period	TTNT will be defined as the interval (in weeks) between the start of the index treatment and the date of the next-line treatment as documented in the iKM EHR database. Patients who did not advance to the next treatment within the study observation period will be censored on the study end date or the last visit date available in the dataset, whichever occurred first. TTNT will be analyzed using the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients at 6, 12, 18, 24, 30, and 36 months.

Provider-documented tumor assessments				
Provider-documented tumor assessment	Chart review	Clinical outcomes	Study observation period	In prospective clinical trials, response is generally assessed according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria. However, the parameters underlying these criteria are less reliably available in retrospective, observational studies.[20] Instead, for this study, we will rely on provider documented assessments of response. No attempts will be made to mimic the RECIST guidelines. Response assessments documented for the index treatment (depending on cohort). It is possible that patients have multiple response assessments in their charts during this period. All documented responses described in scan reports and progress notes (along with the associated note date) will be captured. Response assessments will be classified as: Complete response: Documented as "a complete response" to therapy; indication patient is in "remission"; "all lesions" have disappeared or "no evidence of disease"). Response not otherwise specified (partial response or response not otherwise): any documentation of improved disease or responding disease not definitively classified as a complete response. Stable disease: Documented as disease is stable (not progressed or not improved; e.g. Stable appearance of lobe nodules). Mixed response: Combination of improved and worsened disease. Progressive disease: Documented as disease has "progressed"; or worsening of disease. Not evaluated: No documentation of status of disease.
Best overall response (BOR)	Chart review (derived)	Clinical outcomes	Study observation period	Each patient will be assigned one BOR based on all recorded response assessments captured during chart review. The responses will be ranked in the following order (from best to worst): Complete response Improved disease Stable disease Mixed response Progressive disease Not evaluated The proportion of patients with each BOR category will be reported.
Date of provider-documented progression or recurrent disease	Chart review	Clinical outcomes	Study observation period	The date of provider-documented progression or recurrent disease as explicitly noted by a clinician in a scan report or progress note. Frequently, this will be the date the provider recorded evidence of progression, not

				necessarily the date the radiologic assessment was made.
Real-world complete, improved or stable disease rate (clinical benefit rate)	Chart review (derived)	Clinical outcomes	Study observation period	In real-world research, the parameters underlying response as defined by RECIST criteria are often unavailable. As such, this study will assess response to treatment as documented by providers and capture real-world assessments of response, including complete response, improved disease and stable disease. This measure will be similar to clinical benefit rate as defined by RECIST criteria.
Clinical outcomes				
Last USON visit date	iKM structured data + chart review	Clinical outcomes	Study observation period	Each patient's most recent visit date, prior to or on close of study observation period will be recorded. A visit is defined as a physician encounter with the practice where either treatment is given or vital signs are recorded. For patients with a death date, this last visit date should occur prior to the death date. This will not be reported separately; it will be used in calculating the patient's available follow-up time as a descriptive measure. available follow-up time = Integer (latest of last visit date or death date – index date +1)
Death date	iKM structured data, chart review + external sources	Clinical outcomes	Study observation period	Date of death will be captured from the iKM EHR, limited access death master file (LADMF), national death index (NDI) and, possibly, other commercial sources of death information (the study team is confirming the utility of these sources). If dates conflict among the sources, the NDI, followed by the LADMF date will be prioritized. If severe data discordance is observed (i.e., death is reported to occur prior to the index date), then the iKM death date will be used. Further information on the sources of death information is presented in **Section 8.4**.
Follow-up duration	iKM structured data, chart review + external sources (derived)	Clinical outcomes	Study observation period	The duration between index and last follow-up date. Findings will be summarized as the mean (± SD) and median (range) for all patients within the specified cohort. The number of patients with available data will be reported.
Vital status	iKM structured data, chart review + external sources (derived)	Clinical outcomes	Study observation period	Patients without a date of death recorded in iKM, LADMF, NDI or other commercial sources of death information used for the study will be assumed to be alive at the end of the study. Those with a date of death in available records will be flagged as deceased. Further information on the sources of death information is presented in **Section 8.4**.
Overall survival (OS)	iKM structured data, chart	Clinical outcomes	Study observation period	OS will be defined as the interval (in weeks) between index treatment and the date of death (any cause) as documented in the iKM EHR database, LADMF, NDI and other

	review + external sources (derived)			commercial sources of death records that may be used for this study. Patients who did not die within the study observation period will be censored on the study end date or the last visit date available in the dataset, whichever occurred first. OS will be analyzed using the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients 6, 12, 18, 24, 30, and 36 months.
Survival rate	iKM structured data, chart review + external sources (derived)	Clinical outcomes	Study observation period	Survival rates will be provided along with the Kaplan-Meier OS analyses described above as survival rates at 6, 12, 18, 24, 30, and 36 months.
Real-world progression-free survival (rwPFS)	iKM structured data, chart review + external sources (derived)	Clinical outcomes	Study observation period	The rwPFS will be measured from the initiation of the index treatment to the date of progression or date of death due to any cause, censoring patients who are still alive at the end of the study observation period and did not progress at the last visit date. The rwPFS will be estimated in weeks using the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients at 6, 12, 18, 24, 30, and 36 months.
rwPFS rate	iKM structured data, chart review + external sources (derived)	Clinical outcomes	Study observation period	PFS rates will be provided along with the Kaplan-Meier PFS analyses described above as PFS rates at 6, 12, 18, 24, 30, and 36 months.
Real-world time to tumor progression (rwTTP)	iKM structured data, chart review + external sources (derived)	Clinical outcomes	Study observation period	The rwTTP will be measured from the initiation the index treatment to the date of provider-documented progression, censoring patients without evidence of provider-documented progression at the last visit date. The rwTTP will be estimated in weeks using the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients at 6, 12, 18, 24, 30, and 36 months.

8.4. Data sources

Table 2 presents the data elements that will be evaluated through this study and their associated source. Most study data will originate from the EHR system of the USON, iKM. iKM captures outpatient practice encounter histories for patients under community-based care, including, but not limited to patient demographics such as age and gender; clinical information such as disease diagnosis, diagnosis stages, performance status information and

laboratory testing results; and treatment information, such as dosages and treatment administration within the USON.

Structured data fields within the iKM EHR database will provide information needed to address most research questions. These data will be supplemented by additional unstructured data collected through chart review for a subset of the study population (selection methodology described in **Section 8.2.4**). Electronic chart review data was collected by means of a secure, web-based electronic case report form (eCRF) by healthcare professionals with oncology experience.

The study will only use data from USON practices utilizing full EHR capacities of iKM. Data management and administrative processing is supported by McKesson's quality assurance procedures. Additionally, iKM has previously been used to evaluate patient profiles, treatment patterns and outcomes among mBC patients and the results have been consistent with other published studies.[21-33] Thus the study team does not plan to conduct any additional studies to validate the accuracy of demographic, clinical, treatment and outcome information in the iKM EHR database.

The primary source of death information will be structured and unstructured records of death in the iKM EHR database. McKesson has certification to access the LADMF of the Social Security Administration and, as such, this will be a supplementary source of vital (death) records in addition to the NDI of the Centers for Disease Control. The study team is also evaluating the potential for other commercial sources of death information to be used for this study, including ObituaryData.com, Legacy.com, Datavant and others. If it is confirmed that these sources can be used, they will be an additional source of death information.

Death information is updated weekly in the LADMF and is as current as it is reported to the Social Security Administration.[34] However, death dates recorded in the LADMF are not complete due to limitations on access of records for research purposes.[35,36] Levin et al. (2019) compared LADMF and hospital death records after access restrictions imposed in 2011.[35] After 2011, LADMF sensitivity for in-hospital deaths was 14.8% (compared with 88.9% before 2011) and 28.9% for out-of-hospital deaths (compared with 71.4% before 2011). The LADMF specificity, however, was greater than 99% both prior to and after 2011. Peters et al. (2017) compared capture of death dates in the LADMF with a multiphase approach that assessed online databases (including LADMF), EHR records and provider follow-up.[36] The authors reported that 42.7% of death records were identified by the LADMF, with the remainder from another online database (32.6%), EHR records (22.2%) and provider follow-up (3.5%). Overall, the sensitivity was 58.5%, with 100% specificity.

In a study of the iKM EHR database and LADMF, it was observed that 93.3% of all death records were captured in structured fields and 6.7% of death records were solely identified by the LADMF.[37] Among deaths recorded by both structured data and the LADMF, concordance was 88.0%. When both structured and unstructured data are available, 99.4% of death records are captured from these sources, with 0.6% death records solely identified by

the LADMF. Between 2015 and 2019, the proportion of death records captured by structured data trended upward (slope = 4.04).

Death records in the NDI index are updated quarterly with a lag time of approximately 1 year. Curtis et al. (2018) compared several sources of death, including EHR data, Social Security Death Index and commercial death data, with the NDI, for a cohort of patients with non-small cell lung cancer.[38] The sensitivity between the NDI and structured data was 66% and the specificity was 97%. With combined EHR and commercial death dataset, sensitivity increased to 84%. Inclusion of the Social Security Death Index increased sensitivity to 89% and, last, with supplementation of missing death information through chart abstraction (unstructured data), sensitivity increased to 91%. No studies to date have compared the capture of death information with the iKM EHR to the NDI.

Some data elements will be available from multiple sources, structured data (i.e. from iKM), unstructured data (i.e. chart review), the LADMF, NDI and, possibly, commercial sources of death records. During chart review, abstractors reviewed patients' entire medical record, including information that is also captured in structured fields. Discrepancies in the medical record will be reviewed by McKesson's Data Quality Manager, Medical Director/Physician Investigator to determine the most appropriate value to be abstracted based on clinical judgement and operational guidelines.

If there is a discrepancy in dates of death among the sources, the LADMF date, followed by the NDI date will be prioritized as it reflects the official date of death reported to government agencies unless: 1) EHR activity indicates that a patient visit occurred after date of death as documented in the LADMF or NDI; 2) date of deaths between the two sources vary by more than 6 months. In these cases, the date of death recorded in the iKM EHR as part of patient follow-up by USON physicians and staff may be sourced from non-official records, including telephone conversations with the patient's family.

Data from all sources and any derived variables will be merged into one master dataset for analysis. Data will be handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and Health Information Technology for Economic and Clinical Health (HITECH).

8.5. Study size

A feasibility assessment from iKM identified 783 patients who met study eligibility criteria and initiated PB+FUL and CCI [redacted] (**Table 3**). The 1035 patients who initiated PB+FUL and CCI [redacted] in the first- through third-line setting were selected for chart review (633 PB+FUL and CCI [redacted]). During chart review, these patients' eligibility was confirmed and some patients were disqualified. The final sample size for analysis will consist of the confirmed eligible patients who initiated first-line PB+FUL CCI [redacted]

Table 3. Initial feasibility assessment

Eligibility criteria	Patient count - Excluded	Patient count - remained
Documented diagnosis of hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive), human epidermal growth factor receptor 2-negative metastatic breast cancer (mBC) who received a qualifying treatment (i.e., palbociclib, letrozole, exemestane, anastrozole or fulvestrant) within the USON during the study identification period [1]	-	19,720
Aged 18 years at initial recorded diagnosis of mBC	1	19,719
Exclusion of patients enrolled in an interventional clinical trial during the study observation period	1216	18,503
Did not receive a treatment indicated for another primary cancer during the study observation period	1572	16,931
Received care at a USON site(s) utilizing the full EHR capacities of iKM at the time of treatment.	0	16,931
EHR data available from the USON site(s) where the patient received treatment are accessible for research purposes	0	16,931
Exclusion of patients with qualifying treatments (i.e., palbociclib, letrozole, exemestane, anastrozole or fulvestrant) received only prior to metastases date and not after metastatic diagnosis	2558	14,373
Exclusion of patients with start of first regimen more than 120 days after metastases date	1455	12,918
Exclusion of patients whose data are inaccessible for research purposes	5594	7,324
Initial cohort counts (patients who initiated the cohort-specific regimen in an appropriate LOT)		
PB+FUL: Palbociclib combination therapy with fulvestrant following as first-line or beyond therapy in the metastatic setting. Patients with evidence of prior treatment with CDK 4/6 inhibitors (ribociclib or abemaciclib) in the metastatic setting were excluded. Study identification period: 01 February 2015 - 31 December 2019.	-	840
CCI [redacted]	[redacted]	[redacted]

Exclusion of patients who initiated qualifying regimens prior to the start of the study period (by cohort)		
PB+FUL	47	793
	First-line = 39	
	CCI	
	Third-line = 2	
	Fourth-line = 1	
	Fifth-line or beyond = 3	
CCI		
Exclusion of patients with fewer than 2 visits after index (by cohort)		
PB+FUL	10	783
		First-line = 488
		CCI
		Third-line = 53
		Fourth-line = 45
		Fifth-line or beyond = 105
	CCI	
Patients selected for chart review (PB+FUL and CCI who initiated 1L-3L treatment; n= 1035)		
Exclusion of patients whose data were inaccessible for chart review	29	1006
Exclusion of patients who were not diagnosed with HR+ mBC	45	961
Exclusion of patients who were not diagnosed with HER2- disease	10	951
Exclusion of patients who did not receive a qualifying treatment	124	828
Exclusion of patients who participated in clinical trials	21	807
Exclusion of patients with other primary cancers	40	767
Exclusion of patients who do not receive 1L-3L qualifying treatment (sequencing activities performed during analysis)	52	715
Exclusion of patients with an index date prior to 01 Feb 2016 (by cohort)		
PB+FUL	-	428
CCI		
Final cohort counts		
1L PB+FUL	-	317
2L PB+FUL	-	78

1L [redacted]	[redacted]	[redacted]	

8.6. Data management

A description of the data sources to be used for this study is provided in **Section 8.4**. Operational definitions, periods of assessment and data sources of all data elements to be used for this study, along with descriptions of how raw data elements will be transformed into derived variables, is presented in **Table 2**.

The McKesson study team will collaborate with McKesson's Commercial Intelligence group to collect the structured iKM data that will be used for analysis. The Commercial Intelligence team will be provided with a Data Collections Variable List, which will detail the specific data elements that will need to be included in the study dataset. A Data Analyst will begin by generating high-level study sample counts that demonstrate attrition rates of the inclusion/exclusion criteria.

The study team will review the attrition count and the Data Analyst will proceed with collecting the remaining data elements on the Data Collections Variable List. The Data Analyst will perform an initial quality control check of the study dataset before providing the file to the study team's Biostatistician on a secure server. Once received by the Biostatistician, data validation will continue and will consist of, but is not limited to, quality control checks for appropriate values, logical sequences and quantity of missing values.

A list of patients eligible for chart review was generated by the Data Analyst and the Biostatistician applied the agreed upon sampling technique to identify the specific patients that underwent chart review. This list of patients was then securely transmitted to the Chart Review Team Manager. The chart review team consists of experienced oncology healthcare providers.

The McKesson study team led a training session with chart abstractors to discuss study specific considerations. Reference materials were provided to abstractors at this time. If chart abstractors have questions during the abstraction process, these were first raised to the Chart Review Team Manager. As needed, questions were escalated to the Outcomes Researcher and Principal Investigator.

Chart review was accomplished by use of a secure, web-based eCRF. The main purpose of the eCRF is to obtain data required by this non-interventional study protocol in a complete, accurate, legible and in a timely manner.

Analyses will be conducted using statistical analysis software (SAS®; SAS Institute Inc., Cary, NC, US) and/or R: A Language and Environment for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria) as appropriate.

8.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/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. McKesson shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

McKesson 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 the investigator or by an authorized staff member 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.

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

8.8. Record retention

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

If McKesson 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.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless McKesson and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

McKesson 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 statistical analysis plan (SAP), which will be dated, filed and maintained by Pfizer. 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.*

8.7.1. Analysis sets

Separate analysis sets will be created to address the study objectives based on the cohorts of patients to be included (an overview of these analyses is presented in **Table 2**). For the primary and secondary objectives, the analyses will consist of patients who initiated first-line PB+FUL, CCI [redacted]

8.7.2. Derived and transformed data

Some of the data elements needed for the study objectives will be derived from available data during the analysis phase of the study. Details about these calculations are provided along with the operational definition in **Table 2**. Prior to constructing these variables, the McKesson biostatistician will perform data validation activities. Data validation will continue and will consist of, but is not limited to, quality control checks for appropriate values, logical sequences and quantity of missing values.
Missing data will be identified and reported in the results tables as percentages for all variables. If there is a large amount of missing or illogical data, a decision to include, exclude or impute that variable will be subsequently made based on the study sponsor's decision.

8.7.3. Statistical methods

Description of study enrollment
To be included in the study patients must meet each of the inclusion criteria and none of the exclusion criteria listed in **Sections 8.2.1-8.2.2**. Counts of patients excluded for each criterion will be summarized.

Description of patient demographic, clinical and treatment characteristics
Descriptive analyses will be conducted to evaluate the demographic, clinical and treatment characteristics overall, as well as for the cohorts and stratifications defined above. Results will be reported in aggregate. Categorical variables (e.g., ECOG performance status) will be reported as frequency and percentage. Continuous variables such as age will be reported as mean, standard deviation, median and range (minimum-maximum). In the case of missing observations, the number and percentage of missing values will be reported.

* If the SAP is modified, the study protocol will be updated accordingly and re-submitted to the IRB.

All descriptive tables will be presented overall and for each of the Cohorts defined above and, as supported by the final sample size, stratified to present the results for the subgroups defined in **Section 8.2.4**.

Clinical outcomes
Time-to-event outcomes, time to chemotherapy, rwDOT, TTNT, OS, rwTTP and rwPFS, will be assessed using the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients at 6, 12, 18, 24, 30, and 36 months among those who initiated first-line PB+FUL. Further details about these calculations are presented in **Table** 2.

CCI [redacted]

To reduce the effect of selection bias, the study team will first consider baseline variables/covariates compared among propensity score matched cohorts. The propensity score, defined as the probability of being initiated on PB+FUL treatment, will be estimated using a multivariate logistic regression model conditional on the baseline covariates (e.g., age, gender, ethnicity, body mass index (BMI), menopausal status, comorbidities, ECOG, stage of diagnosis, count of metastatic sites and site of metastases). Each individual will have a propensity score that represents the probability of being treated with PB+FUL. Pairs of treated and untreated subjects will be matched on the logit of the propensity score using a caliper of width equal to 0.2 of the standard deviation of the logit of the propensity score, as this caliper has been shown to be optimal in a range of settings.

Alternatively, if propensity score matching is not supported by the sample size, standardized or normalized inverse probability of treatment weighting (IPTW) using propensity score may be applied to balance baseline demographic and clinical characteristics between the 2 comparison cohorts. For standardized IPTW, the propensity score weight will be calculated as the inverse of the propensity score (1/propensity score), then create a weight reflect the sample size for each of the treatment groups, i.e., (1/propensity score)*(number of obs. in treatment A)/(number of obs. in entire study group). For normalized IPTW, the weights will be calculated as the inverse of patients' estimated probability of being in treatment. Finally, the normalized weights will be calculated by dividing each weight by the overall mean weight. After weighting, the sum of weights attributed to each patient in a given cohort may not be equal to the sample size of this cohort, consequently, the effective sample size after weighting may be different than the original sample size (i.e., before weighting), although the total size of whole study population will not be changed.

Last, during analysis, multivariable Cox regression models will be used to further reduce bias associated with underlying characteristics of the patient populations that may affect treatment selection. Specifically, all variables will be fitted into a multivariable Cox proportional hazard regression model to assess independent associations between clinical outcomes and probability of an event (hazard ratio) adjusting for the influence of other variables within the model.

Additional analyses
An intent-to-treat approach will be taken for the analyses.

Based on the resulting sample sizes, a decision to proceed with sensitivity analyses or additional stratifications will be made. In particular, the team may opt to pursue an analysis to assess the impact of follow-up duration on outcomes, endocrine sensitivity time periods (12 vs. 24 months) or compare the patient population with clinical trials. These additional analyses will require a study amendment.

8.7.4. Sequence of analyses

An initial feasibility assessment has been performed based solely on structured data. Following chart review, analyses will be undertaken to meet the primary and secondary objectives for the final study population using both structured an unstructured data. CCI [redacted]

8.8. Quality control

For structured data, McKesson's Commercial Intelligence and Real World Evidence teams conduct quality assurance checks on all analytics projects. The process includes both technical and clinical quality checks. Technical review of the dataset consists of identifying inappropriate values (e.g., out of range, illogical), logical sequences and quantity of missing values. Illogical and missing data will be reported to the study team, which may opt to exclude or impute these values. Clinical review of the data subsequently occurs to ensure aggregate data are aligned with expectations and prior publications.

The quality assurance process includes the following areas:

- Project scope and study rules
- Protocol/statistical analysis plan (SAP) development
- Data extraction and integrity
- Populated tables and Study Report development

As results of quality assurance and quality control, we confirm:

- The source of the data and/or results will be documented and that results/data will be verified against the source
- The internal consistency of the medical research data presented
- The conclusions are objective, balanced and consistent with the study results

- The format and content of the document are aligned with the agreed upon template and standards

Quality control and validation of chart review (unstructured) data occurred in multiple phases. Prior to full chart review, a pilot was conducted with at least 5% of the patient population, up to 25 patients. Charts were reviewed by each reviewer on the team to ensure inter-rater reliability. Data Collection Manager/Team Lead reviewed pilot data for accuracy and consistency, including implausible dates (i.e., date of death prior to last date of treatment), non-standard treatments, results which are inconsistent with known clinical parameters or other clinical data which is inconsistent with known standards and outcomes. Chart review team met following pilot and before launch of full chart review to clarify ambiguous or conflicting data and address potential problems and questions. Pilot data were presented to the research team for review and approval. As necessary, revisions to the tool and/or additional training were implemented.

Once the pilot chart review was complete, the remaining chart reviews proceeded. During this phase of chart review, Data Collection Manager/Team Lead performed random and detailed checks of the data by verifying original source data. The Data Collection Manager also initiated queries, quality control of randomly selected charts and review of final data set before submission to researcher. Finally, the researcher and study's statistical lead provided a final examination of the final dataset by looking for missing or illogical data before preparing it for analyses. This analysis included a descriptive analysis of the provider characteristics, demographics, baseline clinical and disease characteristics, and characteristics of treatment patterns. Data points flagged as outliers were reviewed by the Chart Review Team Lead.

Based on extensive experience with chart abstraction of real-world oncology data, the McKesson Life Sciences team has created chart abstraction guidelines to reflect best practices in data collection across a number of disease areas.[39] The intent of this document is to ensure accurate, objective and consistent data capture.

8.9. Limitations of the research methods

8.9.1. Internal validity of study design

Measurement error(s)/misclassification(s)
This observational and retrospective study uses iKM EHR data. The iKM database is not collected for research purposes but for clinical practice reasons. This may impede the standardization of the data collection methods and instruments and the reporting practices of the physician. As with all administrative databases, iKM data are subject to coding errors of omission and commission. Problems with inadequate or inaccurate codes in the databases may introduce some level of misclassification bias of certain diagnoses, events, or procedures of interest. Likewise, some variables of interest may not be as complete across the entire population. The iKM EHR contains information on patients only when they are seen by USON physicians. Services and procedures provided outside of the USON are not captured by the database, as well as drugs received by patients from pharmacies not affiliated with USON practices.

A patient's treatment history prior to his/her first encounter at a USON practice may be only available in physician progress notes and is not well captured in the iKM EHR. We cannot rule out the possibility that some patients coded as receiving being treatment naïve for metastatic disease in iKM EHR actually had previous chemotherapy for metastatic disease in healthcare facilities outside the USON.

Information bias

Due to the nature of the study design, there is potential for bias to be introduced into the calculations of clinical outcomes. Specifically, patients who initiated treatment during the patient identification period may be meaningfully different from other patients who initiated therapy prior or after the study identification period.

Confounding

The iKM system is used for clinical practice reasons, not solely for research purposes. As such, associations but not causality can be detected, thus bias may be introduced by confounding factors. For example, data may be collected with an intent-to-treat approach, meaning based on when treatment is assigned rather than received. In particular, it will not be possible to determine if oral therapies were dispensed or taken; therefore, we'll use an intent-to-treat approach for analysis, with the assumption that all prescribed oral therapies were taken. Likewise, patients who do and do not receive the treatment at one point in time may be fundamentally different than those who received treatment during the observation period. These confounding factors are most likely to affect the outcomes being considered for this estimation study.

8.9.2. External validity of study design (generalizability)

Not all community oncology practices are included in the iKM dataset. Furthermore, not all of the USON utilize the full capabilities of the iKM EHR. The USON encourages use of evidence-based treatment guidelines. Therefore, practices that participate in the USON may be different from other community oncology practices in the patient population that is seen or the prescribing practices of the physicians.

8.9.3. Analysis limitations

As a retrospective observational study, data entry errors at the point of care cannot be detected or corrected during analysis.

8.9.4. Limitations due to missing data and/or incomplete data

Although data quality checks are conducted, it is possible that some variables of interest may not be as complete across the entire population.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

This study will include both a structured data analysis and human-level review of unstructured (chart review). As such, separate patient protections and reporting requirements are described below for each phase.

9.1. Patient information

Structured data analysis
This study involves data that exist in anonymized structured format and contain no patient personal information.

Human Review of Unstructured Data

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.
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 McKesson contract and applicable privacy laws.

IRB approval will be received prior to any patient level data transfer that occurs between McKesson and Pfizer. All other data will be reported to the Sponsor only in aggregate form and with attention to results that represent small counts of patients.

Study data will be reported in aggregate; no identifiable data will be transferred to Pfizer.

9.2. Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

The McKesson study team will submit a request for exemption, waiver of informed consent and authorization to the Intuitional Review Board (IRB). This project involves the study of existing data and records; study information will be analyzed by the McKesson study team in such a manner that research participants will not be directly identified. Once exemption status and a waiver of informed consent are met, a waiver of authorization can be approved, allowing the retrospective study to occur.

9.3. Patient withdrawal

Not applicable, as this project does not require informed consent.

9.4. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

All study data will be reported to the Sponsor only in aggregate form and with attention to results that represent small counts of patients.

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 International Society for Pharmacoepidemiology, Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research, International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, 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 REQUIREMENTS

Structured Data Analysis

This study involves EHR data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

Human Review of Unstructured Data

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 eCRF 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 (e.g., 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 (e.g., 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.

Study reporting

The completed study will be summarized in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study and interpretation of the findings.

Publication

It is anticipated that the results of this analysis will be disseminated in the following publications:

- At least one conference abstract
- At least one manuscript

The McKesson study team will collaborate with the Sponsor to determine the appropriate conference(s) and journal(s) for submission, following assessment of the study findings.

Authorship will follow the guidelines proposed by the International Committee of Medical Journal Editors. All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Any potential conflicts of interest will be disclosed. Authors will adhere to the International Committee of Medical Journal Editors (ICMJE) guidelines, specifically, all authors will have (1) made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) participated in drafting the article or revising it critically for important intellectual content; (3) approved the version to be published, and (4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Acquisition of funding, collection of data, or general supervision of the research group does not justify authorship. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Study Sponsor Sign-Off page

This Protocol/Statistical Analysis Plan has been reviewed and agreed upon by the study sponsor and McKesson project team. Sign-off is required prior to submission to McKesson's Privacy and Compliance Review.

Study Sponsor Lead
Signature:_____
Name: PPD
Title: PPD , PPD
Pfizer, Inc
Date:_____

PPD **, Principal Clinical Investigator**
Signature:
Name: PPD
Title: PPD , PPD
_
Date:_____

PPD **, Outcomes Researcher**
Signature:_____
Name: PPD
Title: PPD , PPD _
Date:_____