Non-Interventional Study Protocol
A5481128

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

Statistical Analysis Plan
(SAP)

Version: 2

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

The strategic aim of study A5481128 has shifted to focus on patients who received palboclcib plus fulvestrant (PB+FUL) in the first-line (1L) setting.

The following is a summary of the changes:

- Revised objectives to focus on patients who received first-line PB+FUL, CCI [redacted]
- 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.
- Updated Background section with newly published literature.
- Changed the Pfizer study leads.
- Removed the provider-documented response to treatment (real-world response rate) endpoint.

2 INTRODUCTION

Note: in this document, any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

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.[16] 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.[17] 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.

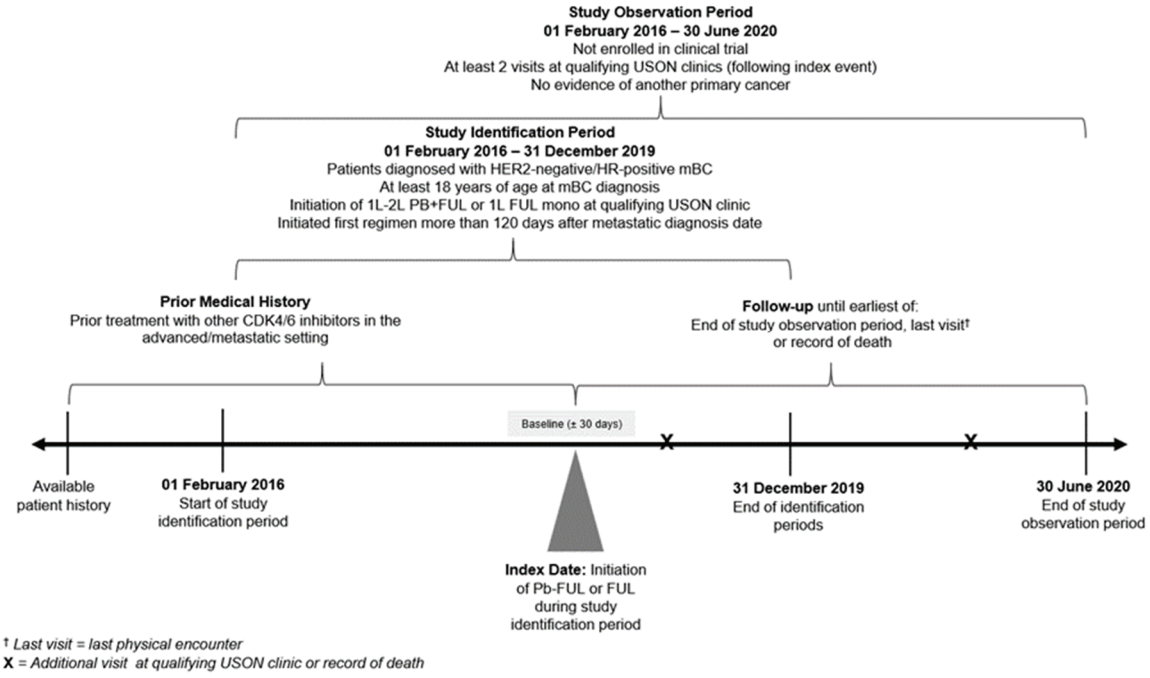
2.1 STUDY DESIGN

2.1.1. Study population

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*** *4Error! Reference source not found.. 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.

The study time periods 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* CCI *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 1****.*
- *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 1****.*
- *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.*

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 4****. Next, chart review was performed to verify patients' eligibility and capture additional details about eligible patients.*

2.1.2. Data source

Table 1 *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.

[*] 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.

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.[18-30] 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.[31] However, death dates recorded in the LADMF are not complete due to limitations on access of records for research purposes.[32,33] Levin et al. (2019) compared LADMF and hospital death records after access restrictions imposed in 2011.[32] 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.[33] 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.[34] 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.[35] 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).

2.1.3. Treatment/cohort labels

Patients will be classified into one of the following treatment groups:

- PB+FUL as first-line therapy in the metastatic setting (for primary and secondary objectives)
- CCI [redacted]

2.2 STUDY 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 4**. If supported by the final sample size, all study results will be stratified by the subgroups defined in **Section 4.4**.*

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

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)*

CCI [redacted]

3 HYPOTHESES AND DECISION RULES

3.1 STATISTICAL HYPOTHESES

The primary objectives of this study are intended to be hypothesis-generating, as such no hypothesis will be tested for these.

CCI [redacted]

3.2 STATISTICAL DECISION RULES

An alpha level of 0.05 will be the primary criterion for statistical significance of this study.

4 ANALYSIS SETS/POPULATIONS

4.1 FULL ANALYSIS SET

Inclusion criteria

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

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]

[*] 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.

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.*

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.*

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

4.2 SAFETY ANALYSIS SET

A separate safety analysis set will not be included in this study.

4.3 OTHER ANALYSIS SET

*Study objectives are described in **Section** 2.2. The primary objectives will be assessed among patients who initiated first-line PB+FUL.* CCI [redacted]

4.4 SUBGROUPS

[*] 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.

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)*

5 ENDPOINTS AND COVARIATES

5.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

Time to chemotherapy

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.

Reasonf for treatment discontinuation

Data for discontinuation reason will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts.

Real-world duration of treatment (rwDOT)

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)

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 progression

The proportion of patients with provider-documented progression will be reported.

Real-world time to tumor progression (rwTTP)

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.

Real-world progression-free survival (rwPFS)

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.

Overall survival (OS)

OS will be defined as the interval (in weeks) between index treatment and the date of death (any cause) as documented in the LADMF, NDI and the iKM EHR database. 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.

5.2 SAFETY ENDPOINTS

No safety endpoints will be evaluated in this study.

5.3 OTHER ENDPOINTS

Not applicable.

5.4 COVARIATES

Table 1 *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 1. 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:* *Visceral (asymptomatic or symptomatic*)* *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
Peripheral vascular disease</td>
</tr>
</table>

				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 as:* *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	*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*

disease rate (clinical benefit rate)				*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 2.1.2****.*
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 2.1.2****.*
Overall survival (OS)	*iKM structured data, chart review + external sources (derived)*	*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 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.*

6 HANDLING OF MISSING VALUES

In the case of missing observations, the number and percentage of missing values will be reported. No imputation for missing values will be performed.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

Descriptive analyses will be conducted to evaluate the demographic, clinical and treatment characteristics for the study cohorts defined in ***Section*** *4. 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). Chi-square testing will be used to assess associations between categorical variables when patient counts for single cells within the results tables are greater or equal to 5. When distribution cannot be assumed to be Chi-square, then Fisher's exact test will be used. Depending on normality, analysis of variance (ANOVA)/t-tests or Kruskall-Wallis tests will be used for continuous variables. An alpha level of 0.05 will be the primary criterion for statistical significance of this study.

Time-to-event outcomeswill 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.

CCI [redacted]

To reduce the effect of selection bias, the study team will first consider clinical outcomes 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. The propensity score will be used to select patients for chart review, as well as the single confounding variable during analysis. 1:n matching could be done by propensity score matching, n could be 1, 2, 3, etc.

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.

Analyses will be conducted using statistical analysis software 9.4 (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.

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

7.2 STATISTICAL ANALYSES

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 ***Section 4.1****. Counts of patients excluded for each criterion will be summarized.*

Description of patient demographic, clinical and treatment characteristics
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 4.4.

Clinical outcomes
Estimates of time to chemotherapy, rwDOT, TTNT, OS, rwTTP and rwPFS will be presented. Further details about these calculations are presented in ***Table 1****.*

Additional 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.

7.2.1 Safety Analyses

Not applicable.

7.2.2 Summary of Analyses

Table 2 presents an overview of the planned analyses for this study. As supported by the final sample size, each of the results tables and figures will be stratified to present the data for the stratifications defined in **Section 4.4**.

Table 2. Overview of study analyses

Analysis	Data source	Statistical method	Missing data
Baseline demographic and clinical characteristics	Structured + chart review data	Descriptive statistics	Missing values reported
Provider- and clinic-level characteristics	Structured data only	Descriptive statistics	Missing values reported
Treatment patterns	Structured + chart review data	Descriptive statistics	Missing values reported
Time to chemotherapy	Structured + chart review data	Kaplan-Meier methods	Patients without the event will be censored
Real-world duration of therapy (rwDOT)	Structured + chart review data	Kaplan-Meier methods	Patients without the event will be censored
Time to next treatment (TTNT)	Structured + chart review data	Kaplan-Meier methods	Patients without the event will be censored
Overall survival (OS)	Structured data + chart review data + LADMF/NDI	Kaplan-Meier methods	Patients without the event will be censored
Real-world time to tumor progression (rwTTP)	Structured data + chart review data + LADMF/NDI	Kaplan-Meier methods	Patients without the event will be censored
Real-world progression-free survival (rwPFS)	Structured data + chart review data + LADMF/NDI	Kaplan-Meier methods	Patients without the event will be censored

8 LIST OF TABLES AND TABLE SHELLS

Table shells and mock figures for the planned analyses are embedded into this document. Final results will be delivered in an Excel format.

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10 APPENDICES

None.