Study Information

Title	Real-World Tumor Response of Palbociclib in Combination With an Aromatase Inhibitor as First-Line Therapy in Pre/perimenopausal Women With Metastatic Breast Cancer
Protocol number	A5481159
Protocol version identifier	FINAL Version 1.0
Date	21 December 2020
Active substance	Palbociclib (IBRANCE®; PD-0332991)
Medicinal product	Palbociclib (IBRANCE®; PD-0332991)
Research question and objectives	**Primary objective** • To estimate real-world response rate (rwRR) for pre/perimenopausal patients treated with palbociclib + AI compared to AI alone as first-line therapy for HR+/HER2– MBC.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	first line
ABC	advanced breast cancer
AE	adverse event
AEM	Adverse Event Monitoring
AI	aromatase inhibitor
AIDS	acquired immune deficiency syndrome
ASCO	American Society of Clinical Oncology
BC	breast cancer
BRCA	**br**east **ca**ncer susceptibility protein gene
CBR	clinical benefit rate
CCI	Charlson comorbidity index
CDK	cyclin-dependent kinase
CI	confidence interval
CR	complete response
CRF	case report form
DCT	data collection tool
DEI	Data, Evidence and Insight
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ER	estrogen receptor
ET	endocrine therapy
EHR	electronic health record
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
FUL	fulvestrant
GOS	goserelin
GPP	Good Pharmacoepidemiology Practices
HER	human epidermal growth factor receptor
HIPPA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health
HIV	human immunodeficiency virus
HR	hormone receptor *or* hazard ratio
ICD	International Classification of Diseases
IEC	Independent Ethics Committee
IHC	immunohistochemistry
iKM	iKnowMed
ILD	interstitial lung disease
IPTW	inverse probability treatment weighting

Abbreviation	Definition
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intent-to-treat
IV	instrumental variable
LADMF	Limited Access Death Master File
LHRH	luteinizing hormone releasing hormone
LOT	line of therapy
MBC	metastatic breast cancer
NDI	National Death Index
NE	not evaluated; not estimable
NGS	next generation sequencing
NIS	non-interventional study
NOS	not otherwise specified
NSAI	non-steroidal aromatase inhibitor
OR	odds ratio; outcomes researcher
ORR	objective response rate
OS	overall survival
p	p-value
PALOMA	**PAL**bociclib **O**ngoing Trials in the **MA**nagement of Breast Cancer
PASS	Post Authorization Safety Study
PBO	placebo
PD	progressive disease
PFS	progression-free survival
PR	progesterone receptor; partial response
PS	propensity score
PSM	propensity score matching
QC	quality control
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
rwPFS	real-world progression-free survival
rwRR	real-world response rate
rwTR	real-world tumor response
SAP	Statistical Analysis Plan
SD	standard deviation; stable disease
SSDI	Social Security Death Index
SSN	social security number
TMN	Tumor, Node, Metastasis
US	United States
USON	US Oncology Network
USPI	United States Package Insert

3. RESPONSIBLE PARTIES

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PPD , MDCM	PPD , PPD	PPD	PPD

4. ABSTRACT

Not applicable.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Start of data collection (analyses for primary objectives)	1Q2021
Start of data collection (analyses for other objectives)	1Q2021
End of data collection	2Q2021
Final study report	4Q2021

7. RATIONALE AND BACKGROUND

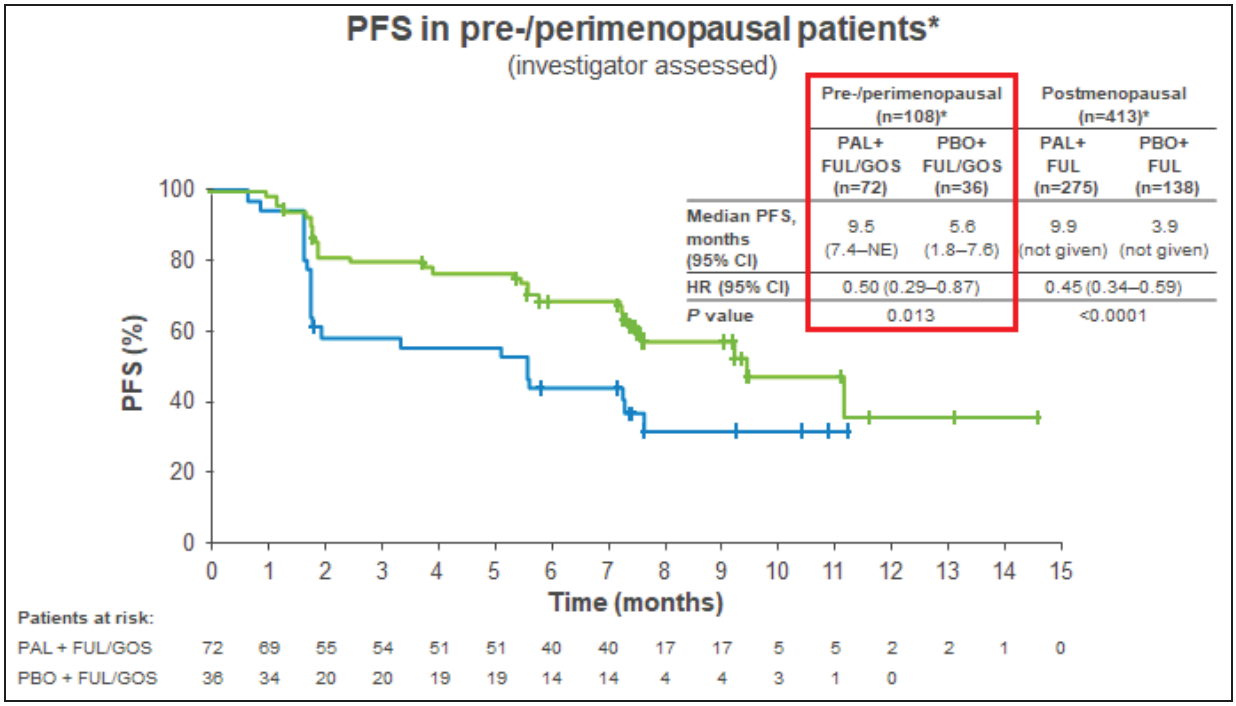
Breast cancer (BC) is the most common cancer in women and the second leading cause of cancer deaths. Currently, the average risk of a woman in the United States (US) developing breast cancer sometime in her life is about 13% with 276,480 new cases of invasive BC and 42,170 deaths from BC expected this year in the US. At this time there are more than 3.5 million women living with a history of BC in the US including women who are still being treated (Miller et al, 2016).[21] In the US, women under the age of 50 years-old comprise 20% of all BC diagnoses (Siegel et al, 2017; DeSantis et al, 2017)[29,8] and young women with hormone receptor-positive (HR+) disease are seeing an annual increase of over 8% yearly from 1992-2009 (Shah et al, 2020).[28] In 2017, it was estimated that 154,794 women in the US were living with metastatic BC (MBC); of these 3 out of 4 progressed from an early stage BC (Mariotto et al, 2017).[19] MBC remains an incurable disease with 5-year survival rates of 27% (American Cancer Society Facts and Figures, 2020)[1] with young women presenting with more aggressive disease than those who are postmenopausal (Shah et al, 2020).[28] HR+ BC is the most commonly diagnosed subtype (approximately 70-80%) (Kumler et al, 2016).[16] The goal of treatment for MBC is to prolong the time to disease progression or extend life to the extent possible or improve/maintain quality of life of that survival (Tanguy et al, 2018).[31]

Palbociclib, an oral CDK4/6 inhibitor, is approved for HR+/HER2– advanced or MBC in combination with an aromatase inhibitor (AI) or fulvestrant. Palbociclib was approved in the US based on improved median progression-free survival (PFS) demonstrated in 3 pivotal clinical trials: PALOMA-1 and PALOMA-2 (initial endocrine-based therapy in combination with letrozole for advanced disease) and PALOMA-3 (in combination with fulvestrant after progression on or after prior endocrine therapy). An accelerated approval was first granted based on results from the Phase 2 PALOMA-1 trial (Finn et al, 2015)[11] in February 2015. The median PFS in the palbociclib and letrozole arm was 20.2 months versus 10.2 months in the letrozole only arm (hazard ratio [HR] = 0.488, 95% confidence interval [CI]: 0.319, 0.748; 1-sided p=0.0004).

Palbociclib in combination with fulvestrant was approved 1 year later (February 2016) in pre or postmenopausal women with disease progression following endocrine therapy based on results from the PALOMA-3 trial (Turner et al, 2015; Cristofanilli et al, 2016)[33,6] which showed a statistically significant improvement in the median PFS for the palbociclib + fulvestrant arm compared with placebo + fulvestrant arm (11.2 versus 4.6 months, respectively; HR = 0.50 [95% CI: 0.40, 0.62; p<0.001]). Final overall survival (OS) data from that study has been reported (Turner et al, 2018)[34] demonstrating median OS of 34.9 months versus 28 months in the palbociclib + fulvestrant arm versus the placebo + fulvestrant arm (HR = 0.81; 95% CI; 0.64, 1.03; 1-sided p=0.0249), which was not statistically significant.

The Phase 3 PALOMA-2 study confirmed the findings from the PALOMA-1 trial, demonstrating a median PFS in the palbociclib + letrozole arm of 24.8 months compared to 14.5 months in the placebo + letrozole arm (HR = 0.58; 95% CI: 0.46, 0.72; 1-sided p<0.001) (Finn et al, 2016).[12] Subgroup PFS analyses according to stratification factors and demographic characteristics or prognostic factors revealed consistent results in PALOMA-2 (Finn et al, 2016)[12] and PALOMA-3 trials (Turner et al, 2015; Cristofanilli et al, 2016)[33,6] in all subgroups. The objective response rate (ORR) from PALOMA-2 was 42.1% (95% CI: 37.5, 46.9) in the palbociclib group versus 34.7% (95% CI: 28.4, 41.3) in the placebo group (odds ratio [OR]=1.40 [95% CI: 0.98, 2.01], p=0.06). Of note, pre/perimenopausal women were not included in the PALOMA-1 or -2 trials investigating palbociclib + letrozole as first-line treatment for women with ER+/HER2- advanced disease. The PALOMA-3 study investigating palbociclib + fulvestrant *did* include pre or perimenopausal women, and the study evaluated patients who were considered endocrine resistant. The subgroup of 108/521 (21%) pre or perimenopausal women randomized to palbociclib + fulvestrant + goserelin versus placebo + fulvestrant + goserelin showed a statistically longer median PFS of 9.5 months versus 5.6 months, respectively (HR = 0.50; 95% CI: 0.29, 0.87) (Figure 1) (Loibl et al, 2017).[17] The ORR in this subgroup was 25% versus 11% (OR: 3.06; 95% CI: 0.82, 13.38) and the clinical benefit rate (CBR) was 69.4% and 44.4% (OR: 2.89; 95% CI: 1.15, 7.34), respectively (Loibl et al, 2017).[17] The safety profile from the PALOMA-2 and -3 trials were consistent, with no new safety signals identified across the Phase 3 studies. Long-term pooled safety analyses of the 3 randomized Phase 2 and 3 studies demonstrated no evidence of specific cumulative or delayed toxicities with palbociclib + endocrine therapy (Dieras et al, 2018; Finn et al, 2019).[9,13] The most frequently reported adverse event (AE) of palbociclib was neutropenia, which could be managed with dosing interruption and/or dose reduction.

Figure 1. PALOMA-3 Subgroup Analysis by Menopausal Status



Source: CSR A5481023.

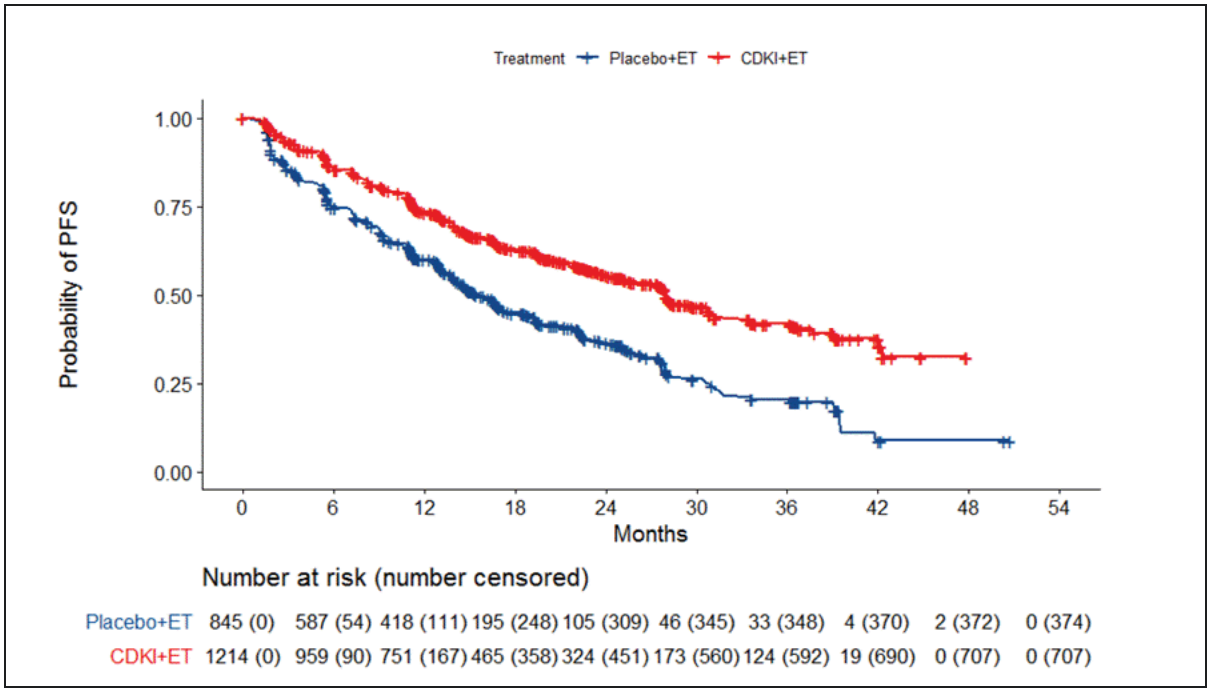
*Data cutoff: 16 March 2015; overall ITT population.

FUL = fulvestrant; GOS = goserelin; ITT = intent-to-treat; NE = not estimable; PAL = palbociclib; PBO = placebo; PFS = progression-free survival.

CCI [redacted] Furthermore, in the MONALEESA 7 randomized controlled trial (RCT), ribociclib, another approved CDK 4/6 inhibitor, in combination with a non-steroidal aromatase inhibitor (NSAI) demonstrated a significant median PFS benefit (23.8 versus 13.0 months; HR = 0.55; 95% CI: 0.44, 0.69; p<0.0001) in patients treated with ribociclib plus endocrine therapy (ET) versus ET alone (Tripathy et al, 2018).[32] Similar results were demonstrated in the NSAI combination subgroup excluding tamoxifen patients (27.5 versus 13.8 months and HR = 0.57 [95% CI: 0.44, 0.74]; n = 495). OS benefit in the pre or perimenopausal patient population treated with ribociclib + NSAI was also statistically significant, with median OS of not estimable (NE) versus 42 months in the AI subgroup population (HR = 0.70; 95% CI: 0.50, 0.98) (Im et al, 2019).[15] The recently published FDA pooled analysis of CDK 4/6 inhibitor treatment for patients with HR+/HER2– advanced or MBC, reported for patients aged 40 years and under who were treated with a CDK 4/6 inhibitor in combination with an AI in first-line, showed an HR = 0.50 (95% CI: 0.34, 0.74)

for PFS with a median of 19.8 versus 11.2 months, respectively (Figure 2) (Gao et al, 2020).[14] Lastly, results from the Phase 2 Young-PEARL study examined palbociclib and exemestane (and leuprolide) (n=92) versus capecitabine (n=86) in premenopausal women with advanced or metastatic HR+/HER2– BC with a primary endpoint of PFS. Median PFS in the palbociclib combination arm was 20.1 months versus 14.4 months in the capecitabine arm (95% CI: 14.2, 21.8) with HR = 0.659 (95% CI: 0.44, 0.10); 1-sided p=0.024. There was an ORR of 37% (34/92 patients) in the palbociclib group and 34% (29/86 patients) in the capecitabine group which achieved an objective response (p=0.781). The CBR differed between the groups, but the difference did not reach statistical significance (80.4% versus 69.9%, p=0.105) (Park et al, 2019).[22]

Figure 2. Progression-Free Survival for Patients ≤40 Years of Age in Pooled Studies of CDK 4/6 Inhibitors



Source: Gao et al, 2020.[14]

Understanding the effectiveness of new treatments in diverse clinical practice as a complement to RCT data is important as this provides evidence of the clinical benefit of these treatments in a more heterogeneous population with comorbid conditions and variations in care delivery seen in routine clinical practice. Since its approval in February 2015, palbociclib has rapidly become the standard of care in the treatment of HR+/HER2- advanced breast cancer (ABC) and is globally available commercially. Palbociclib has been available for use in the US for over 5 years with over 315,000 patients treated worldwide and nearly 130,000 in the US as of June 2020 making it possible to study comparative effectiveness in a large and diverse US HR+/HER2– MBC population.

Real world (rw) assessment has also been shown to be feasible and meaningful. Analysis of data for patients with MBC has been conducted to show that clinically meaningful information can be derived from the assessment of real-world progression-free survival (rwPFS) and real-world tumor response (rwTR) based on electronic health record (EHR) data abstraction when proper quality controls and analytic methods are incorporated based on concordance shown between RCTs and rw data. Concordance of rwPFS and real world tumor response (rwTR) from the US EHR with RCT data in MBC was recently demonstrated in a retrospective analysis comparing the PALOMA-2 trial letrozole + placebo control arm population cohort with a corresponding real-world cohort of US MBC patients treated with letrozole alone indicating the potential for real-world data to provide clinically consistent outcomes information (Bartlett et al, 2020).[3]

Real-world effectiveness for palbociclib combination therapy has been reported through retrospective analysis; however, follow-up has been limited. In a single-arm retrospective chart review, the palbociclib + AI treatment, landmark analyses showed that 84.1% of patients were progression-free and 95.1% were alive at 12 months with an ORR of 79.5% (Taylor-Stokes et al, 2019[30] Real world effectiveness of palbociclib + letrozole versus letrozole alone on rwPFS and OS was evaluated as an exploratory objective in a HR+/HER2– US MBC population (pre and postmenopausal patients) (DeMichele et al, 2019).[7] This study analysis suggests an associated rwPFS and OS benefit for palbociclib in combination with letrozole versus letrozole alone in 772 patients and 658 patients, respectively (464 in each propensity score matched group). The HR for PFS was 0.54 (95% CI: 0.46, 0.65; p<0.0001) and HR for OS was 0.58 (95% CI: 0.46, 0.73; p<0.0001) in the propensity score matched population. Tumor response was not reported in this analysis. In the subgroup of younger patients (patients aged 18-50 years), a benefit in OS was seen in patients treated with palbociclib + letrozole versus letrozole alone with a HR = 0.40 (95% CI: 0.13, 1.20); however, the sample sizes, (n=37 and n= 31, respectively) were limited. Another analysis of the EHR database assessed comparative real-world tumor response (rwTR) in a cohort of HR+/HER2– MBC patients receiving palbociclib + letrozole versus letrozole alone who had at least 1 tumor assessment postbaseline. rwTR was assessed using the treating physicians' clinical assessment of changes in disease burden based on radiologic scans. In 430 propensity score matched patients (215 in each group), patients were more likely to respond to first-line palbociclib + letrozole than letrozole alone after propensity score matching (PSM) with a real-world best tumor response (defined as patients with a complete response or partial response) of 58.6% versus 39.1%, respectively; OR = 2.2 (95% CI: 1.5, 3.2), p<0.0001). In the same PSM-matched patients, a consistent benefit was demonstrated in additional effectiveness endpoints in the palbociclib combination arm with respect to PFS with a HR = 0.60 (95% CI: 0.46, 0.79), p=0.0002) and OS with a HR = 0.58 (95% CI: 0.39, 0.85; p=0.0052) (Brusfky et al, 2020).[4]

CCI [redacted] This would be consistent with current guidelines category 1 recommendation for use of any CDK 4/6 inhibitor drug in this class (National Comprehensive Cancer Network, 2020).[25]

The study described in this protocol will evaluate data for all patients initiating palbociclib + AI or AI alone within the US Oncology Network (USON) who meet the entry criteria and initiated palbociclib combination therapy between 01 January 2010 and 30 June 2020. Data will be sourced from the USON's iKM EHR.

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

8. RESEARCH QUESTION AND OBJECTIVES

This study aims to assess real-world tumor response in pre/perimenopausal HR+/HER2– MBC patients initiating palbociclib + AI or AI alone as first-line therapy during the period on or after 01 January 2010 to on or before 30 June 2020. Data will be obtained from structured data fields within the iKM EHR database and will be supplemented by additional unstructured data collected through a targeted chart review.

Primary Objective

- To estimate the rwRR for pre/perimenopausal patients treated with palbociclib + AI compared to AI alone as first-line therapy for HR+/HER2– MBC.

9. RESEARCH METHODS

9.1. Study Design

Protocol Component	Description
Eligibility criteria	All pre or perimenopausal patients with HR+/HER2– MBC who have not received prior systemic treatment for their MBC and initiating therapy during the period on or after 01 January 2010 to on or before 30 June 2020 registered in the USON.
Treatment cohorts	Palbociclib + AI versus AI alone as the first-line MBC treatment.
Assignment procedures	Patients will be assigned to either cohort at baseline according to their observed first-line MBC treatment received.

Protocol Component	Description
Follow-up period	Begins at their starting date of the first-line MBC treatment during the period of 01 January 2010 through 30 June 2020 to study end (data cutoff 31 December 2020).
Primary endpoint	rwRR defined as proportion of patients with real-world tumor response consisting of complete response (CR) or partial response (PR) based on all recorded response assessments during first-line therapy captured with chart review.
Analysis plan	The primary endpoint rwRR will be estimated. PSM approach will be applied to adjust for potential imbalance in baseline prognostic factors.

This is a retrospective observational cohort study utilizing data derived from the USON's iKM EHR database combined with chart review to estimate real world tumor response outcomes in pre or perimenopausal patients receiving palbociclib + AI or AI alone as first-line MBC treatment for HR+/HER2– MBC. All patients meeting the entry criteria with HR+/HER2– MBC who have not received prior systemic treatment for their MBC during the period on or after 01 January 2010 to on or before 30 June 2020 will be included and analyses will be conducted utilizing secondary de-identified EHR data in the US. Structured data fields within the iKM EHR database will be supplemented by additional unstructured data collected through a targeted chart review.

9.2. Setting

This study uses secondary de-identified EHR data that involve patients who have been diagnosed with MBC and received treatment within the USON.

9.2.1. Inclusion Criteria

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

1. At least 18 years old at initial recorded MBC diagnosis.
2. Pre or perimenopausal at MBC diagnosis (Table 1 Key variables for definition).
3. Diagnosis of MBC at any point in patient history as recorded in the iKM database.
    a. 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 (specifically, the provider will select "breast cancer" from a list of diagnoses; International Classification of Diseases [ICD] codes will not be used).

b. Evidence of stage IV or recurrent MBC with a metastatic diagnosis date in the USON iKM EHR, as confirmed by unstructured clinical documents.

i. To identify patients with metastatic disease status, patients must have at least one of the following indicators: 1) receipt of a numbered line of therapy (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.

4. Confirmed HR+/HER2– status as defined as:

   a. HR+: ER+ or PR+ test;

   b. HER2–: any HER2 negative test and the absence of a positive test (IHC positive 3+, fluorescence in situ hybridization [FISH] positive/amplified, positive not otherwise specified [NOS]).

5. Received one of the following regimens as first-line treatment for MBC during the period from 01 January 2010 through index period 30 June 2020 until the data cutoff date of 31 December 2020.

   - Palbociclib + AI as first-line treatment for MBC.

   or

   - Monotherapy AI as first-line treatment for MBC.

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

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

9.2.2. Exclusion Criteria

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

1. Evidence of prior treatment with CDK 4/6 inhibitors (palbociclib, ribociclib or abemaciclib) in the early BC or MBC setting.

2. First structured activity (clinical visit) greater than 120 days after MBC diagnostic date with chart review to confirm no initial MBC treatment outside USON.

3. Receipt of treatment indicated for another primary cancer during the study observation period (after initiation of Palbociclib + AI or AI monotherapy and before 31 December 2020) or history of another primary cancer within USON.

4. Enrolled in any interventional clinical trial after initiation of Palbociclib + AI or AI monotherapy AND before 31 December 2020.

9.3. Variables

All variables are assessed using the operational definitions shown in Table 1. 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 (eg, age from date of birth). Derived and transformed data needed for the analysis are described and presented along with the operational definitions in Table 1.

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 (eg, response and progression).

Variables described as being captured at "baseline" will be captured at the date closest to the index date initiation within 90 days prior. 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. If multiple values are available during the time period of measurement, either baseline or prior medical history, 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.

As this study is expected to obtain an exception and waiver of informed consent from The US Oncology Institutional Review Board, a deidentified dataset will be used for analysis. To comply with applicable data regulations and to reduce the risk of patient reidentification, the deidentified dataset will be certified through an expert determination process before it is transferred to Pfizer. This expert determination will be performed by an experienced professional with appropriate statistical and scientific training. During the process, this individual will confirm which data elements can be transferred in the deidentified dataset. Some of the variables anticipated in the protocol may also need to be modified based on guidance received during expert determination, including the granularity of dates, race categories, and geographic location.

Table 1. Key Variables

Variable	*Source(s)*	*Period of measurement*	*Operational definition*
Demographic and patient characteristics			
Hormone receptor status	*iKM structured data + chart review*	*Prior medical history*	*Patients who have a documented hormone receptor-positive status, either estrogen and/or progesterone, will be included in the study.* *Categories:* *ER positive only* *PR positive only* *ER and PR positive*
Human epidermal growth factor receptor 2-negative status	*iKM structured data + chart review*	*Prior medical history*	*Patients who have a documented human epidermal growth factor receptor 2-negative status will be included in the study.* *Documentation of human epidermal growth factor receptor 2 will be captured as recorded in the iKM EHR database.*
Sex	*iKM structured data + chart review*	*Prior medical history*	*Patients will be categorized as:* *Male* *Female* *No information* *For patients lacking a documented menopausal status, sex assigned at birth will be verified through chart review.*
Age	*iKM structured data (derived)*	*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].*
Age groups	*iKM structured data (derived)*	*Baseline*	*Multiple age categories will be created based on the continuous age data:* *<30* *≥30-45* *≥45* *No information*
Race	*iKM structured data*	*Prior medical history*	*Categorized as:* *White/Caucasian* *Black/African American* *Other* *No information*
Height	*iKM structured data*	*Baseline*	*Patient's height in meters.*
Weight	*iKM structured data*	*Baseline*	*Patient's weight in kilograms.*
Body mass index (BMI) at index date	*iKM structured data (derived)*	*Baseline*	*BMI value as calculated from height and weight values will be provided.*
Smoking history	*iKM structured data*	*Baseline*	*Categorized as:* *Never smoked* *Current smoker* *Former smoker* *No information*
Family history of cancer	*iKM structured data + chart review*	*Baseline*	*Categorized as:* *Yes* No information
Menopausal status	*iKM structured data + chart*	*Baseline*	*Menopausal status will be first categorized as explicitly documented by physician as:*

Variable	*Source(s)*	*Period of measurement*	*Operational definition*
	review		*Pre-menopausal* *Peri-menopausal* *Among patients lacking a physician-documented menopausal status record, pre-menopausal status will be assigned to those whose sex assigned at birth is female, who are aged less than 60 years and meet either of the following criteria:* – *No documented history of a prior bilateral oophorectomy and received an LHRH analog* *AND/OR* – *Not amenorrhoeic*
Healthcare setting and provider characteristics			
Practice location	*iKM structured data (derived)*	*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 (eg, 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.*
CCI [redacted]	[redacted]	[redacted]	[redacted]
Practice size	*iKM structured data (derived)*	*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*

Variable	*Source(s)*	*Period of measurement*	*Operational definition*
			≥150 patients/year
Physician BC patient volume	*iKM structured data (derived)*	*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*
Disease characteristics			
Time since initial BC diagnosis	*iKM structured data + chart review (derived)*	*Medical history prior to index*	*The duration of time, in weeks, between the date of BC diagnosis and presentation of metastatic disease.* *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.*
Time since MBC diagnosis	*iKM structured data + chart review (derived)*	*Medical history prior to index*	*The duration of time, in weeks, between the index date and presentation of metastatic disease.* *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.*
Distant metastatic site(s)	*iKM structured data + chart review*	*Baseline*	*Baseline metastatic location(s) will be captured as documented in patients' charts.* *Note, patients that lack documented metastatic sites can indicate that metastases were not documented in the chart, not necessarily that patients did not have metastases.*
Visceral/non-visceral	*iKM structured*	*Baseline*	*Categorized as outlined below (not mutually exclusive)*

Variable	*Source(s)*	*Period of measurement*	*Operational definition*
status *Bone only*	*data + chart review (derived)*		*except for bone only, in which patients will have bone as their only metastatic site(s) identified:* ***Visceral:*** • *Liver* • *Lung* • *Pleura* ***Other (not exhaustive):*** • *Adrenal gland* • *Ascites* • *Axilla* • *Bilateral intraocular* • *Brain* • *Breast* • *Bronchus* • *Cervical nodes* • *Cervix* • *Chest wall* • *Duodenum, retroperitoneum & mesentery* • *Esophagus* • *Eye* • *Fallopian tube* • *Gallbladder* • *Gastrointestinal tract/stomach* • *Genital organ* • *Intestinal tract* • *Kidney* • *Large intestine* • *Leptomeningeal* • *Leptomeninges* • *Lymph nodes – distant* • *Lymph nodes – NOS* • *Lymph nodes – regional* • *Mediastinum* • *Muscle* • *Omentum* • *Other parts of nervous system* • *Other respiratory organ* • *Other urinary organ* • *Ovary* • *Pancreas* • *Pericardial effusion* • *Pericardium* • *Peritoneum* • *Pleural effusion* • *Rectum* • *Retroperitoneum* • *Skin* • *Small intestine* • *Soft tissue* • *Spinal cord* • *Spleen*

<table>
<tr><th>Variable</th><th>Source(s)</th><th>Period of measurement</th><th>Operational definition</th></tr>
<tr><td></td><td></td><td></td><td>Bone (not exhaustive):
Bone
Bone marrow
Pelvis
Ribs
Skull
Spine</td></tr>
<tr><td>Count of metastatic site(s)</td><td>iKM structured data + chart review (derived)</td><td>Baseline</td><td>The total count of metastatic site(s) at index:
No information
1
2
3
4+
Note, “no information” can indicate that metastases were not documented in the chart, not necessarily that patients did not have metastases.</td></tr>
<tr><td>Stage at diagnosis</td><td>iKM structured data</td><td>Medical history prior to index</td><td>Categorized as:
Stage 0
Stage IA
Stage IB
Stage IIA
Stage IIB
Stage IIIA
Stage IIIB
Stage IIIC
Stage IV
No information</td></tr>
<tr><td>Eastern Cooperative Oncology Group (ECOG) performance status</td><td>iKM structured data + chart review</td><td>Baseline</td><td>The ECOG performance status score is a rating of a patient’s disease status, daily living activities and quality of life, with low scores indicating greater functioning than high scores:
0
1
0/1
2
2+
3+
No information
Karnofsky performance status is a similar measure and will be converted to ECOG using the methodology outlined below. (Ma et al, 2010)[18]
<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-</td></tr>
</table></td></tr>
</table>

Variable	*Source(s)*	*Period of measurement*	*Operational definition*
			10, 20, 30 *4* *Completely disabled* ***0*** *5* *Dead*
CCI (Charlson Comorbidity Index) score	*Chart review*	*Prior medical history*	*Calculated based on the presence of 17 Charlson comorbidities at MBC diagnosis.* *Comorbidities and associated obfuscated dates documented prior to or on the index date will be captured and summarized as:* *Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, hemiplegia, chronic obstructive pulmonary disease, ulcer disease, diabetes with chronic complications, diabetes without chronic complications, renal disease, connective tissue disease such as rheumatoid arthritis or lupus, Alzheimer's or other dementia, cirrhosis or other serious liver disease, non-breast cancer malignancy (excluding sites of breast cancer metastasis and malignant neoplasm of skin), metastatic solid tumor (other than breast cancer), HIV/AIDS.* *In addition, history of interstitial lung disease (ILD) and pneumonitis will be noted but not included in the CCI score.* *Two approaches will be used to capture comorbidities documented in patients' medical records. First, comorbidities explicitly documented by providers will be captured and reported. Separately, patients with suspected comorbidities based on receipt of medications associated with those conditions will be identified.* *To identify suspected comorbidities, an extract of all concomitant meds documented pre-index for the study population cohorts will be generated with patients' entire treatment history documented in the structured data. The study team, including clinical experts and the Physician Investigator, will review the frequency distributions of the medications and map these to chronic conditions.* *For analysis purposes, comorbidities explicitly documented by providers versus those imputed by medication use will be differentiated.*

Variable	*Source(s)*	*Period of measurement*	*Operational definition*
Disease histology	*iKM structured data*	*Baseline*	*Categorized as:* *Ductal* *Lobular* *Mixed* *Metaplastic* *Tubular* *Mucinous* *Other* *No information*
BRCA 1/2 status	*iKM structured data + chart review*	*Baseline*	*Categorized as:* *Positive* *Negative* *No information*
ESR1 status	*iKM structured data + chart review*	*Baseline*	*Categorized as:* *Positive* *Negative* *No information*
NGS status	*iKM structured data + chart review*	*Baseline*	*Categorized as:* *Positive* *Negative* *No information*
Treatment characteristics			
Pre-index treatment(s)	*iKM structured data + chart review*	*Medical history prior to index*	*Patients' treatments received prior to index, along with obfuscated dates. This includes prior adjuvant hormonal treatment or prior neo-adjuvant/adjuvant chemotherapy.*
Adjuvant treatment end dates	*iKM structured data + chart review*	*Medical history prior to index*	*Obfuscated date of adjuvant treatment discontinuation.*
Endocrine sensitivity	*iKM structured data + chart review (derived)*	*Medical history prior to index*	*Relapse more than 12 months after completing adjuvant endocrine therapy.*
Disease-free interval	*iKM structured data + chart review (derived)*	*Medical history prior to index*	*Obfuscated dates between discontinuation of adjuvant therapy and the start of treatment for unresectable and/or metastatic disease.*
Radiotherapy	*iKM structured data + chart review*	*Medical history prior to index and study observation period*	*All radiotherapy, along with obfuscated dates, received prior to or during the study observation period will be captured. During analysis, 2 variables will be constructed:* *"Concomitant radiotherapy" will be defined as radiotherapies given during 1L treatment* *"Prior radiotherapy" will be defined as all radiotherapies prior to index date*
Index treatment regimen	*iKM structured data + chart review*	*Study observation period*	*Patients' index treatment will be categorized based on the cohort descriptions in Section 9.1:* *Palbociclib combination therapy with an AI (letrozole, exemestane or anastrozole) or AI monotherapy*
LHRH treatment	*iKM structured data + chart review*	*Study observation period*	*LHRH treatment received during the study observation period will be captured.*
Date of treatment initiation during the	*iKM structured data + chart*	*Study observation*	*The obfuscated date of initiation with a palbociclib-based combination regimen or AI monotherapy*

Variable	*Source(s)*	*Period of measurement*	*Operational definition*
patient identification period (ie, index date)	*review*	*period*	*(letrozole, exemestane or anastrozole) during the study identification period. If a 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.*
Index treatment end date(s)	*iKM structured data + chart review*	*Study observation period*	*Obfuscated date of final treatment for each drug or regimen. If a regimen consists of more than one drug with drugs ending on different dates, the date of the last administration of any drug will be used. 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*	*Study observation period*	*LOT will be operationally defined as a course of care that continues until disease progression or unacceptable toxicity. As such, advancement in LOT will be assigned if there is documented or inferred progression or toxicity.* *Switching between aromatase inhibitors (exemestane, letrozole, anastrozole) will not constitute a change in regimen, unless the next aromatase inhibitor is started due to provider-documented progression or toxicity. In contrast, switching between other classes of treatments (eg, CDK 4/6 inhibitors, chemotherapies), will constitute a change in regimen.*
Number of cycles (index treatment)	*iKM structured data*	*Study observation period*	*The number of provider-documented therapy cycles received for the index treatment.*
Index treatment schedule (cycle length and frequency)	*iKM structured data + chart review*	*Study observation period*	*The planned frequency and cycle length of the index treatment.*
Index treatment schedule changes	*iKM structured data + chart review*	*Study observation period*	*Each index treatment (either AI monotherapy or palbociclib combination therapy) schedule change will be captured and reported, along with the obfuscated date.*
Index palbociclib treatment starting dose	*iKM structured data + chart review*	*Study observation period*	*The actual index treatment starting palbociclib dosage received.* *Categories to be presented:* *75 mg* *100 mg* *125 mg* *Other* *No information*
Palbociclib combination regimen	*iKM structured data + chart review*	*Study observation period*	*Classification of patients into the following treatment groups:* *Palbociclib-letrozole* *Palbociclib-anastrozole* *Palbociclib-exemestane*
Reason for palbociclib dose changes	*Chart review*	*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:*

Variable	*Source(s)*	*Period of measurement*	*Operational definition*
			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 (all treatment lines)	*Chart review*	*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:* *Provider-documented disease progression* *Toxicity* *Decline in performance status* *Financial/insurance* *Completed planned treatment* *Death* *Hospice* *Patient preference* *Physician preference* *Other* *No information* *Reviewers will specify other reasons.*
Reason for treatment initiation (all treatment lines)	*Chart review*	*Study observation period*	*Data for treatment initiation reason will exclusively come from chart review. Reviewers will be asked to select reason(s) as explicitly documented in patients' charts.* *If available, reason for treatment initiation will be abstracted:* *Initial diagnosis* *Initial diagnosis with unresectable disease* *Initial diagnosis with metastatic disease* *Progressive disease* *Other reasons; non-progression* *Toxicity on prior therapy* *Reason not specified* *Reviewers will specify other reasons.*
Post-index treatment(s)	*iKM structured data + chart review*	*Study observation period*	*Patients' treatments received after index, along with obfuscated dates.*

Variable	*Source(s)*	*Period of measurement*	*Operational definition*
Provider-documented tumor assessments			
Provider-documented tumor assessment	*Chart review*	*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. Instead, for this study, provider documented assessments of tumor response will be used. 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 to the index treatment (AI monotherapy or palbociclib combination therapy) described within progress notes (along with the associated, obfuscated progress note date) will be captured. For each tumor assessment, it will be documented if a scan report was documented as the basis of the assessment.* ***Tumor 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").* ***Partial response:*** *Documented as partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease (decrease in disease volume even though disease is still present).* ***Stable disease****: Documented as disease is stable (not progressed or not improved; eg Stable appearance of lobe nodules and 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.*
Clinical outcomes			
Last USON visit date	*Chart review*	*Study observation period*	*Patients' last visit date will be captured through chart review as a verified physical encounter with the practice as evidenced by treatment administration, measurement of vital signs, laboratory specimen collection or other office procedures. For patients with a death date, this last visit date should occur prior to the death date.*
Death date	*iKM structured data + LADMF/NDI + chart review*	*Study observation period*	*Obfuscated date of death will be captured from the LADMF, NDI as well as iKM. If dates conflict between the 3 sources, the NDI, followed by the LADMF date will be prioritized. If severe data discordance is observed (ie, death is reported to occur prior to the index date and/or there is a difference of more than 6 months between them), then the iKM death date, as verified through chart review, will be used.*
Pneumonitis and	*Chart review*	*Study*	*Explicit attribution to treatment within chart will be*

Variable	*Source(s)*	*Period of measurement*	*Operational definition*
interstitial lung disease		*observations period*	*documented. Yes/No*

9.4. Data Source

Table 1 represents 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. The USON includes 1,200 affiliated physicians operating in over 470 sites of care in the US and treats approximately 1 million US cancer patients annually (https://www.usoncology.com/our-company). 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 (methodology described in Section 9.6). Electronic chart review data will be 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. (Patt et al, 2015, Patt et al, 2016, Robert et al, 2015).[23,24,27]

Real-world evidence sourced retrospectively from the EHR of the USON have previously been used to support FDA approval of a new drug application for Merkel cell carcinoma (Cowey et al, 2017).[5]

The Limited Access Death Master File (LADMF) of the Social Security Death Index (SSDI) and the National Death Index (NDI) of the Centers for Disease Control will be additional sources of vital status (death), in addition to death dates recorded in the EHR. Common patient identifiers (patient identification, name, and birth date) will be used to link patients from the iKM data warehouse and iKM chart review. Patients' names, dates of birth and social security numbers (SSN) will be used to link patients from iKM, LADMF and NDI data sources. All patients within iKM are assigned a unique patient identifier by iKM version (eg, some large practices have separate installations by location). When linking to the LADMF, patient SSN is used. Some practices do not collect SSN and some patients may not report it.

At the time structured EHR data are extracted for this project, an extract of the LADMF will also be requested from the Social Security Administration. Approximately 1 month prior to the deidentified data transfer to Pfizer, updated LADMF will be requested and updated death information from structured fields of the EHR will be extracted.

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).

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

9.4.1. Patient Selection

Structured data will be used to screen patients who received treatment within the USON based on the eligibility criteria described in Table 2. The patient attrition will be based on this initial screening.

Study-eligible patients who received first-line AI monotherapy or palbociclib + AI combination therapy will be selected to undergo a targeted chart review. During the course of abstraction, patients' eligibility for the study will be verified and some of these patients may be found to be ineligible. Reasons for disqualification will be captured and reported.

Table 2. Patient Attrition (01 January 2010 - 30 June 2020)

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 (ie, palbociclib, letrozole, exemestane or anastrozole) within the USON during the study identification period.	-	27,835
Aged 18 years at initial recorded diagnosis of MBC	3	27,832
Exclusion of patients enrolled in an interventional clinical trial during the study observation period.	2,299	25,533
Did not receive a treatment indicated for another primary cancer during the study observation period.	2,548	22,985
Received care at a USON site(s) utilizing the full EHR capacities of iKM at the time of treatment.	0	22,985
Exclusion of patients with qualifying treatments (ie, palbociclib, letrozole, exemestane or anastrozole) received only prior to metastases date and not after advanced diagnosis.	1,143	21,842
Exclusion of patients with start of first regimen more than 120 days after metastases date.	2,345	19,497
Exclusion of patients from sites without USON data access agreement.	8,440	11,057

Initial cohort counts (patients who initiated the cohort - specific regimen in an appropriate LOT)		
Pb-AI: Palbociclib combination therapy with an aromatase inhibitor (letrozole, exemestane, or anastrozole) among patients as first-line therapy in the advanced or metastatic setting. Patients with evidence of prior treatment with other CDK 4/6 inhibitors (ribociclib or abemaciclib), aromatase inhibitors (letrozole, exemestane, or anastrozole), tamoxifen, raloxifene, toremifene, or fulvestrant in the advanced or metastatic setting were excluded.	-	1,524
AI mono: Aromatase inhibitor (letrozole, exemestane or anastrozole) monotherapy as first-line treatment in the advanced or metastatic setting. Patients with evidence of prior treatment with other CDK 4/6 inhibitors (ribociclib or abemaciclib), aromatase inhibitors (letrozole, exemestane, or anastrozole), tamoxifen, raloxifene, toremifene, or fulvestrant in the advanced or metastatic setting were excluded.	-	4,395
Exclusion of patients who initiated qualifying regimens prior to the start of the study period (by cohort)		
Pb-AI: aromatase inhibitor (letrozole, exemestane, or anastrozole) + palbociclib.	15	1,509
AI mono: aromatase inhibitor (letrozole, exemestane, or anastrozole) mono.	461	3,934

Table 3. Menopausal Status by Cohort (Based on Structured Data Alone)*

Status	AI Mono (n=3,934)	PB-AI (n=1,509)
Perimenopausal	50 (1.3%)	12 (0.8%)
Premenopausal	185 (4.7%)	136 (9.0%)
Postmenopausal	2,363 (60.1%)	1,082 (71.7%)
Not documented	1,336 (34.0%)	279 (18.5%)

* Based on initial feasibility estimate with menopausal status to be confirmed through chart review. Chart review will also examine those patients where menopausal status is “not documented” in the structured field.

9.5. Study Size

All eligible patients will be included for the primary analysis. Approximately 385 patients will be included with close to a 1:2 ratio between palbociclib + AI and AI alone cohorts based on examination of structured iKM data applying inclusion/exclusion criteria (Table 2 and Table 3) between 01 January 2010 and 30 June 2020 (see Section 9.7.2).

9.6. Data Management

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 will be generated by the Data Analyst and the Biostatistician will apply the agreed upon sampling technique to identify the specific patients that will undergo chart review. This list of patients will then be securely transmitted to the Chart Review Team Manager.

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

Chart review will be 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.

Once on Pfizer servers, Pfizer staff perform a semi-automated process for quality assurance on the data, checking that the metadata align with the data dictionary from USON dataset, the number of records equals that expected from the vendor, and that the data types and controlled vocabularies are correct. The data are then loaded into a secure Pfizer server. Pfizer servers are backed up nightly and have failover and off-site redundancy. Access to data is limited only to Pfizer colleagues and is monitored with all end user activity is logged.

Pfizer maintains copies of all EHR or other real-world data in accordance with the FDA's July 2018 Industry Guidance on Use of Electronic Health Record Data in Clinical Investigations (FDA, 2018),[10] though Pfizer maintains its data in excess of the guidance – for a minimum of 7 years.

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

As 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.

9.6.2. 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, eg, CRFs and hospital records), copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by 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.

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.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of the data collected in this study are outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.7.1. Statistical Hypotheses

The primary purpose of this study is to estimate real world tumor response for pre/peri-menopausal patients treated with palbociclib + AI or AI alone as first line treatment for HR+/HER2- MBC in the US clinical practice setting. No formal hypothesis testing will be performed.

9.7.2. Sample Size Determination

Approximately 385 patients will be included with close to a 1:2 ratio between palbociclib + AI and AI alone cohorts based on examination of structured iKM data applying inclusion/exclusion criteria (Table 2 and Table 3) between 01 January 2010 and 30 June 2020. It is estimated that there will be approximately 135 patients in the palbociclib + AI arm and 250 patients in the AI alone arm of which a subset will have documented post-baseline tumor assessment.

9.7.3. Cohort for Analysis

All effectiveness analyses will be based on the pre/perimenopausal cohort. Eligible pre/perimenopausal patients with HR+/HER2- MBC will be included into the following cohorts:

Cohort to be analyzed for the primary objective:

a. Pre/perimenopausal patients treated with palbociclib + an AI as the initial therapy for the treatment of MBC.

b. Pre/perimenopausal patients treated with an AI alone as the initial therapy for the treatment of MBC.

9.7.3.1. Propensity Score Matching (PSM)

Propensity score matching (PSM) will be used to create matched sets of palbociclib treated and untreated patients who shared similar value of the propensity score. The propensity scores produce a set of matched pairs with similar distributions of the covariates but does not require close or exact matches for each individual matched pair of patients. Once the matched sample has been formed, the treatment effect can be estimated by directly

comparing outcomes between palbociclib treated and untreated patients in the matched sample. Variables to be used in the estimation of propensity scores (PS) may include key baseline demographics (ie, age, race) and clinical characteristics (Eastern Cooperative Oncology Group [ECOG] performance score, disease stage at initial diagnosis, visceral metastasis, Charlson Comorbidity Index, and number of disease sites). A final list will be specified in the SAP.

9.7.3.2. Analyses of Primary Endpoint

The primary endpoint is real-world response rate (rwRR) and the rwRR will be calculated as the proportion of patients with a real-world complete response (CR) or real-world partial response (PR) by treatment cohort. Patients with a best response of CR or PR are those patients with a CR or PR after 30 days of treatment initiation without a PD at any prior assessment.

Real-world tumor responses (rwTR) are assessed based on treating clinician's assessment of radiological evidence for change in burden of disease over the course of treatment. Assessments were not performed on a schedule and responses were not confirmed by subsequent assessment. Each assessment will be classified as follows:

- **Complete response (CR):** Documented as "a complete response" to therapy; indication patient is in "remission"; "all lesions" have disappeared or "no evidence of disease").

- **Partial response (PR):** Documented as partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease (decrease in disease volume even though disease is still present).

- **Stable disease (SD):** Documented as disease is stable (not progressed or not improved; eg, stable appearance of lobe nodules) or Mixed response, which is a combination of improved and worsened disease.

- **Progressive disease (PD):** Documented as disease has "progressed"; or worsening of disease.

- **Not evaluated (NE):** No documentation of status of disease.

To overcome the potential imbalance of baseline characteristics between the 2 cohorts, the propensity score (PS) will be computed by a logistic regression model using baseline characteristics for each patient. The PSM technique will be used to control for potential confounding factors when comparing the cohorts. Each patient in the palbociclib + AI cohort will be matched (1:1) to a patient in the AI alone cohort using a greedy matching algorithm, which sequentially without replacement selects the control patient whose propensity score is closest to that of the particular patient in the palbociclib + AI cohort. This matching process will be performed independently and prior to the access of rwTR outcome data.

The analysis of the primary endpoint is to estimate the rwRR between the 2 cohorts (palbociclib + AI compared to AI alone) using PSM method to balance baseline demographic and clinical characteristics between the two real world treatment cohorts.

The number and percentage of patients with a best overall response of CR, PR, SD, PD, and NE will be tabulated. The number and proportion of patients achieving rwTR (CR or PR) will be summarized along with the corresponding exact 2-sided 95% confidence interval calculated using a method based on Clopper-Pearson method. The odds ratio and the corresponding 2-sided 95% confidence interval will be calculated to contrast the treatment effectiveness on response rates.

Two analyses of rwRR will be performed:

1. rwRR among those patients who had at least one post-baseline tumor assessment documented in the database.

2. rwRR among all eligible patients who met the inclusion and exclusion criteria as defined in study protocol.

The rwRR rates will be estimated for each treatment cohort and compared by using PSM methodology to control potential baseline confounding factors.

9.7.3.3. Sensitivity Analyses

Sensitivity analysis will be performed to exam the robustness of the primary analysis.

Sensitivity analysis 1: **Inverse probability treatment weighting (IPTW)**

Inverse probability treatment weighting will be used to balance baseline demographic and clinical characteristics between comparison cohorts in this analyses (Austin and Stuart, 2015).[2] In the event that IPTW method does not balance potential confounder variables, analysis by PS quintiles will be used.

Sensitivity analysis 2: **Stratification by propensity score**

This analysis will divide patients into 5 equal-sized groups using quintiles of the estimated propensity score. The treatment effect of rwRR can be estimated by comparing rwRR rates directly between patients in two cohorts within strata. The stratum-specific estimates of treatment effect can then be pooled across stratum to estimate an overall treatment effect.

Sensitivity analysis 3: **Best tumor response imputation**

For patients who did not have any post baseline tumor assessment information, their rwTR may be imputed using logistic regression predictive modelling to predict response for patients with similar baseline characteristics from known patients.

9.7.3.4. Subgroup Analyses

While inclusion of patients between 2010 and 2015, allows for patient to be included in the control arm prior to palbociclib being approved, which may help to reduce bias in physician choice of treatment and allow for more patients being matched, however, the varying time periods between cohorts may be a limitation.

A subgroup analyses will be performed including patients only after palbociclib approval in the US. Patients included in this analysis with be those who meet inclusion and exclusion criteria during an index period on and after 01 February 2015 until on or before 30 June 2020.

Other subgroup analyses may be performed according to patient demographics and baseline characteristics as appropriate, based on availability of the data and sample sizes.

9.7.3.5. Other Analyses

Descriptive analyses for patient baseline characteristics will be conducted.

9.7.3.6. Analyses of AEs of Special Interest

The number of cases of pneumonitis and interstitial lung disease (ILD) which are directly attributable to the treatment will be reported for each treatment cohort which occurred while on first line treatment plus 30 days.

9.8. Quality Control

With the exception of supplementary vitality status and date of death, study data will originate in the EHR, then be extracted into a study dataset through a manual chart review process or programmatic queries. Following analytic file construction and deidentification process, the dataset will be securely transferred to Pfizer. Sites cannot enter data into the eCRF directly; to support consistency and accuracy of abstraction, dedicated abstractors from McKesson will have centralized access to the EHR from all practice sites, and enter retrospective data into the eCRF.

This is a retrospective study, therefore issues of quality control at study sites, eg data clarification queries, do not apply. Analyses are programmed according the specifications in the protocol's SAP and all code and other technical artifacts are documented and stored following established programming practices on Pfizer servers and in Pfizer’s Global Document Management System. Quality control (QC) will follow the USON dataset’s standard procedure for quality control and assurance as described below.

For structured data, McKesson’s Data, Evidence and Insight (DEI) team conducts 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 (eg, 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/SAP development;
- Data extraction and integrity;
- Populated tables and Study Report development.

As results of quality assurance and quality control, McKesson confirms:

- 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.

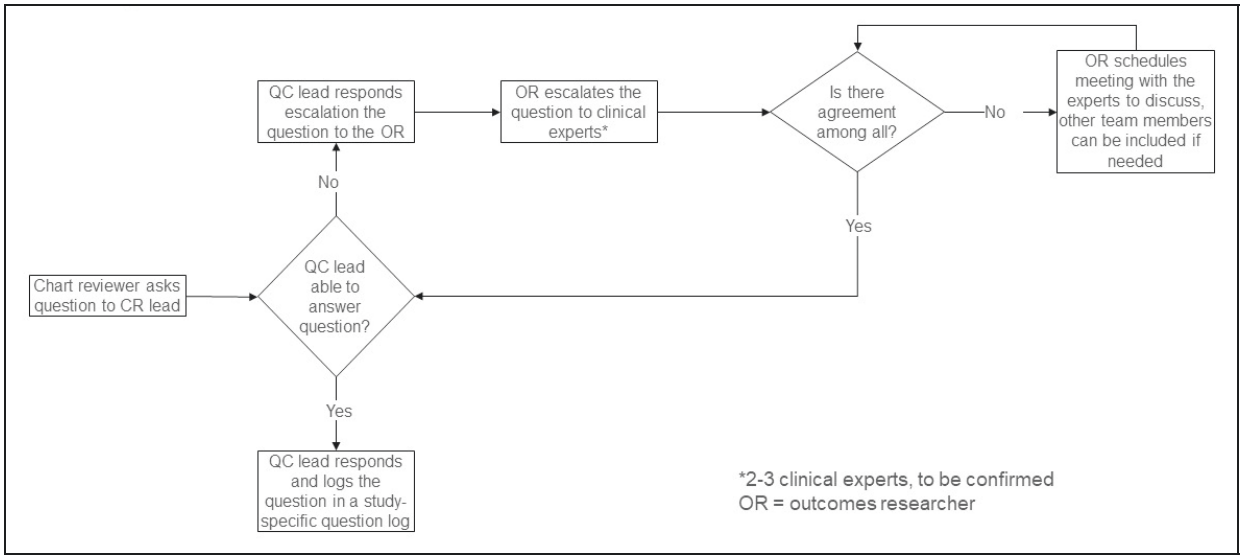
Quality control and validation of chart review (unstructured) data will occur in multiple phases. Chart review processes require that no interpretations be made during the data collection; instead, all data will be collected as documented by the physician in the chart. Prior to full chart review, a pilot will be conducted with at least 5% of the patient population, up to 25 patients. Charts will be reviewed by each reviewer on the team to ensure inter-rater reliability. Data Quality Specialists will review pilot data for accuracy and consistency, including implausible dates (ie, 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 will meet following pilot and before launch of full chart review to clarify ambiguous or conflicting data and address potential problems and questions. Pilot data will be presented to the research team for review and approval. If necessary, revisions to the tool and/or additional training will be implemented.

Once the pilot chart review is complete, the remaining chart reviews will proceed. During this phase of chart review, Data Quality Specialists will perform random and detailed checks of the data by verifying original source data. The Data Quality Specialist will also initiate queries, quality control of randomly selected charts and review of final data set before submission to researcher. Finally, the researcher and study's Biostatistician will provide a final examination of the final dataset by looking for missing or illogical data before preparing

it for analyses. This analysis will include a descriptive analysis of the provider characteristics, demographics, baseline clinical and disease characteristics, and characteristics of treatment patterns. Data points flagged as outliers will be reviewed by the Data Quality Specialist.

Data queries are handled through multiple steps. Questions from the abstractors or first level monitors are submitted to the McKesson Data Quality Specialist via a question log. Questions are logged and answers documented in the log for reference throughout the study. The McKesson Data Quality Specialist will answer questions directly, or escalate to the lead McKesson Researcher or Physician Investigator as appropriate. Queries and flags generated directly by the Monitor/Data Quality Specialist are communicated and resolved through the electronic data capture system. A scheme of the adjudication process is presented in Figure 3.

Figure 3. Adjudication Process Scheme



The eCRF will be hosted by the OpenClinica electronic data capture system, which allows review/signature by investigator on all data entered into the eCRFs, to attest the data accuracy. CCI [redacted]

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. (Robert et al, 2019)[26] The intent of this document is to ensure accurate, objective and consistent data capture. Algorithms used in data handling are validated through the QC and source data verification process.

Biostatisticians use SAS programs to QC data sets provided either by a structured database pull and from manual chart review. The team of biostatisticians and data analysts maintains a library of programming codes and algorithms that are used to analyze and classify any variables required for analyses. These codes are validated by the statistical analysis team. Any discrepancies are discussed and shared with the primary coder, data management, and biostatistician team.

For the primary endpoint, rwRR, chart abstraction will be undertaken to capture all tumor assessments associated with the index treatment (AI monotherapy or palbociclib + AI) documented in progress notes by treating physicians. Chart reviewers will classify these tumor assessments into the categories defined in Section 9.7.3.2, as well as capture the dates of assessment and whether they were based on radiologic imaging reports. As described above, McKesson Data Quality Specialists will perform random and detailed checks of the tumor assessment data by verifying original source data. If questions arise during capture of tumor assessments, these will be addressed with the adjudication process defined above.

Risks involved in the handling of data and mitigation strategies are described below:

- **Transferring from EHR to database.** McKesson's product management team manages the transfer of data entered into the EHR by practices into the centralized EHR database. Primary data management is handled by the DEI data management team. This is an automated process and does not require manual data entry. Prior to analysis the biostatistician will examine the data to ensure that all needed elements are within the datasets. During analysis, if the biostatistician discovers any data issues, this is first communicated to the project lead and/or research management for discussion. Data issues that require clinical judgement are examined and discussed with the physician investigator. Any systemic issues are then reported to the data management team. For instance, issues may be caused due to migration of data from one server to another and the data management team must be notified of any abnormalities. Further, the data management team communicates with DEI leadership and biostatisticians regarding any upcoming changes in the data.

- **Transferring from EHR database to eCRF.** There is not direct transfer from the database to the eCRF. Data entered into the eCRF is manually performed via chart abstraction. Subsequently, data that is captured in the eCRF is automatically transferred to a dataset within the eCRF application. The dataset can be pulled from the application via automated process that is manually initiated. A multipronged approach is taken to reduce the potential of capturing incorrect information from the chart via manual abstraction. First, fields in the eCRF are built with logic checks ensure data entered fit the parameters of the field and the study. Second, quality monitors perform checks on data captured by verifying data entered to the chart. Last, McKesson Data Quality Specialists perform QC on the data set to determine the overall quality level meets McKesson standards/expectations.

9.9. Limitations of the Research Methods

9.9.1. 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 in the study. 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 advanced disease in iKM EHR actually had previous chemotherapy for advanced disease in healthcare facilities outside the USON.

To minimize this risk, a targeted chart review is being performed to verify patients' eligibility and data elements that may not be reliably captured in structured fields. With chart review, progress notes and additional free-text can be reviewed to provide much richer source of information. All patients in the study sample will be selected for this chart review.

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. To minimize this risk, the study observation period will begin on the date palbociclib was approved for the treatment of metastatic breast cancer so that the study cohorts will both represent the treatment landscape after this approval.

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 (ITT) 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. To reduce this potential for bias, an ITT approach will be used 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. Statistical methodology such as IPTW and PSM will be employed to try to mitigate these potential biases.

9.9.2. External Validity of Study Design

Not all community oncology practices are included in the USON, which utilizes the iKM EHR and decision-support technology. Therefore, the results of this study will be most generalizable to other community oncology practices that adhere to evidence-based treatment guidelines.

9.9.3. Analysis Limitations

As a retrospective observational study, data entry errors at the point of care may occur and influence the results. To reduce this risk, a targeted chart review will be performed to capture or verify data elements that may not be reliably sourced through structured data. Additionally, Section 9.8 describes the quality control process that will be taken to ensure data from the EHR are captured correctly, which includes additional verification of outlying and missing values.

9.9.4. 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. To reduce this risk, a targeted chart review will be performed to capture or verify data elements that may not be reliably sourced through structured data.

Prescriber bias is a component of real-world treatment patterns in the absence of randomization and with a change in standard of care and can be adjusted for when confounders are known with statistical approaches including propensity score matching and inverse probability of treatment weighting. Addressing unobserved variables presents greater challenges and requires the ability to discern their influence. The USON iKM EHR dataset represents information collected as part of routine clinical practice and thus has limitations typical of data collected for purposes other than research.

9.9.5. Real-World Tumor Response

Given the retrospective nature of the study, some limitations are present including those typical of a data source where the primary purpose for collection was other than research. These include incomplete or missing data, potential for inaccurate data capture, lack of scheduled assessments and lack of standardized tumor assessments. In addition, response to treatment and disease progression were determined based on the individual treating physician’s clinical assessment or interpretation of radiographic scans or pathology results rather than a standard criterion such as RECIST.

The USON has deployed the iKM EHR and decision-support technology to encourage the use of evidence-based treatment and complete documentation. Therefore, it is expected that high proportion of patients will have tumor assessments documented. As evidence of this, based on a preliminary feasibility assessment, it is estimated that over 80% of patients will have tumor assessments documented.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. 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.

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

Patient personal data will be stored with the USON's iKM EHR database in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The McKesson study team will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, McKesson shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study,

linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the research agreement 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 only in aggregate form and with attention to results that represent small counts of patients.

10.2. 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 IRB. This project involves the study of existing data and records; the McKesson team will prepare a de-identified dataset with study information. The Pfizer study team will not perform any analysis intended to re-identify research participants. Once exemption status and a waiver of informed consent are met, a waiver of authorization can be approved, allowing the retrospective study to occur.

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

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, 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.

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

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS REQUIREMENTS

Structured Data Analysis

This study involves data that exists 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 (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, 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 and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

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

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

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

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

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

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

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if McKesson is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.