Study information

Title	Real-World Treatment Effectiveness of Palbociclib in Combination With an Aromatase Inhibitor as 1st line Therapy in Metastatic Breast Cancer
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Active substance	Palbociclib (IBRANCE®; PD-0332991)
Medicinal product	Palbociclib (IBRANCE®; PD-0332991)
Research question and objectives	**Primary objective** • To compare overall survival (OS) of first line palbociclib + AI versus AI alone for postmenopausal women or men with HR+/HER2- MBC **Secondary objectives** • To compare real-world progression free survival (rwPFS) and real-world tumor response (rwTR) of first line palbociclib + AI versus AI alone for postmenopausal women or men with HR+/HER2- MBC • To describe treatment patterns of palbociclib, including initial dose, dose adjustments, treatment duration, subsequent treatments, and time to chemotherapy CCI [redacted]

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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
BSO	bilateral salphino-oopherectomy
BRCA	**br**east **ca**ncer susceptibility protein gene
CDK	cyclin-dependent kinase
CCI	Carlson comorbidity index
CI	confidence interval
CRF	case report form
DCT	data collection tool
DFI	disease-free interval
ECOG	Eastern Cooperative Oncology Group
ER	estrogen receptor
ET	endocrine therapy
EHR	electronic health record
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
GPP	Good Pharmacoepidemiology Practices
HCP	Health Care Professional
HER	human epidermal growth factor receptor
HIPPA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hormone receptor *or* hazard ratio
ICD	International Classification of Diseases
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IPTW	Inverse probability treatment weighting
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intent-to-treat
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
MACS	Model-Assisted Cohort Selection

Abbreviation	Definition
MBC	metastatic breast cancer
ML	machine learning
NA	not applicable
NCCN	National Comprehensive Cancer Network
NDI	National Death Index
NE	not estimated
NI	non-interventional
NIS	non-interventional study
NOS	not otherwise specified
NSAI	Non-steroidal aromatase inhibitor
OS	overall survival
p	p-value
PALOMA	**PAL**bociclib **O**ngoing Trials in the **MA**nagement of Breast Cancer
PASS	Post Authorization Safety Study
PD	progressive disease
PDF	portable document format
PFS	progression-free survival
PR	progesterone receptor
PS	propensity score
PSM	propensity score matching
QC	quality control
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	rank preserving structural failure time
rwCR	real-world complete response
rwPD	real-world progressive disease
rwPFS	real-world progression-free survival
rwPR	real-world partial response
rwTR	real-world tumor response
rwRR	real-world response rate
SAP	Statistical Analysis Plan
SD	standard deviation
SSDI	Social Security Death Index
TBC	to be confirmed
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title: Real-World Treatment Effectiveness of Palbociclib in Combination With an Aromatase Inhibitor as 1st line Therapy in Metastatic Breast Cancer

Date of Abstract: 6 August 2021

Version: DRAFT version 2.0

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Rationale and Background:

Palbociclib is an oral CDK4/6 inhibitor, approved for the treatment of adult patients with HR+/HER2– advanced or metastatic breast cancer (MBC) in combination with (1) an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men; or (2) fulvestrant in patients with disease progression following endocrine therapy. Since its approval in February 2015, palbociclib has rapidly become a standard-of-care in the treatment of HR+/HER2- MBC.

According to American Cancer Society, in the US, there will be an estimated 281,550 new cases of invasive breast cancer in women, 2,650 cases in men and 44,130 patients are estimated to die from breast cancer in 2021[1]. The goal of treatment is to prolong the time to disease progression or extend life to the extent possible or improve/maintain quality of life of that survival[2]. The Phase 2 PALOMA 1 study comparing palbociclib + letrozole versus letrozole alone demonstrated a significant longer PFS and numerical but not statistically significant longer in median overall survival (OS) for the combination arm versus letrozole[3]. In the confirmatory Phase 3 PALOMA-2 trial, first-line palbociclib plus letrozole therapy significantly improved median progression-free survival (PFS) compared with placebo plus letrozole (27.6 vs 14.5 months; $P<0.0001$; data cutoff: May 31, 2017) in postmenopausal women with estrogen receptor–positive (ER+)/HER2– MBC[4]. The objective response rate (defined as confirmed complete response [CR] or partial response [PR] based on Response Evaluation Criteria in Solid Tumors [RECIST]) was 42.1% with palbociclib plus letrozole compared with 34.7% with placebo plus letrozole (odds ratio [OR], 1.40 [95% CI, 0.98–2.01], $P=0.06$)[5]. In PALOMA 2, OS is the secondary endpoint and the data is not yet available. The PALOMA 3 trial, comparing palbociclib + fulvestrant versus placebo + fulvestrant in patients with HR+/HER2- ABC who progressed on or after prior endocrine therapy, demonstrated a significant longer PFS and numerical difference in OS of 34.9 versus 28.0 months HR: 0.81 (95% CI, 0.64 to 1.03; p = 0.09) for the combination arm versus fulvestrant alone arm for the ITT population[6].

Using real-world evidence to complement data from randomized controlled clinical studies is important because the stringent inclusion and exclusion criteria of oncology clinical studies

exclude a substantial proportion of the patient population with cancer [7, 8]. Growing evidence has demonstrated safety and effectiveness of palbociclib in combination with endocrine therapy in real-world clinical practice with over six years of availability in the US[9-12]. Although multiple real-world studies have been conducted, most studies share one or more limitations, such as small sample size, short follow-up, inconsistent definitions of outcomes, and lack of a control arm. Findings from previous studies cannot be directly compared and may not be generalizable to other patients [11, 13-18].

To our knowledge, only one comparative study has been specifically conducted to compare the effectiveness of palbociclib in combination with endocrine therapy vs endocrine alone in the real-world setting[12, 19]. This analysis included 1430 patients in the Flatiron Health Analytic Database and had a median follow-up of 24.2 months. Results showed that first-line palbociclib plus letrozole was more effective than letrozole alone based on median real-world PFS (20.0 vs 11.9 months; hazard ratio, 0.58 [95% CI, 0.49–0.69]; $P<0.0001$) and overall survival (OS) results (median OS not reached vs 43.1 months; hazard ratio, 0.66 [95% CI, 0.53–0.82]; $P<0.001$) [19]. Tumor response analysis demonstrated that the real-world best tumor response rate was 58.6% in the palbociclib plus letrozole group versus 39.1% in the letrozole group (odds ratio, 2.21 [95% CI, 1.50–3.25], $P<0.0001$) after propensity score matching (PSM), suggesting that HR+/HER2– MBC patients were more likely to respond to palbociclib plus letrozole compared to letrozole alone[12]. CCI [redacted] While this OS analysis was based on a total of 476 deaths, this comprised 33% of the entire cohort studied (N=1430), with a median follow-up of 24.2 months, the endocrine partner analyzed was letrozole only, and only women were included[19]. Therefore, additional research with both men and women, AI as endocrine partner as per the label, and longer-term follow-up is warranted to more thoroughly evaluate the finding

Study 1151 will investigate the effectiveness of 1st line palbociclib in combination with AI vs AI alone in HR+/HER2- postmenopausal women or men. CCI [redacted]

Research question and objectives:

This study will compare real-world effectiveness outcomes for patients treated with palbociclib +AI versus AI alone as first line treatment for HR+/HER2- MBC in the Flatiron dataset initiating therapy between 03 February 2015 and March 2020. The primary endpoint will be overall survival (OS).

Primary Objective

- To compare overall survival (OS) of first line palbociclib + AI versus AI alone for postmenopausal women or men with HR+/HER2- MBC

Secondary objectives

- To compare real-world progression free survival (rwPFS) and real-world tumor response (rwTR) of first line palbociclib + AI versus AI alone for postmenopausal women or men with HR+/HER2- MBC
- To describe treatment patterns of palbociclib, including initial dose, dose adjustments, treatment duration, subsequent treatments, and time to chemotherapy

CCI [redacted]

Study design:

The study is designed to evaluate the effectiveness of palbociclib + AI versus AI alone as first line treatment for HR+/HER2- MBC.

This is a retrospective observational cohort study utilizing data derived from the Flatiron Health Analytic Database to compare effectiveness outcomes in patients receiving palbociclib + AI versus AI alone as first line treatment for HR+/HER2- MBC. Study patients have HR+/HER2- MBC and have initiated palbociclib + AI or AI alone as the first line of anti-cancer treatment during the period of February 2015 through March 2020 in the US real-world clinical practice setting.

The date of the initiation of palbociclib + AI or AI alone as the first line of therapy in the metastatic setting between 03 February 2015 and March 31, 2020 is defined as the index date.

Overall survival is defined as the number of months from start of palbociclib + AI or AI alone to death. Patients who did not die will be censored at the date of last follow-up or date of data cutoff during the study period from February 2015- September 2020. Real-world PFS (rwPFS) will be defined as the number of months from start of palbociclib + AI or AI alone to death or disease progression (based on clinical assessment or by radiographic scan/tissue biopsy per Flatiron rules), whichever occurred first. Patients who did not die or did not have disease progression, will be censored at the date of initiation of next line of therapy for patients with 2 or more lines of therapy or the date of their last visit during the study period (February 2015- September 2020) for patients who only received 1 line of therapy. 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.

The comparative analyses for the study objectives of assessing effectiveness outcomes of palbociclib + AI versus AI alone will be conducted applying inverse probability treatment

weighting (IPTW) to balance baseline demographic and clinical characteristics between the comparison cohorts.

Population Setting: This study uses secondary de-identified Flatiron Healthcare Analytic data that involve men and women who have been diagnosed with MBC in the United States.

Study Population: Patients who were 18 years of age or older at MBC diagnosis, had HR+/HER2- confirmed and initiated palbociclib + AI or AI alone as first line therapy in the metastatic setting during the period from February 2015 through March 2020 will be included in the analyses. Eligible patients will be identified from the Flatiron Health Analytic Database.

Variables: Variables will be obtained from both structured and unstructured data using Flatiron's technology-enabled data processing. The following variables will be included for the analyses: demographics (e.g., age, race, menopausal status, region), baseline clinical characteristics (e.g., date of initial BC diagnosis, date of MBC diagnosis, endocrine sensitivity, ECOG performance status, disease stage at initial diagnosis, site of metastasis, and number of disease sites), treatment patterns (e.g., AI therapy partner, starting dose, dose adjustment, duration of treatment, discontinuation, reasons for discontinuation, time to subsequent therapy, and time to chemotherapy), and effectiveness outcomes (i.e., OS, rwPFS, rwPFS2, rwTR).

Data source:
The Flatiron Health Analytic Database is a nationwide longitudinal, demographically, and geographically diverse de-identified database derived from electronic health record (EHR) data in the US. The Flatiron Health EHR-derived database includes structured and unstructured data from over 280 cancer clinics (~800 sites of care) representing more than 2.4 million US cancer patients available for analysis (see Section 9.4 for a more detailed description of the Flatiron Health Analytic Database).

Study Size: Based on an initial feasibility assessment using Flatiron Health Analytic Database between February 2015 –February 2020, there are over 1,500 patients in the database with HR+/HER2- MBC who received palbociclib + AI and AI alone as first line therapy for their metastatic disease, respectively. Of these, ~200 patients are thought likely to be pre/perimenopausal based on age at metastatic diagnosis. All patients who meet inclusion and exclusion criteria will be included in the statistical analyses.

Data Analysis:

The primary effectiveness endpoint (i.e., OS) of palbociclib + AI versus AI alone will be compared by weighted log-rank tests based on the IPTW approach. The method of IPTW will be the initial method used to address the potential effects of observed confounders. Participant characteristics such as age, race, practice type, ECOG performance score, disease stage at initial diagnosis, visceral metastasis, number of disease sites, endocrine sensitivity, and comorbidities will be examined for unequal baseline distributions. These variables will

be used to compute a propensity-to-treatment score (PS) by a logistic regression model, where the outcome variable is being in the palbociclib + AI group (yes, no). The individual PS is used to obtain the individual IPTW which is applied to the observations to assess the balance between treatment arms in the potential confounders after weighting.

If the method of IPTW yields balanced treatment groups with respect to the potentially measured confounders, then a weighted log-rank test using IPTW will be used to compare OS between the palbociclib + AI group and the AI alone group, with a nominal $p< 0.05$, two-sided, indicating an OS benefit in the palbociclib + AI group. The weighted Cox proportional hazards model will be used to compute the hazard ratio and the corresponding 95% CI. If the method of IPTW does not yield balanced treatment groups with respect to the potential confounders, analysis by PS quintiles will be used. All subjects will be stratified in quintiles based on the PS. A stratified log-rank test (stratified by PS quintiles) will be used to compare OS between the palbociclib + AI group and the AI alone group, with a nominal $p< 0.05$, two-sided, indicating an OS benefit in the palbociclib + AI group. This method allows for the comparison of subjects with similar PS without the potential loss of subjects in 1-1 matching. A stratified Cox proportional hazards model (stratified by PS quintiles) will be used to compute the hazard ratio and the corresponding 95%CI.

These time-to-event endpoints will also be summarized using the weighted Kaplan-Meier method and displayed graphically where appropriate. Similar analyses will be performed for rwPFS. Logistic regression analysis will be performed to compare rwTR between the 2 treatment groups. Descriptive analyses will be performed to report baseline patient demographics and clinical characteristics, treatment patterns, and time to next line of systemic anticancer therapy from palbociclib + AI initiation. Subgroup analyses will be conducted according to age, ethnicity, ECOG performance, metastatic site (i.e. visceral, bone only, etc.), and endocrine sensitivity as sample sizes allow.

A detailed statistical analysis plan (SAP) will be developed separately.

5. AMENDMENTS AND UPDATES

Version	Effective Date	Substantial or administrative amendment	Protocol sections changed	Summary of amendments	Reason
Version 2	06/08/2021	Version 2 is developed because the study purpose has been changed from potential label expansion to publication only			
Amend-ment 1	02/16/2022	Administrative updates	Header, section 3 Investigator, section 6 milestone dates,	Header updated to reflect Amendment 1, not draft Author placeholder removed Milestone dates updated	Adminstrative changes to reflect final status of protocol, current authors, updated milestones to reflect later dates of analyses start for secondary and [redacted]

6. MILESTONES

Milestone	Planned Date
Completion of data curation by Flatiron Health Analytic Databases per Flatiron's rules	30 June 2021
Protocol and SAP development and approval	31 August 2021
Start of data analyses for primary objectives	01 September 2021
Start of data analyses for secondary objectives	01 March 2022
CCI [redacted]	[redacted]
Final study report	31 Dec 2023

7. RATIONALE AND BACKGROUND

According to American Cancer Society, breast cancer is the most common cancer in women and the second leading cause of cancer deaths (only lung cancer kills more women each year)[1]. In the US, there will be an estimated 281,550 new cases of invasive breast cancer in women, 2,650 cases in men and 44,130 patients are estimated to die from breast cancer in 2021[1]. In 2017, it was estimated that 154,794 women were living with metastatic BC in the US; of these 3 out of 4 progressed from an early stage BC[20]. Metastatic breast cancer remains an incurable disease with 5-year survival rates of 28%[1] . Hormone receptor-positive (HR+) breast cancer is the most commonly diagnosed subtype (~70-80%)[21]. 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[2].

Palbociclib, an oral CDK4/6 inhibitor, is approved for HR+/HER2– advanced and metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant. Palbociclib is approved in the US based on improved median 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). Approval was first granted based on findings from the Phase 2 PALOMA-1 trial[3] in February 2015.

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 phase 3 PALOMA-3 trial.[22] Final OS data from that study has been reported,[6] demonstrating median of 34.9 months versus 28 months in the palbociclib +

fulvestrant group versus fulvestrant alone (HR 0.81; 95% CI; 0.64, 1.03; 1-sided p=0.0249), which was not statistically significant.

The pre-specified analysis of patients who were endocrine sensitive demonstrated an OS HR of 0.72; 95% CI: 0.55, 0.94 in those without sensitivity to previous endocrine treatment (HR of 1.14; 95% CI; 0.71, 1.84). 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 of 0.58; 95% CI: 0.46, 0.72; 1-sided p<0.001)[5]. With extended follow-up, the median PFS was 27.6 vs 14.5 months; P<0.0001; data cutoff: May 31, 2017)[4]. Subgroup PFS analyses according to stratification factors and demographic characteristics or prognostic factors revealed consistent results in PALOMA-2[5] and PALOMA-3 trial[22, 23] in all studied subgroups. Results for the secondary endpoint of OS data from PALOMA-2 are event driven and not yet available.

Of note, a patient population *not* included in the PALOMA-1 or -2 trials investigating palbociclib + letrozole as first line treatment for women with ER+/HER2- advanced disease was the pre or perimenopausal population. The PALOMA-3 study investigating palbociclib + fulvestrant did include pre or perimenopausal patients, however the study evaluated patients who were progressed following endocrine therapy. The subgroup of 108 pre or perimenopausal women (out of the total 521) randomized to palbociclib + fulvestrant + goserelin versus placebo + fulvestrant + goserelin in a 2:1 fashion showed a statistically longer median PFS of 9.5 versus 5.6 months respectively (HR of 0.50; 95% CI: 0.29, 0.87)[24]. 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.[25] The primary toxicity of palbociclib is neutropenia, which can be managed with dosing interruption and/or dose reduction.

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 [7, 8]. Accumulating evidence has demonstrated real-world safety and effectiveness of palbociclib in combination with endocrine therapy since its approval in February 2015. For example, in a retrospective chart review[11], the palbociclib + AI treatment landmark analyses showed that 84.1% of patients were progression free and 95.1% were alive at 12 months. CCI [redacted] A total of 1,430 female patients with HR+/HER2-MBC in the first line setting were included in the analysis. The analysis demonstrated that first-line palbociclib plus letrozole versus letrozole alone significantly prolonged patients' median rwPFS (20.0 vs 11.9 months; hazard ratio, 0.58 [95% CI, 0.49–0.69]; *P*<0.0001) and overall survival (OS) results (median OS not reached vs 43.1 months; hazard ratio, 0.66 [95% CI, 0.53–0.82]; *P*<0.001) [19]. Furthermore, tumor response analysis demonstrated that the real-world best tumor response rate was 58.6% in the palbociclib plus

letrozole group versus 39.1% in the letrozole group (odds ratio, 2.21 [95% CI, 1.50–3.25], *P*<0.0001) after propensity score matching (PSM), suggesting that HR+/HER2– MBC patients were more likely to respond to palbociclib plus letrozole compared to letrozole alone[12].

In another retrospective analysis of Flatiron database, Downer et al included 5,259 HR+/HER2- patients diagnosed with MBC[9]. Median overall survival was longer in patients receiving CDK 4/6 inhibitor (palbociclib, ribociclib, and abemaciclib) in combination with endocrine therapy (ET) than for patients receiving ET alone, or chemotherapy. Patients receiving CDK 4/6 in combination with ET compared to ET alone demonstrated a HR of 0.73 (95% CI: 0.65, 0.83) using multivariable Cox proportional hazards models. The median OS in the CDK4/6 inhibitor arm was 44.9 months (95% CI: 40.8, NA) versus 35.8 months (95% CI: 33.1, 38.9) in the ET alone arm versus 24.2 months (95% CI: 22.2, 26.9) in chemotherapy arm. Palbociclib, the first approved CDK 4/6 inhibitor, comprised 94% of CDK 4/6 inhibitor use in the study.

However, most studies share one or more limitations, such as small sample size, short follow-up, inconsistent definitions of outcomes, and lack of a control arm. Findings from previous studies cannot be directly compared and may not be generalizable to patients in other routine clinical practice settings [11, 13-18]. Further real-world studies in diverse patient populations and with longer follow-ups are needed.

While peri or premenopausal women with HR+/HER2-MBC were not included in the PALOMA study program in combination with an AI for initial endocrine-based therapy for MBC, an analysis of the subgroup of patients in PALOMA 2 who were between 18 and 50 years of age (n=60 palbo combination, n=35 letrozole alone) demonstrated an HR of 0.59 (95% CI: 0.23, 1.51) in favor of the palbociclib arm. Furthermore, in the MONALEESA 7 trial, ribociclib, another approved CDK 4/6 inhibitor, in combination with a non-steroidal aromatase inhibitor (NSAI) demonstrated 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 [26]. Similar results were demonstrated in the NSAI combination subgroup excluding tamoxifen patients (27.5 versus 13.8 median months and HR of 0.57 [95% CI: 0.44, 0.74]; n = 495). Overall survival benefit in the pre or perimenopausal patient population treated with ribociclib + NSAI was also statistically significant: median NE versus 40.7 months in the AI subgroup population (HR of 0.70; 95% CI: 0.50, 0.98). Finally, in the PALOMA 3 study a PFS benefit for premenopausal women with an HR of 0.46 (95% CI: 0.28, 0.75) with a median PFS of 9.5 versus 5.6 months for the combination arm versus fulvestrant alone was demonstrated. The recently published FDA pooled analysis of CDK 4/6 inhibitor treatment for patients with HR+/HER 2- advanced or metastatic breast cancer reported for patients aged 40 and under treated with a CDK 4/6 inhibitor in combination with an AI in first line an HR of 0.50 (95% CI: 0.34, 0.74) for PFS with a median of 19.8 versus 11.2 months respectively[27]. Some real-world evidence of effectiveness for palbociclib + letrozole in women younger than 50 years of age was reported based on a descriptive analysis of palbociclib + letrozole patients from the Flatiron dataset[28].

However, there is no real-world comparative effectiveness research that has specifically compared the effectiveness of first line palbociclib plus letrozole versus letrozole alone in peri or premenopausal women with HR+/HER2-MBC.

The study described in this protocol will evaluate data for all patients initiating palbociclib + an AI or AI alone from the Flatiron dataset who meet the inclusion and exclusion criteria between February 2015 and March 2020. This study will differ from the prior analysis (1122) by the inclusion of all patients (women and men) treated with palbociclib in combination with any aromatase inhibitor and a longer index period from product approval, a minimum of 6 months of available follow-up from index treatment and more baseline patient characteristics to be included. Longer median follow-up is expected although the increase in median follow-up cannot be predicted despite the additional observation interval due to the changing cohort within the Flatiron dataset; patients and practices are added to and leave the Flatiron EHR system and thus longitudinal follow-up of a specific cohort is not possible. CCI [redacted] Additional variables will be added for the 1151 study including menopausal status, endocrine sensitivity, and comorbid conditions. Sensitivity analysis will also be conducted to assess internal validity of the data and are defined in the Statistical Analysis Plan.

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 effectiveness in HR+/HER2- MBC patients initiating palbociclib + AI or AI alone as first-line therapy during the period 01 February2015 through March 2020.

Primary Objective

- To compare overall survival (OS) of first line palbociclib + AI versus AI alone for postmenopausal women or men with HR+/HER2- MBC

Secondary objectives

- To compare real-world progression free survival (rwPFS) and real-world tumor response (rwTR) of first line palbociclib + AI versus AI alone for postmenopausal women or men with HR+/HER2- MBC
- To describe treatment patterns of Palbociclib, including initial dose, dose adjustment, treatment duration, subsequent treatments, and time to chemotherapy

CCI [redacted]

9. RESEARCH METHODS

9.1. Study design

The primary objective of the retrospective EHR database analysis is to compare effectiveness outcomes of palbociclib + AI versus AI alone as first line MBC treatment for HR+/HER2- MBC postmenopausal women or men. CCI [redacted] The following table lists 7 key components of the study protocol.

Protocol Component	Description
Eligibility criteria	All patients with HR+/HER2- MBC who were initiated with palbociclib + AI or AI alone as 1st line therapy for their MBC during the period of February 2015 through March 2020 were registered in the Flatiron Health Analytic Database
Treatment regimen	Palbociclib + AI or AI alone as the first line MBC treatment
Study cohorts	Patients will be divided into either Palbociclib + AI or AI alone cohort according to their first line MBC treatment received
Follow-up period	From index date (i.e., starting date of the first line MBC treatment during the period of 03 February 2015 through March 2020) to death or study end (date of data cutoff, September 30, 2021), whichever occurred first
Primary outcome	Overall survival (OS)
Causal contrasts of interest	Intention-to-treat effect
Analysis plan	Intention-to-treat effect requires adjustments for baseline prognostic factors using IPTW approach. In addition, to address unmeasured confounding, sensitivity analyses will also be performed to determine the robustness of the estimated intention-to-treat effects.

9.2. Setting

This study uses secondary de-identified Flatiron Healthcare Analytic data that involve patients who have been diagnosed with MBC in the United States.

9.2.1. Inclusion criteria

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

1. At least 18 years old at MBC diagnosis
2. Diagnosis of MBC at any point in patient history
    a. ICD-9 (174.x, 175.x) or ICD-10 (C50.xx) diagnosis of BC
    b. At least 2 documented clinical visits on or after 01 January 2011
    c. Evidence of stage IV or recurrent MBC with a metastatic diagnosis date on or after 2011, as confirmed by unstructured clinical documents
3. Confirmed HR+/HER2- status as defined as
    a. HR+: ER+ or PR+ test before or up to 60 days after MBC diagnosis
    b. HER2-: any HER2 negative test and the absence of a positive test (IHC positive 3+, FISH positive/amplified, positive NOS) before or up to 60 days after MBC diagnosis
4. Received Palbociclib + AI or AI as first line treatment for MBC during the period from 03 February 2015 through March 2020

5. A potential minimum follow-up of 6 months from index treatment until the data cutoff date, September 30, 2020:

9.2.2. Exclusion criteria

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

1. Evidence of any prior treatments with CDK 4/6 inhibitors (i.e., palbociclib, ribociclib or abemaciclib), endocrine treatments (e.g., tamoxifen, raloxifene, toremifene, or fulvestrant), or chemotherapy in the MBC setting
2. First structured activity greater than 90 days after MBC diagnostic date
3. Lacks relevant unstructured documents in the Flatiron Health database for review by the abstraction team

9.3. Variables

All variables are assessed or defined by Flatiron using business rules before and after Palbociclib + AI or AI alone initiation.

Variable	Operational definition
Demographic characteristics	
Age	Age at MBC diagnosis, years
Age category	<50, 50-64, 65 –74, ≥75 years
Index treatment year	2015, 2016, 2017, 2018, 2019, 2020
Gender	Male, female, unknown
Race	White, Black, Asian, other, unknown
Region of residence	Based on region where the patient resides: Northeast, Midwest, South, West
Practice type	Academic, community
Insurance type	Commercial, Medicare, Medicaid

Menopause status	Pre or perimenopausal, postmenopausal, Unknown as defined by Flatiron. Menopausal status was either assigned or abstracted, depending on the patient's age at 1L start. The following was used to determine menopausal status: ● Patients age 60 years or older at 1L start date are assigned as "postmenopausal". ● Patients younger than age 60 at 1L start underwent abstraction for menopausal status and are categorized as follows: ○ If there was explicit documentation by the clinician of the patient being "postmenopausal" or patient was stated as being menopausal at a certain age prior to the start of first-line therapy for metastatic breast cancer, or implicit documentation of "Prior Bilateral Salpingo-Oophorectomy (BSO) with or without hysterectomy" prior to or within 30 days after the 1L start, the patient's menopausal status was derived as "postmenopausal" ○ If there was explicit documentation by the clinician of the patient being "premenopausal" or implicit documentation of "Regular menses", between the metastatic breast cancer diagnosis date and up to 30 days following the start of first-line therapy the patient's menopausal status was derived as "premenopausal" ○ If there was explicit documentation by the clinician of the patient being "perimenopausal" between the metastatic breast cancer diagnosis date and up to30 days following the start of first-line therapy the patient's menopausal status was derived as perimenopausal ○ If there is no explicit or implicit documentation of menopausal status prior to or within 30 days after the 1L start, the patients were considered as having "Unknown" menopausal status ● Menopausal status was not defined for male patients and such patients were omitted from the table.
Duration of follow-up	Duration of follow-up was defined as the number of months from index date to death from any cause or end of study (date of data cut-off).
Clinical characteristics	
Type of MBC	De novo MBC (newly diagnosed): Stage 4 at initial BC diagnosis Recurrent MBC: Stages 0-3 at initial BC diagnosis

ECOG performance score	ECOG performance at index date: 0, 1, 2, 3, 4, unknown
Stage at initial BC diagnosis	Stage I, II, III, IV, unknown/undocumented
Time from initial BC diagnosis to first MBC diagnosis	Months from the date of initial BC diagnosis to the date of metastatic diagnosis
ER status	Positive, negative, or unknown
PR status	Positive, negative, or unknown
HER2 status	Positive, negative, or unknown
BRCA status	BRCA 1 and BRCA 2: positive, negative, unknown/unassessed
Organ-level metastatic sites	Number of sites Sites of metastases (lymph nodes, bone, adrenal gland, liver, brain, lung, pleura, peritoneum, skin/subcutaneous, CNS sites, bone marrow, kidney, ovary, pancreas, soft tissue, spleen, thyroid, other) Visceral versus non-visceral, bone only
De novo metastatic	Yes or no
Endocrine sensitivity	Endocrine sensitive: Patients met any of the following criteria: ● Stage IV at initial diagnosis (i.e. naive) ● Did not have any episode of endocrine therapy that started more than 14 days prior to metastatic diagnosis (i.e., no endocrine therapy and progressed) ● Had a progression event that was more than 12 months after completion of endocrine therapy (among patients not meeting the definition of resistant). Endocrine resistant: Patients progressed on or within 12 months of completion of endocrine therapy received for the primary breast cancer being followed in the MBC EDM Unknown
Modified Charlson comorbidity index (CCI)	Documented histories of comorbidities using condition categories based on a modified Charlson Comorbidity Index (CCI) and captured from unstructured documents any time prior to start of 1L therapy for MBC.
CCI [redacted]	[redacted]
Longitudinal treatment patterns	From index treatment date to death or end of follow-up
Lines of therapy	Lines of therapy in the metastatic setting are assigned by Flatiron based exclusively on abstracted data to evaluate systemic treatment on or after the MBC date.

	The start of the first line of therapy is defined as the first episode of an eligible therapy that is given after or up to 14 days before index MBC diagnosis and after the patient's start of structured activity. The definition of a line of therapy is generally the first eligible drug episode plus other eligible drugs given within 28 days. However, a 60-day time threshold is employed before advancing the line of therapy when CDK4/6i treatment is added to treatment with Aromatase Inhibitor (AI). The line number is only advanced with an addition of a new drug after the 28-day line definition period. The end of a lone of therapy is defined as the date of last patient-level structured activity, death, or the day before the start date of the next line of therapy, whichever occurred first.
Initial prescribed dose	Palbociclib: 125 mg, 100 mg, 75 mg
Dose adjustment	Dose strength other than initial/previous prescription
Type of the first dose change	Dose reduction 125 mg to 100 mg, 125 mg to 75 mg, 100 mg to 75 mg Dose increase 75 mg to 100 mg, 100 mg to 125 mg, 75 mg to 125 mg
Time to the first dose change	Days from index date to first dose change.
Number of dose adjustment	Number of dose reduction and number of dose increase over the calendar time (quarter since February 2015) and over treatment cycle since index date
Reasons for discontinuation	Disease progression, toxicity, financial, patient request, other
Duration of treatment	Days from index prescription order date to end of treatment, start of subsequent line of therapy, or death from any cause, whichever occurred first
Combination endocrine partner	Letrozole, Anastrozole, Exemestane
Concomitant LHRH Agonists	Goserelin (Zoladex), Histrelin (Vantas), Leuprolide (Eligard, Lupron), Triptorelin (Trelstar)
Other concomitant anti-cancer therapies	Chemotherapy (See Table 1 for detail)
Time to 1st subsequent therapy	Months from the start of palbociclib plus AI or AI alone to next line of anticancer therapy, death from any cause, or last visit, end of study, whichever came first
Time to 1st subsequent chemotherapy	Months from the start of palbociclib plus AI or AI alone to next line of anticancer therapy/chemotherapy, death form any cause, last visit, or end of study, whichever came first
Effectiveness outcomes	
Real-world PFS (rwPFS)	Real-world PFS is defined as the number of months from start of palbociclib + AI or AI alone to death from any cause or disease progression (based on clinical assessment or by radiographic

	scan/tissue biopsy), whichever occurred first. Patients who did not die and did not have disease progression will be censored at the date of initiation of next line of therapy for patients with 2 or more lines of therapy or at the date of their last visit during the study period (February 2015- September 2020) for patients with only 1 line of therapy.
rwPFS2	rwPFS2 is defined as the number of months from start of palbociclib + AI or AI alone to disease progression (based on clinical assessment or by radiographic scan/tissue biopsy) on the 2nd line of therapy or death from any cause, whichever occurred first. Patients who did not die and did not have disease progression on the 2nd line of therapy will be censored at the date of initiation of 3rd line of therapy for patients with 3 or more lines of therapy or at the date of their last visit during the study period (February 2015- September 2020) for patients with only 1 or 2 lines of therapy[29].
Overall survival (OS)	Overall survival (OS) was defined as the number of months from start of palbociclib + AI or AI alone to death. Patients who did not die, will be censored at the end of study date. Date of death. In most Flatiron deliverables, death data is delivered with a month granularity. Date of death is a consensus variable across the three data sources (EHR, SSDI and obituary data). Flatiron generates the variable according to the following rules and hierarchy (preference is based on comparative analyses with the National Death Index as the gold standard): Use abstracted dates over structured dates when the abstracted date granularity is at the day level. Use the following rules when there are multiple structured dates of death: If all three dates are in agreement, that date of death is selected If any two dates are in agreement, that date of death is selected If none of the dates are in agreement, then the rank order to which the date of death is selected is: SSDI→Obituary data→EHR
Real-world tumor responses (rwTR)	Real-world best responses are assessed based on treating clinician's assessment of radiological evidence for change in burden of disease over the course of treatment after 1 month of index treatment initiation. • Complete response: complete resolution of all visible disease. • Partial response: partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease.

	• Stable disease: no change in overall size of visible disease; also included cases where some lesions increased in size and some lesions decreased in size • Progressive disease: an increase in visible disease and/or presence of any new lesions; included cases where the clinician indicated progressive disease

9.4. Data source

Flatiron Health operates a real-world oncology data platform that aggregates and processes patient-level data such as demographics, diagnostic information (e.g. stage, pathology, molecular information and radiology), extent of disease, lab values, treatments (ego line of therapy, dosing and regimens), and patient outcomes. This detailed information facilitates insight into real-world cancer care, for example, permitting hypothesis generation and retrospective research. Pfizer considers the Flatiron dataset to be fit for purpose for this objective due to the large number of oncology practices using the EHR distributed broadly across the United States, the type and extent of patient level data, the minimal lag time for data availability and the processes employed by Flatiron for quality control and verification including 7 year record retention and traceability to source documentation as outlined below. Flatiron has also validated the OS endpoint as captured by 3 different data sources[30, 31].

This retrospective observational study will utilize Flatiron Health's longitudinal, demographically, and geographically diverse database derived from EHR data from over 265 cancer clinics (~800 sites of care) including more than 2.2 million active US cancer patients available for analysis. Across the clinics in the Flatiron Health Network, data become available in near real time after each clinical encounter and contribute to Flatiron's continuously aggregating centralized dataset. The patient-level data in the EHRs includes structured data (i.e., data points that are organized in a predefined manner, such as dropdown fields that reside in an EHR to capture a patient's gender or date of birth or laboratory data), unstructured data collected via expert human chart abstraction of physician's notes and other free text fields coupled with quality controlled natural language processing and business rules technology, and other unstructured documents (i.e., information from PDF laboratory reports or narratives from synoptic reports). Flatiron integrates the structured EHR data with quality controlled curated data from unstructured EHR data into a single data model, where all data are certified HIPAA-compliant with all de-identified patients being assigned a longitudinally stable identifier. Details of de-identification procedure and data management are outlined in Flatiron's parent database protocol (RWE-001v2.0, "The Flatiron Health Real-World Evidence Parent Protocol"). CCI [redacted] The data used in these analyses already exist within this model, stored in an electronic database.

All data, code to create the MBC dataset, and other technical artifacts are version-controlled and managed within a Flatiron repository. These artifacts are stored and backed up on Flatiron's servers for at least 7 years. All data within the dataset can be traced back to the original source data or documents within the EHR, and appropriate change management and provenance best practices are maintained by Flatiron in the event of a regulatory audit.

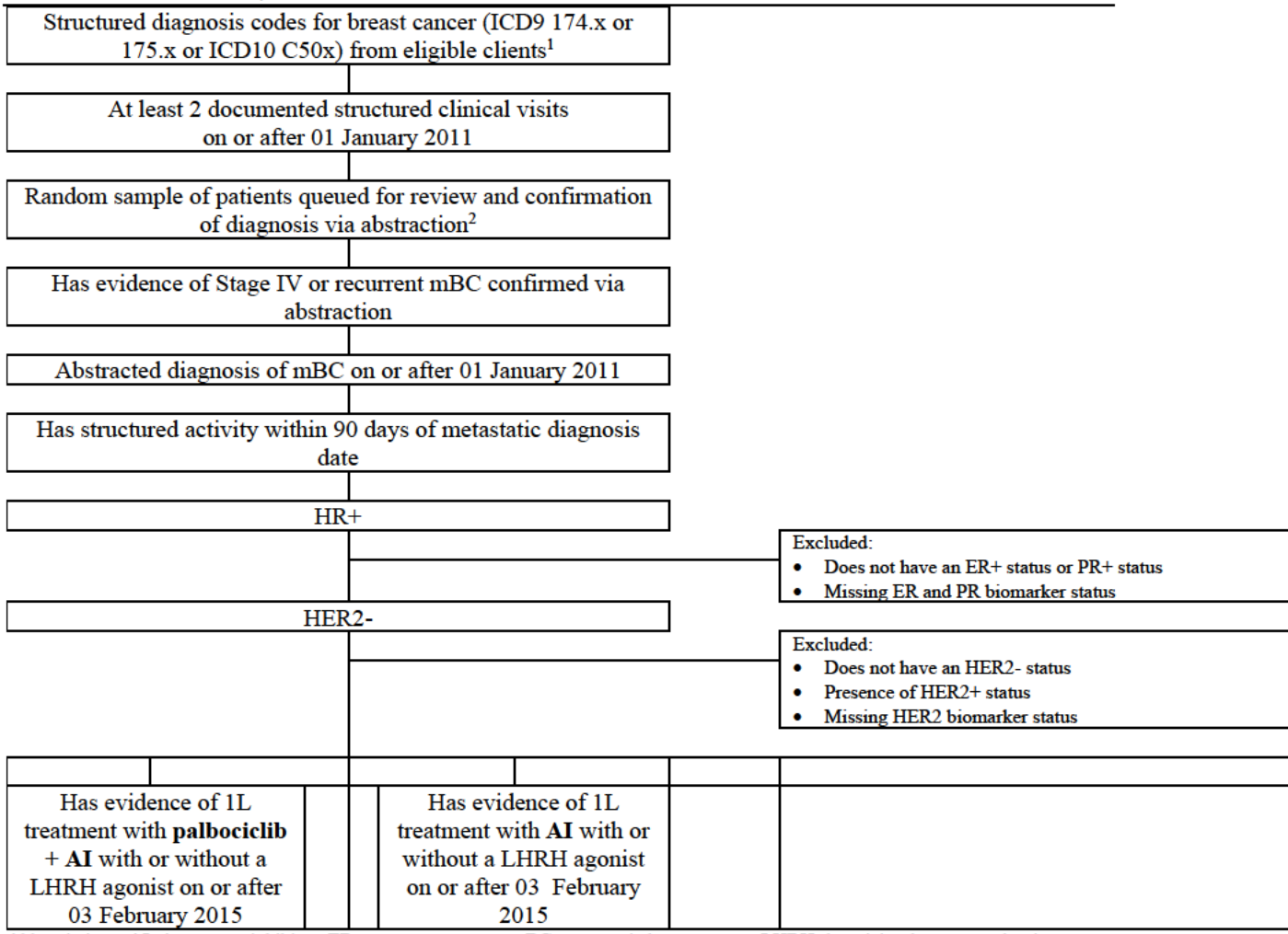
Flatiron generates and continually maintains a set of quality standards and versioned business rules. These QC standards cover themes such as demographics, biomarkers, treatment, therapy shares, treatment length/dosage, lines of therapy, real-world recurrence, and real-world PFS. They have a team of 900 expert nurse and physician abstractors that cocreate and version rules, and also to create QC that includes both medical considerations (e.g. what are expected based on the literature and clinical practice) and data considerations (e.g., stability from prior months).

QC will be performed for the results of the study, including reviewing and double checking for correct data, consistency, spelling, grammar, and structure. It is also reviewed to ensure that it conforms to Flatiron's data dictionary, has internal consistency (e.g., that date of diagnosis occurs after date of birth) and meets the study objectives. The final review of the findings and content will be conducted in a summary presentation.

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

9.4.1. Patient Selection

Patients from the Flatiron database are selected into a broad cohort based on ICD codes for the disease of interest. Then, Flatiron randomly selects a broad sample of these patients who undergo manual review of the full patient chart to confirm the MBC diagnosis on or after 01 January 2011. Following confirmation of these data elements, project-specific cohort criteria are applied to the analytic cohort to reach the final study cohort of interest. The selection criteria are shown below.



Abbreviations: AI=Aromatase inhibitor; ER=estrogen receptor; mBC=metastatic breast cancer; LHRH=lutenizing-hormone-releasing hormone

Notes:

1. A select number of practices are excluded from this project due to known documentation limitations.

CCI [redacted]

9.4.2. Overall Survival for Real-world patients

A key goal of evidence-based medicine is to identify survival benefit associated with a treatment regimen, and therefore, considerable effort is dedicated to collecting mortality information in clinical trials to enable outcomes analyses, one of which is overall survival. With respect to the primary endpoint OS, Flatiron curates mortality information from 3

sources. These include EHR capture of patient's date of death as entered a structured field in the EHR or information captured in unstructured documents such as clinician notes and condolence letters. Additionally, the EHR data is linked with external death data sources to add in dates of death that might be missing from the EHR. In order to determine the optimal external death data source(s), options are evaluated on the basis of completeness, accuracy, and recency. Based upon this review, Flatiron selected to combine 2 external sources: the SSDI, and a commercial death dataset that mines data from obituaries, funeral homes, and other sources to provide death data that is current within a week of the death. A deterministic matching algorithm is employed to link these external datasets to patient-level data. Dates known to be incorrect (for instance, death dates that occur before abstracted diagnosis dates), as well as those required to be removed for de-identification reasons, specifically when a date of death occurs in the same month as the patient's advanced or metastatic diagnosis date are removed. Date of death is a consensus variable across the 3 data sources (EHR, SSDI and commercial death dataset)[30, 31]. The variable is generated according to the following rules and hierarchy (preference is based on comparative analyses with the National Death Index as the gold standard):

1. Use abstracted dates over structured dates when the abstracted date granularity is at the day level.

2. Use the following rules when there are multiple structured dates of death:

    1. Social Security Death Index

    2. Commercial death dataset

    3. EHR

    4. If all 3 dates are in agreement, that date of death is selected

    5. If any 2 dates are in agreement, that date of death is selected

    6. If none of the dates are in agreement, then there is a rank order to which the date of death is selected: SSDI, Obituary data, and EHR

Flatiron Health's publication in Health Services Research, "Development and Validation of a High-Quality Composite Real-World Mortality Endpoint," describes how Flatiron Health's mortality variable is benchmarked through comparisons with the National Death Index (NDI)[31], which is widely considered a gold standard death dataset in the United States (. This publication concluded that Flatiron Health's mortality data has high sensitivity (85-90%), specificity (97-98%) and date accuracy (95-97%) varying across 4 different tumor types, (i.e. advanced non-small-cell lung cancer, advanced melanoma, metastatic colorectal cancer, and metastatic breast cancer). Recent analysis confirmed the validity of the approach to identify mortality[30].

9.5. Study size

All eligible patients will be included for the primary analysis.

9.6. Data management

Flatiron Health Database (https://flatiron.com/real-world-evidence/) collects data through a HIPAA-compliant process that results in de-identified patient data as described above. De-identified data are prepared by Flatiron and transferred securely to Pfizer in a standard flat file format. 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 Flatiron Health, 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 though Pfizer maintains its data in excess of the guidance – for a minimum of 7 years.

9.6.1. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Flatiron Health has agreed to keep all study-related records, including electronic health records, data curated by Flatiron from unstructured fields within those records, rationale for a curated data point, query code and the dataset provided under this protocol from their larger MBC registry. The records should be retained by Flatiron according to local regulations or as specified in the statement of work, whichever is longer. Flatiron must ensure that the records continue to be stored securely for so long as they are retained.

If Flatiron 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 7 years after completion or discontinuation of the study, as expressly agreed to within the statement of work by Flatiron and Pfizer. Pfizer will retain all analysis datasets, code and other artifacts generated over the course of executing this protocol for at least 15 years or longer if required by applicable local regulations.

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

9.7. Statistical considerations and 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). 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 demonstrate superiority of palbociclib + AI over AI alone in prolonging OS for postmenopausal women or men with HR+/HER2- MBC as first line treatment in the US clinical practice setting. The study is designed to test the null hypothesis H_{10} $\lambda \geq 1$ versus H_{1A}: $\lambda < 1$, palbociclib + AI cohort versus AI alone cohort. λ stands for the hazard ratio.

CCI [redacted] The study is designed to test the null hypothesis H_{30} $\lambda \geq 1$ versus H_{3A}: $\lambda < 1$, palbociclib + AI cohort versus AI alone cohort in pre or perimenopausal women.

The unadjusted analysis in Study 1122 showed: HR = 0.63 (0.53, 0.76) p< 0.0001 with a total of 476 deaths. The proposed expansion will include a total of 750 deaths. Thus, approximately 75% of the deaths in Study 1151 will come from Study 1122, where a strong OS benefit has already been observed, p < 0.0001.

9.7.2. Sample size determination

Approximately 3000 patients will be included with close to a 1:1 ratio between palbociclib + AI and AI alone cohorts. The median OS for AI alone is assumed to be 40 months. An improvement of 25% to a median OS of 50 months (corresponding to a hazard ratio of 0.80) would be considered clinically meaningful. Therefore, 750 OS events will be required to have at least 80% power to detect a hazard ratio of 0.80 using a two-sided log-rank test at a significance level of 0.05 based on the exponential distribution assumptions of OS for both cohorts.

9.7.3. Cohorts for Analysis

All effectiveness analyses will be based on the following 4 cohorts.

Cohort 1: Patients treated with palbociclib + an AI as the first line therapy in postmenopausal women or men with MBC

Cohort 2: Patients treated with an AI alone as the first-line therapy in postmenopausal women or men with MBC

Cohort 3: Pre or perimenopausal women treated with palbociclib + an AI as the first line therapy for MBC

Cohort 4: Pre or perimenopausal women treated with an AI alone as the firs-line therapy for MBC

9.7.4. Statistical Analysis

All analyses will be performed by using SAS® Version 9.1.4 or higher.

9.7.4.1. Inverse probability treatment weighting (IPTW)

Inverse probability treatment weighting will be used to balance baseline demographic and clinical characteristics between comparison cohorts (for instance, palbociclib + AI versus AI alone) in statistical analyses[32]. Variables to be used in the computation of propensity scores (PS) required to perform IPTW include key baseline demographics (e.g. age, race, practice type) and clinical characteristics (e.g. ECOG performance score, disease stage at initial diagnosis, visceral metastasis, number of disease sites, disease free interval, and comorbidities). In the event that IPTW method does not balance potential confounder variables, analysis by PS quintiles will be used.

9.7.4.2. Analyses of primary endpoint

The primary endpoint OS is defined as the time from the starting index date (01 February 2015) to the date of death. Patients who did not die within the follow up cut-off date are censored at data cutoff date.

A weighted log-rank test using IPTW (one-sided) will be used to compare OS time between palbociclib + an AI and an AI alone cohort at the analysis with the significance level at 0.05 (two-sided). OS time associated with each treatment arm will be summarized for Cohort 1 using the weighted Kaplan-Meier method and displayed graphically where appropriate. CIs for the 25th, 50th and 75th percentiles of the event-free time will be reported. OS rates at 12, 24, 36, 48, and 60 months will be estimated with corresponding 2-sided 95% CIs using the weighted Kaplan-Meier method. The weighted Cox Proportional hazards model will be fitted to compute the hazard ratio and the corresponding 95% CI.

9.7.4.3. Analyses of secondary/CCI [redacted]

Real-world progression-free survival (rwPFS) is defined as the time from index date to the date of the first documentation of a rwPD or death due to any cause, whichever occurs first. Patients last known to be alive and progression-free within the follow up cut-off date are censored at the date of the last clinic note. rwPFS2 is defined as the time from the index date to the date of the first documentation of a rwPD or death due to any cause after starting 2nd line of therapy, whichever occurs first.

rwPFS and rwPFS2 will be summarized using the weighted Kaplan-Meier method and displayed graphically where appropriate. The median rwPFS/PFS2 time will be estimated and corresponding 2-sided 95% CI for the median using the Brookmeyer-Crowley method.

rwPFS rates at 6, 12, 18, 24, 30, and 36 months will be estimated with corresponding 2-sided 95% CIs using the weighted Kaplan-Meier method. The weighted Cox Proportional hazards model will be fitted to compute the hazard ratio and the corresponding 95% CI.

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 after 30 days of index treatment initiation.

- Complete response: complete resolution of all visible disease.
- Partial response: partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease.
- Stable disease: no change in overall size of visible disease; also included cases where some lesions increased in size and some lesions decreased in size
- Progressive disease: an increase in visible disease and/or presence of any new lesions; included cases where the clinician indicated progressive disease.

Real-world tumor response rate (rwTR) is defined as the proportion of patients with a real-world complete response (rwCR) or real-world partial response (rwPR). Patients who have inadequate data for tumor assessment (e.g. no baseline assessment or no post-baseline follow-up assessments), who receive anticancer medication other than the study medication prior to reaching a rwCR or rwPR, or who die, progress, or drop out for any reason prior to reaching a rwCR or rwPR will be counted as non-responders in the rwTR analysis.

9.7.4.4. Sensitivity analyses

A concern with observational data is confounded by unmeasured or uncontrolled confounders; that is, could an unobserved factor related to both the treatment and outcome of interest explain an association, in the absence of a true causal effect. Sensitivity analyses are useful in assessing how robust an association is to potential unmeasured or uncontrolled confounding and are important tools to evaluating evidence for causation in the face of unmeasured confounding. Sensitivity analyses consider how strong unmeasured confounding would have to be to explain away the association, that is, how strongly the unmeasured confounder would have to be associated with the treatment and outcome for the treatment–outcome association not to be causal. Sensitivity analyses of missing data are also critical to evaluating the sensitivity of conclusions to violations in missing data assumptions.
The following sensitivity analyses will be performed for the primary endpoint:

- Propensity score matching (PSM) will be used as a sensitivity analysis to control confounding. Propensity score matching creates sets of patients for treatment and control cohorts. A matched set consists of at least 1 patient in the treatment group and 1 in the control group with similar propensity scores. The goal is to approximate a random clinal trial, eliminating many of the problems that come with observational data analysis. Matches will be made using 1:1 nearest neighbor matching without replacement.

- Sensitivity analyses with the definition of the line of regimen by A1122 (i.e., the combination drugs were given within 28 days).

- Other sensitivity analyses may be conducted as needed, which will be described in the SAP.

9.7.4.5. Subgroup analyses

- Subgroup analyses will be conducted according to age, minority, ECOG performance, de novo metastatic, visceral, non-visceral, bone only, disease sites, endocrine sensitivity, endocrine AI partner, comorbidities, subsequent treatments as appropriate based on availability of the data and sample sizes.

CCI [redacted]

[redacted]

[redacted]

9.8. Quality control

This is a retrospective study, therefore issues of quality control at study sites, e.g. 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 Flatiron's standard procedure for quality control and assurance as described in Flatiron Health Analytic Database Parent Protocol. QC for structured and unstructured data is conducted prior to delivery of each dataset. For each data model, Flatiron generates and continually maintains a set of quality standards and versioned business rules. These QC standards cover themes such as demographics, biomarkers, treatment, therapy shares, treatment length/dosage, lines of therapy, real-world recurrence, and real-world progression free survival. They have a team of

900 expert nurse and physician abstractors that co-create and version rules, and also to create QC that includes both medical considerations (e.g. what are expected based on the literature and clinical practice) and data considerations (e.g. stability from prior months). Missingness of death data is a major confounding factor for many real-world oncology analyses. For survival data, Flatiron Health utilizes 4 resources, including the National Death Index, US Social Security Death Index, obituaries, and commercial death data published from a vendor to identify when patients have died (https://onlinelibrary.wiley.com/doi/full/10.1111/1475-6773.12872). In a study of advanced non-small cell lung cancer patients, sensitivity increased from 66% from Flatiron's EHR-based registry alone to over 91% from the composite of the 4 sources.

QC will be performed for the results of the study, including reviewing and double checking for correct data, consistency, spelling, grammar, and structure. It is also reviewed to ensure that it conforms to Flatiron's data dictionary, has internal consistency (e.g. that date of diagnosis occurs after date of birth) and meets the study objectives. The final review of the findings and content will be conducted in a summary presentation.

9.9. Limitations of the research methods

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 potential bias in treatment selection,incomplete or missing data, limited data on comorbidities, potential for inaccurate data capture, lack of scheduled assessments and lack of standardized assessment of tumor response or progression free survival. 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.

Although IPTW will be used to balance patient characteristics and sensitivity analyses (e.g., PSM) will be conducted, other variables unavailable in the database, such as disease-free interval and prior therapy in neoadjuvant setting cannot be statistically controlled. Sample size may not be large enough for some subgroup analyses. Additionally, no causality could be made from the retrospective analysis. Moreover, these findings may not be generalizable to other patient populations.

9.10. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such

measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient personal data will be stored at Flatiron in encrypted electronic form and will be password protected to ensure that only authorized study staff has access. Flatiron 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, Flatiron 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, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the statement of work with Flatiron and applicable privacy laws.

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.

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

The IRB approval of this observational study with secondary data use from an existing EHR database is covered by IRB approval on Flatiron parent protocol. Data provided by Flatiron to third parties were de-identified and provisions were in place to prevent re-identification in order to protect patients' confidentiality. This study is exempt from institutional review board approval because it is retrospective, non-interventional, and will use anonymized data provided by Flatiron.

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

This study involves data that exist as structured data by the time of study start.

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

13. REFERENCES

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14. LIST OF TABLES

Table 1. List of Medications for the Treatment of HR+/HER2- Metastatic Breast Cancer

Drug Name	Brand Name	Type of therapy	Code
Anastrozole	Arimidex	Endocrine	S0170
Exemestane	Aromasin	Endocrine	S0156
Fulvesterant	Faslodex	Endocrine	J9395
Letrozole	Femara	Endocrine	N/A
Megestrol acetate	Megace	Endocrine	S0179
Raloxifene	Evista	Endocrine	N/A
Tamoxifen	Nolvadex	Endocrine	G8376, G8380, G8381, S0187
Toremifene	Fareston	Endocrine	N/A
Everolimus	Afinitor	Target therapy	J7527, J8561
Palbociclib	Ibrance	Target therapy	N/A
Ribociclib	Kisqali	Target therapy	N/A
Abemaciclib	Verzenio	Target therapy	N/A
Capecitabine	Xeloda	Chemotherapy	J8520 , J8521
Cyclophosphamide	Cytoxan	Chemotherapy	• C9420 - Cyclophosphamide (2) *(HCPCS Procedure Drug)* • C9421 - Cyclophosphamide (2) *(HCPCS Procedure Drug)* • J8530 - Cyclophosphamide oral 25 mg (2) *(HCPCS Procedure Drug)* • J9070 - Cyclophosphamide 100 mg inj (2) *(HCPCS Procedure Drug)* • J9080 - Cyclophosphamide 200 mg inj (2) *(HCPCS Procedure Drug)* • J9090 - Cyclophosphamide 500 mg inj (2) *(HCPCS Procedure Drug)* • J9091 - Cyclophosphamide 1.0

Drug Name	Brand Name	Type of therapy	Code
			grm inj (2) *(HCPCS Procedure Drug)* • J9092 - Cyclophosphamide 2.0 grm inj (2) *(HCPCS Procedure Drug)* • J9093 - Cyclophosphamide lyophilized (2) *(HCPCS Procedure Drug)* • J9094 - Cyclophosphamide lyophilized (2) *(HCPCS Procedure Drug)* • J9095 - Cyclophosphamide lyophilized (2) *(HCPCS Procedure Drug)* • J9096 - Cyclophosphamide lyophilized (2) *(HCPCS Procedure Drug)* • J9097 - Cyclophosphamide lyophilized (2) *(HCPCS Procedure Drug)*
Nab-paclitaxel	Abraxane	Chemotherapy	No code specific to Abraxane
Paclitaxel	Taxol	Chemotherapy	• C9127 - Paclitaxel (2) *(HCPCS Procedure Drug)* • C9431 - Paclitaxel (2) *(HCPCS Procedure Drug)* • I - PACLITAXEL NO STRENGTH *(Uncoded Product Identifier)* • J9264 - Paclitaxel protein bound (2) *(HCPCS Procedure Drug)*

Drug Name	Brand Name	Type of therapy	Code
			• J9265 - Paclitaxel injection (2) *(HCPCS Procedure Drug)* • J9267 - Paclitaxel injection (2) *(HCPCS Procedure Drug)*
Doxorubicin	Taxotere	Chemotherapy	• C9415 - Doxorubicin (2) *(HCPCS Procedure Drug)* • J9000 - Doxorubicin hcl injection (2) *(HCPCS Procedure Drug)* • J9001 - Doxorubicin hcl liposome inj (2) *(HCPCS Procedure Drug)* • Q2050 - Doxorubicin inj 10mg (2) *(HCPCS Procedure Drug)*
Carboplatin	Paraplatin	Chemotherapy	• C9418 - Cisplatin (2) *(HCPCS Procedure Drug)* • J9060 - Cisplatin 10 mg injection (2) *(HCPCS Procedure Drug)* • J9062 - Cisplatin 50 mg injection (2) *(HCPCS Procedure Drug)*
Eribulin	Halaven	Chemotherapy	• C9280 - Injection, eribulin mesylate (2) *(HCPCS Procedure Drug)* • J9179 - Eribulin mesylate injection (2) *(HCPCS Procedure Drug)*
Gemcitabine	Gemzar	Chemotherapy	J9201
Ixabepilone	Ixempra	Chemotherapy	J9207
5-fluorouracil	Adrucil	Chemotherapy	J9190
Epirubicin	Pharmorubicin	Chemotherapy	J9178
Vinorelabine	Navlabine	Chemotherapy	J9390

Drug Name	Brand Name	Type of therapy	Code
Methotrexate	NA	Chemotherapy	J8610, J9250, J9260,
Mitomycin	NA	Chemotherapy	J9280
Mitoxantrone	Novantrone	Chemotherapy	J9293

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable