NON-INTERVENTIONAL STUDY PROTOCOL

A5481151

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

Statistical Analysis Plan (SAP)

Version: 1

Author: PPD

Date: 05-Sep-2021

TABLE OF CONTENTS

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable. First draft.

2. INTRODUCTION

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 in February 2015.

The study 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.*

2.1. 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.

The study period is from the index date to data cutoff date (September 2020). Patients are followed up from the index date to data cutoff date or death, whichever came first.

2.1.1. Study population

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.

2.1.2. 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.

2.1.3. Treatment/cohort labels

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

2.2. Study Objectives

2.2.1. Primary Objective

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

2.2.2. 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]

3. HYPOTHESES AND DECISION RULES

3.1. Statistical Hypotheses

Objective 1: To compare overall survival (OS) of first line palbociclib + AI versus AI alone for postmenopausal women or men with HR+/HER2- MBC.

> Null: OS does not differ between Palbociclib + Letrozole compared to Letrozole alone in patients when initiated first line for MBC.

Objective 2: To compare overall survival (OS) of first line palbociclib + AI versus AI alone for peri or premenopausal women with HR+/HER2- MBC.

> Null: OS does not differ between Palbociclib + Letrozole compared to Letrozole alone in patients when initiated first line for MBC.

3.2. Statistical decision rules

The alpha level will be 0.05, 2-sided. No adjustments for multiple comparisons will be made.

3.3. sample size calculation

Approximately 3000 patients will be included with close to a 1:1 ratio between palbociclib + AI and AI alone cohorts. CCI [redacted]

4. ANALYSIS SETS/POPULATIONS

4.1. Full analysis set

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*

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*

4.2. Subgroups

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.

5. ENDPOINTS AND COVARIATES

5.1. Efficacy/Effectiveness Endpoint(s)

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*

Variable	*Operational definition*
	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*

Variable	*Operational definition*
	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 line 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*

Variable	***Operational definition***
	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 in the protocol 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.*
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*

Variable	*Operational definition*
	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*

5.2. Covariates

The primary analysis method is inverse probability of treatment weighting (IPTW) based on the individual propensity score (PS). Variables needed for the PS estimation include age, race, practice type, ECOG performance score, disease stage at initial diagnosis, visceral metastasis, number of disease sites, disease free interval, and comorbidities. The selection of these covariates for analysis are based on the study team's clinical judgment.

6. HANDLING OF MISSING VALUES

For rwTR, 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.

No imputation for other missing values will be performed.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1. Statistical methods

The inverse probability of treatment weighting (IPTW) technique will be used as the primary analysis method to control for confounders when comparing the cohorts. Propensity scores for use in IPTW will be calculated using a multivariable logistic regression model based on

the proposed baseline covariates in Section 5.2. Stabilized weights based on the propensity scores will be computed. The balance in important prognostic baseline characteristics will be assessed using a standardized differences approach, with values ≥0.10 indicating a non-negligible imbalance. After IPTW, no significant differences are expected among all pre-index measures between the patient cohorts, and the treatment effect that is calculated based on the weighted population is considered to be the true effect.

The Kaplan-Meier method adjusted by stabilized IPTW will be used to estimate median survival time and its 95% confidence intervals (CIs) for OS, rwPFS, and duration of treatment. Cox proportional models with a robust sandwich estimator adjusted by stabilized IPTW will be used to estimate hazard ratio and its 95% CIs for OS, rwPFS, and duration of treatment. The Cox model proportionality assumption will be evaluated by visually inspecting the Kaplan-Meier plot among the matched cohorts and confirmed by testing the significance of interactions between treatment modality and the log of time as well as each time-dependent covariate and the log of time. If the proportionality assumption is violated, an interaction term of time may be added.

OS and rwPFS rates at 12, 24, 36, 48, and 60 months will be estimated with corresponding 2-sided 95% CIs using the IPTW weighted Kaplan-Meier method.

Means, medians, and standard deviations will be provided for continuous variables when performing descriptive analysis of continuous data. Numbers and percentages will be provided for dichotomous and polychotomous variables when performing descriptive analysis of categorical data. Bivariate comparisons of baseline characteristics and outcomes measures will be provided. Appropriate tests (e.g., t-test, chi-square test) will be used based on the distribution of the measure. An unadjusted Kaplan Meier curve will be drawn to illustrate time-to-event.

All data analysis will be executed using statistical software SAS version 9.4 or later.

7.2. sensitivity analysis

1. PSM will be performed as a sensitivity analysis. Individual patients in the Palbociclib + Letrozole vs Letrozole alone cohorts will be matched by closest propensity scores. The Nearest Neighbor method (without replacement and with a caliper of 0.01) will be used to select the matched samples.

2. In Flatiron's definition of Line of Therapy, 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). A different time window will be adopted to advance the line of therapy, based on the distribution of the difference in the start time between AI and CDK4/6i as well as clinical judgment.

3. Depending on the pattern of missing tumor response assessments between the Palbociclib+AI and the AI alone arms, various methods will be explored to assess the impact of missing values on the tumor response result.

7.3. summary of Analyses

Outcome	Statistical Method
OS	Kaplan-Meier Plot, Cox proportional hazards model, IPTW/PSM
rwPFS	Kaplan-Meier Plot, Cox proportional hazards model, IPTW/PSM
Tumor response	Descriptive analyses and logistic regression analyses, IPTW/PSM
Time to treatment discontinuation	Kaplan-Meier Plot , Cox regression, summary of reason for discontinuation. Descriptive analysis and multivariate analyses to examine factors associated with time to discontinuation if sample size is large enough.
Time to next line of therapy	Kaplan-Meier Plot , Cox regression. Descriptive analysis and multivariate analyses to examine factors associated with time to next line of therapy if sample size is large enough .
Time to chemotherapy	Kaplan-Meier Plot , Cox regression. Descriptive analysis and multivariate analyses to examine factors associated with time to chemotherapy if sample size is large enough.
Initial dose of Palbociclib	Count of patients by initial dose level; summary of baseline and clinical characteristics by initial dose level; logistic regression of initial dose level on demographic and clinical characteristics; summary of rwTR by initial dose level; logistic regression of rwTR on initial dose level; KM estimates and Cox regression of rwPFS on initial dose level; KM estimates and Cox regression of time to treatment discontinuation on initial dose level; dose change from initial dose.
Dose adjustment	Describe dose changes of Palbociclib from initiation to discontinuation. Sankey diagram will be used as appropriate. Factors associated with dose adjustment will be examined by univariate and multivariate analyses as appropriate. Clinical outcomes (i.e, rwPFS, OS, and tumor response) associated with dose adjustment will be explored by Kaplan-Meier Plot, Cox regression, or logistic regression as appropriate.