Non-Interventional Study Protocol
A5481122

Real-world treatment patterns and effectiveness of Palbociclib in combination with an aromatase inhibitor as initial endocrine based therapy in metastatic/advanced breast cancer

Statistical Analysis Plan
(SAP)
Amendment 3

Amendment Version: 3.0

Author: PPD PhD
Email: PPD

Study Lead: PPD
Email: PPD

Date: 1122-2020

TABLE OF CONTENTS

1 AMENDMENTS FROM PREVIOUS VERSION(S)

Amendment 1.0 expands the description of the statistical methods specified in the approved A5481122 Study Protocol (dated January 22, 2019) CCI methods related to the Exploratory objective: compare effectiveness of Palbociclib + CCI

Amendment 2.0 describes an amendment to the Statistical Analysis Plan for Protocol A5481122, Amendment 1.0 (dated April 4, 2019). The changes to Amendment 1.0 can be identified by using the Track Changes option in Word.

Amendment 3.0 is prepared after the Flatiron Analysis Database transferred and locked. Primary and most secondary analysis had been already performed except detailed updates the analyses of treatment patterns in terms of initial dose, dose adjustment, time to treatment discontinuation, time to next line of therapy, and time to chemotherapy. It also examines the associations of initial Palbociclib dose (125mg, 100/75mg) with demographic and clinical characteristics, time to treatment discontinuation, real world PFS, real world tumour response, and OS if sample size is large enough for meaningful statistical analyses.

Text copied directly from Protocol A5481122 is italicized.

2 INTRODUCTION

Palbociclib, the first oral CDK4/6 inhibitor, is approved for HR+/HER2– metastatic/advanced breast cancer (MBC) in combination with an aromatase inhibitor or fulvestrant. Improved median PFS was observed with Palbociclib plus Letrozole as first-line therapy (PALOMA-2) and with Fulvestrant in patients who have progressed on or after prior endocrine therapy in the adjuvant or metastatic setting (PALOMA-3). Since its approval in February 2015, Palbociclib has been prescribed for more than 100,000 patients. Recent real-world studies support the effectiveness of Palbociclib-based therapy in HR+/HER2– MBC patients. However data published to date have limitations including small cohorts, short duration of follow-up, inconsistent definitions of outcomes, and lack of a comparator. Electronic health record (EHR) data are collected as part of routine clinical practice and enable quick access to richer health information (as compared to claims database) in a timely manner (as compared to primary data collection) in a relatively large population. Utilizing Flatiron Health's longitudinal, demographically and geographically diverse database derived from electronic health

record (EHR)data from over 265 cancer clinics (~800 sites of care), the current study is designed to describe patient characteristics, treatment patterns and effectiveness of Palbociclib in combination with an aromatase inhibitor (AI) as initial endocrine based therapy in HR+/HER2- MBC.

2.1 STUDY DESIGN

Study design: *This is a retrospective cohort study utilizing data derived from the Flatiron Health Analytic Database to describe patient characteristics and effectiveness of* Palbociclib + Letrozole and Letrozole alone as first line therapy *in HR+/HER2- MBC during the period of February/3/2015 through 3 months prior to* the data cutoff date of the current Flatiron data release *in the US real-world clinical practice setting.*

- **Index date:** the start date of the first line therapy for Palbociclib + Letrozole or Letrozole alone between February 3, 2015 and 3 months prior to the cutoff date of the current data release. Index dates will be restricted to a date chosen to allow a potential duration of treatment of at least 3 months for all patients.
- **Observation period**: February 3, 2015 through the cutoff date of the current data release.
- **Follow-up:** Patients will be followed from the index date to the data cutoff date, or death, whichever came first.

Data source: *Flatiron Health's longitudinal, demographically and geographically diverse database is derived from electronic health record (EHR) data from over 265 cancer clinics (~800 sites of care) including more than 2 million active US cancer patients.* The analysis will use the following data sets:

Data Set Name	Description
Demographics	Contains patient demographic information. Data set consists of one record per patient.
Visit	Contains information on all visits including the visit date, type of information (vitals, treatment, and/or lab) collected during the visit. Data set consists of one record per patient per visit.
ECOG	Contains information about ECOG performance status including the ECOG date and value. Data set consists of one record per patient per ECOG record.

LineOfTherapy	Contains information about each line of therapy received by the patient, as defined by Flatiron business rules including the line number, line name, start and stop dates for the line. Data set consists of one record per patient per line of therapy.
Enhanced_Mortality_V2	Contains the month and year in which the patient died. The complete date is not provided due to patient confidentiality reasons. Data set consists of one record per patient for patients who died.
Enhanced_MetastaticBreast	Contains the initial diagnosis date and initial MBC date and the Stage at the initial diagnosis. Data set consists of one record per patient.
Enhanced_MetBreastSitesOfMet	Contains information on the sites of metastasis at the time of MBC diagnosis. Data set consists of one record per patient.
Enhanced_MetBreastProgression	Contains the date of the last clinic visit note in the patient's chart, progression event dates, and information on the source of evidence for progression reported by the treating physician. Data set consists of one record per patient without progression. For patients with progression the data set consists of one record per progression event date.

Treatment/cohort labels: After applying the inclusion and exclusion criteria, eligible patients will be assigned to the following cohorts based on their first line MBC treatment.

- ***Palbociclib + Letrozole Cohort:*** patients who initiated Palbociclib plus Letrozole therapy as their first line MBC treatment
- ***Letrozole alone Cohort:*** patients who initiated Letrozole therapy as their first line MBC treatment

2.2 STUDY OBJECTIVES

The following objective of the study protocol will be addressed by the analysis described in this amendment to the SAP:

CCI [redacted]

3 HYPOTHESES AND DECISION RULES

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

3.2 STATISTICAL DECISION RULES

The alpha level for statistical significance will be set at a two-tailed level equal to 0.05.

3.3 SAMPLE SIZE CALCULATION

All eligible patients meeting study inclusion/exclusion criteria will be included in the analysis. A preliminary count of first-line Letrozole alone and Palbociclib + Letrozole patients indicated each cohort will contain over 650 patients. Based on the PALOMA-2 clinical trial, the median PFS of the Letrozole alone group was equal to 14.5 months compared to 24.8 months for the Palbociclib + Letrozole group. Assuming similar median rwPFS survival rates and using yearly accrual rates from the Flatiron data extract, a survival analysis of rwPFS would require 138 patients in each group. The sample size calculation used the assumptions of a two-tailed alpha of 0.05, power of 90%, an accrual period (i.e., the time period when patients are identified until study end [03FEB2015-31AUG2018]) of 3.6 years. Robust variance estimation will be used to compute the adjusted proportional HR in the IPTW analysis; therefore, the sample size presented here may be overestimated.

4 ANALYSIS SETS/ POPULATIONS

4.1 FULL ANALYSIS SET

Inclusion criteria

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

1. *Female sex*
2. *At least 18 years old at MBC diagnosis*
3. *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. *Confirmation of metastatic disease*

c. *At least 2 document clinical visits*

d. *Evidence of stage IV or recurrent MBC with a metastatic diagnosis date on or after 2011, as confirmed by unstructured clinical documents*

4. *HR+/HER2-*

   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*

5. Palbociclib + Letrozole or Letrozole alone as first line therapy *for MBC during the period from February/2015* through three months prior to data cutoff *to allow for a possible minimum follow-up time of 90 days until the data cutoff date.* Letrozole in the Palbociclib + Letrozole cohort *was administered within (±) 28 days of Palbociclib index date.*

Exclusion criteria

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

1. *Evidence of prior treatment with other CDK4/6I (Ribociclib or Abemaciclib), AI (Letrozole, Exemestane, and Anastrazole), Tamoxifen, Raloxifene, Toremifene, or Fulvestrant for MBC*

2. *First structured activity greater than 90 days after MBC diagnostic date*

4.2 TREATMENT WITH A CDK4/6 INHIBITOR AS PART OF A CLINICAL TRIALSUBGROUPS

Subgroup Analyses. *Analyses of study measures, as described above, may be repeated focusing alternatively on the following subgroups of interest—sample size permitting—which will be defined on the basis of:*

- Age (year)
  ⩽50, 51-64, 65-74, 75+
- Race
  White, Black/Asian/Hispanic/Latino
- Disease stage at initial diagnosis
  I or II, III, IV
- ECOG performance status
  0, 1 or 2, ⩾ 1
- Site of metastasis
  Bone only, Visceral, Non-visceral
- # Metastatic sites

1, 2, ⩾ 3
- Menopausal status
- ER/PR Status (all patients in data received from Flatiron are HR+) ER+/PR-, ER+PR+, ER-/PR+

Sensitivity Analyses. IPTW performed under Amendment I indicated an inability to adequately balance baseline variables and clinical characteristics. Propensity score matching (PSM) balanced the two cohorts, but on a reduced number of patients. Therefore, results using PSM and IPTW will be presented.

5 ENDPOINTS AND COVARIATES

Demographic and clinical characteristics and clinical outcomes including PFS and OS will be compared between patients who were treated with first line Palbociclib + Letrozole versus first line Letrozole alone.

5.1 EFFICACY/ EFFECTIVENESS ENDPOINT(S)

All variables are assessed or defined by Flatiron using business rules before and after first line Palbociclib + Letrozole or first line Letrozole alone initiation

Variable	***Operational definition***
Demographic characteristics	
Age	*Age at MBC diagnosis, years*
Age category	*≤50, 51-64, 65 –74, ≥75 years*
Race	*White, Black, Asian, other, unknown*
Region of residence	*Based on state where the patient resides: Northeast, Midwest, South, West*
Practice type	*Academic, community*
Insurance type	*Commercial, Medicare, Medicaid*
Duration of follow-up	Months from the index date to the date of death, or the data cutoff date, whichever came first.
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*
Disease 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*

Time to treatment discontinuation	• The time from the start of a treatment to the time of treatment discontinuation for any reason in 1LOT • Start date: PAL/AI start date in 1LOT • End date: A. PAL/AI end date in 1LOT B. 2LOT start date C. Death date in 1LOT D. Whichever came first • Censoring date: latest available drug administration or latest visit/activity date (lab, office, radiology, etc), end of study, or loss to follow-up, whichever came first. • 2LOT start date A. Start date of adding any new anti-neoplastic (chemotherapy, target therapy (eg., Abemaciclib, Ribociclib), or endocrine therapy) if there is evidence of disease progression or after 60 days of index date if there is no evidence of disease progression. B. AI discontinuation or exchange from one AI to another AI is not considered as 2LOT start if there is no evidence of disease progression C. Exchange from one PAL to another CDK4/6i AI is not considered as 2LOT start if there is no evidence of disease progression. D. 1LOT was not advanced if PAL and/or AI were paused or stopped and then restarted within 120. Different days (90, 120, and 180) will be used as sensitivity analyses**.**
Organ-level metastatic sites	*Number of sites; Sites of metastases (bone, lung, liver, brain, distant lymph nodes, other)* *Visceral vs. non-visceral, bone only*
Modified Charlson comorbidity index (CCI)	As defined in the Flatiron database
Effectiveness outcomes	
Overall survival (OS)	Time in months from index date to death due to any cause or censoring date will be calculated. Based on an improved understanding of the death information in Flatiron and a better understanding of the OS analysis in PALOMA-2 the following changes will be made to the OS outcome definition. Event: Any death recorded by Flatiron in the data extract. Patients who did not die will be censored at the time of data cutoff.

Real-world PFS (rwPFS)	Time in months from index date to progression or censoring date will be calculated. Based on improved understanding of the PFS analysis in PALOMA-2 the following changes will be made to the PFS outcome definition. Event: Any death or disease progression (concluded by the treating clinician based on radiology, laboratory evidence, pathology, or clinical assessment). If patients did not die or have disease progression, they were censored at the date of initiation of next line of therapy for patients with two or more lines of therapy or their last visit date during the study period for patients with only one line of therapy.
Real-world tumor responses (rwTR)	• 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.
Response rate	• Complete response or partial response divided by the number of patients with at least one tumor assessment while on the index treatment.
Time to next line of anti-cancer therapy	• Defined as the time from the initiation of 1LOT (PAl+AI) until either o the day before the start of 2LOT for patients with evidence of 2LOT, or o death if the death occurred within 60 days following the patient's last administration of 1LOT (Pal\B/AI) o Whichever occurred first. • If a patient did not have evidence of 2LOT and did not die within the 60 days following the last 1LOT administration, the patient was censored at the latest available date that occurred on or before the end of study date of either last drug administration plus the number of days in a treatment cycle (last PAL/AI administration + 28 days) last visit date (e.g., office visit, lab, radiology, etc), or data cutoff date.

Time to chemotherapy	• Defined as the time from the initiation of 1LOT PAL+AI until either
	  o The day before the start of subsequent chemotherapy for patients with evidence of chemotherapy, or
	  o Death for any reasons
	  o Whichever came first
	• If a patient did not have evidence of subsequent chemotherapy and did not die, the patient was censored
	  o at the last visit date (e.g, office visit, lab, radiology), or
	  o data cutoff date
	  o whichever came later

Initial dose of Palbociclib	• Index dose level of Palbociblib: 125mg, 100mg, or 75 mg

6 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

This analysis will compare effectiveness outcomes of real-world progression-free survival (rwPFS) as primary outcome and Overall survival (OS) tumor response and time to next line of anti-cancer therapy/chemotherapy as secondary outcomes (depending on the availabilities of the data) in female patients treated with Palbociclib + Letrozole as first line MBC therapy versus Letrozole alone.

Means, medians, and standard deviations will be provided for continuous variables. Counts and percentages will be provided for dichotomous and polychotomous variables. Appropriate tests (t-tests and chi-square tests) will be provided for baseline demographic and clinical characteristics.

Inverse probability treatment weighting (IPTW) will be used to balance baseline demographic and clinical characteristics and to adjust analyses for differences in observed potential confounders between the two study cohorts.[1,2] The balance in important prognostic baseline characteristics will be assessed using a standardized differences approach, with values ≥0.10 indicating a non-negligible imbalance.

Propensity scores for use in IPTW will be calculated using a multivariable logistic regression model based on the following proposed baseline covariates such as age, race, practice type, type of MBC, ECOG performance score, disease stage at diagnosis (I–IV or unknown/undocumented), number of disease sites at MBC diagnosis (1, 2, ≥3), bone-only metastases, visceral metastases, and individual Charlson comorbidities, depending on data availability. Stabilized weights based on the propensity scores will be computed. The final list of variables to be used in the propensity score model will be discussed and determined during analysis development, after reviewing pre-matched descriptive tables. The selection of covariates for analysis will be based on the study team's clinical judgment.

The Kaplan-Meier method adjusted for weighted stabilized IPTW scores and 95% confidence intervals (CIs) will be used to estimate median rwPFS. Cox proportional hazards analyses adjusted for weighted stabilized IPTW scores will be used to estimate hazard ratios and 95% CIs for PFS.

The Kaplan-Meier method and 95% CIs will be used to estimate:

- proportions of patients surviving by cohort at follow-up years 1 through 4.

The Kaplan-Meier method adjusted for weighted stabilized IPTW scores and 95% CIs will be used to estimate:

- median duration of treatment.

Cox proportional models with a robust sandwich estimator will be used to compare the risk of PFS and OS between the matched study cohorts[3]. 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.

PSM will be performed. A multivariable binomial logistic regression model will be used to generate the propensity scores. 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.

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

6.1 SUMMARY OF ANALYSES

Outcome	Statistical Method	Covariates
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 . This outcome is not intended to be used as an effectiveness	Demographic and clinical characteristics
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 . This outcome is not intended to be used as an effectiveness	Demographic and clinical characteristics

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. This outcome is not intended to be used as an effectiveness	Demographic and clinical characteristics
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.	Demographic and clinical characteristics
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.	Demographic and clinical characteristics
rwPFS	Kaplan-Meier Plot, Cox proportional hazards model, IPTW/PSM	Demographic and clinical characteristics
OS	Kaplan-Meier Plot, Cox proportional hazards model, IPTW/PSM	Demographic and clinical characteristics
Tumor response	Descriptive analyses and logistic regression analyses, PSM/IPTW	Demographic and clinical characteristics

7 LIST OF TABLES AND FIGURES

Table 1. Summary of baseline demographic and clinical characteristic variables (unweighted and weighted results)

Figure 1. Kaplan Meier rwPFS curves

Table 2. Summary of rwPFS IPTW results

Figure 2. Kaplan Meier OS curves

Table 3. Summary of OS results

Figure 3. Kaplan Meier DOT curves

Table 4. Summary of DOT

8 REFERENCES

1. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661-3679.
2. Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. Stat Med. 2016;35(30):5642-5655.
3. Austin PC. The Use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med. 2014;33:1242-1258.