Non-Interventional Study Protocol
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Real-World Treatment Patterns and Outcomes Postmenopausal, Hormone-Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative, Metastatic Breast Cancer Patients Treated with Palbociclib Plus an Letrozole as Initial Endocrine Therapy at Community Oncology Practices in the U.S.

Statistical Analysis Plan
(SAP)

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1 INTRODUCTION

Since the initial approval of palbociclib in February 2015 for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer (MBC) in combination with an aromatase inhibitor (AI) as initial endocrine based therapy in postmenopausal women or in combination with fulvestrant, real-world observational studies have robustly described treatment patterns, dose modifications, and tolerability across multiple distinct retrospective databases.[1-4] Estimates of the clinical benefit (disease response, progression-free survival [PFS]) of palbociclib plus letrozole (palbociclib +LET) have been limited, however as these dataset cover the first two-years post approval which falls short of the 24.8 months PFS of palbociclib+LET observed in PALOMA-2.[5] A recently published retrospective chart review study found the real-world estimate of the 24-month progression-free rate of 64.3%.[4] With now more than 3 years of follow-up for the first palbociclib-treated patient, additional long term clinical benefit evidence can be generated leading to more precise estimates of PFS are available.

Another limitation of the previously conducted real-world research is the lack of a comparator arm for contextualizing the effects of palbociclib+LET therapy. Aromatase inhibitor (AI) monotherapies continue to be prescribed for a large number of HR-positive/HER2-negative MBC patients in lieu of the results of the PALOMA trials.[6] The differences in the demographic and clinical disease characteristics of women receiving first-line (1L) treatment with LET versus those prescribed palbociclib+LET have not been explored.

Finally, since the completion of the previously described real-world research, ribociclib was approved in same indication as ribociclib (March 2017).[7] No real-world data on clinical characteristics, treatment patterns (including dose reductions and rates of discontinuation), or early estimates of rates of progression have been explored in a real-world cohort of ribociclib+AI treated patients.

2 STUDY DESIGN

Patient demographics, clinical characteristics, treatment patterns pre- and post-palbociclib, laboratory monitoring, dosing patterns (and rationale for dosing changes), and clinical outcomes, including disease response and PFS will be described for locoregional recurrent or metastatic patients receiving palbociclib+LET as 1L, [redacted] The data will be collected through a physician-led, retrospective chart review. Providers will identify patients meeting the study selection criteria and abstract data from his/her patients' medical records into an electronic case report form (eCRF). Cardinal Health will conduct data verification via telephone and electronic follow-up. [redacted]

[redacted]

1) Presence of visceral metastases at the initiation of initial endocrine therapy for MBC
2) Receipt of prior neo/adjuvant endocrine therapy
3) De novo metastatic disease, ≤12 months disease free interval since prior neo/adjuvant treatment, >12 months disease free interval since prior neo/adjuvant treatment

[redacted]

2.1 STUDY POPULATION

[redacted]

1) Patients treated with palbociclib+LET as initial endocrine therapy for MBC per the palbociclib U.S. FDA approval label;

[redacted]

The target sample size for each of the three cohorts is 200 patients. Table 1 illustrates the selection criteria for each of the cohorts. Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study. No exclusion criteria will be imposed for the selection of patients.

Table 1. Cohort Selection Criteria.

Palbociclib+LET	CCI
Diagnosed with locoregional recurrent or metastatic female breast cancer	
Pathologically confirmed HR-positive/HER2-negative tumor	
Received treatment with palbociclib in combination with LET as initial endocrine-based therapy for advanced/metastatic breast cancer – Initiated treatment with palbociclib at least 3 months following the provider's first use of palbociclib after 03 Feb 2015 – At least 1 month of follow-up data after initiation of palbociclib	
Postmenopausal (or receiving surgical or medical treatment to induce menopause) at the time of initiation of 1L treatment for locoregional recurrent or BMC	
≥18 year old at initiation of endocrine therapy	

Patient eligibility will be confirmed by the treating physician. Providers may complete a maximum of 20 eCRFs. Providers will be asked to randomly select patients from the pool of eligible patients and verify that they have performed random patient selection.

2.2 DATA SOURCE

Providers will complete data abstraction into the eCRF using all structured and unstructured data, including laboratory, pathology, and radiology files from the selected

patients' electronic health records. The eCRF is designed to allow providers to efficiently move through the patient chart or electronic medical record (EMR) based on the journey of the patient through the course of their disease. All study data are secondary data that will have been collected retrospectively from existing clinical data originally collected as part of routine care. Unknown or missing options will be provided as applicable or when a data element is not required for the patient to be eligible.

All submitted eCRFs will be subject to at least one data quality control assessment. First, all submitted data will be analysed to identify response patterns which substantially deviate from the population average. A list of those variables which will be examined through this manner of assessment is presented in Section 5.1. Next, a random sample of 10% of the submitted eCRFs will be reviewed by clinical research team members to identify any missing data, questionable data such as implausible dates, or values for variables which are inconsistent with known clinical parameters. Records with flagged data will be presented to the providers for review and update. Finally, 10% of submitted eCRFs will have providers re-enter data for three selected variables (see Section 5.1). Records which cannot be verified will be removed from the analytical dataset. Should >50% of the eCRFs submitted by a provider be flagged for review and the provider is unable to validate all of the records all eCRFs from that provider will be removed from the dataset. Replacement sampling will not be conducted.

The eCRF conforms to the rules and regulations of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 governing the abstraction and storage of protected health information (PHI). No PHI will be collected in the course of the chart review or stored in the eCRF.

2.3 TREATMENT/COHORT LABELS

In this study, a line of therapy is defined as one or more anti-cancer agents given in combination over a period of time. Providers will be informed as to the definition of a regimen *but will make the determination themselves as to what constituted a line of therapy for the treatment of locoregional recurrent or metastatic breast cancer*. The first line of therapy is the first regimen initiated following the diagnosis of locoregional recurrent or metastatic breast cancer. Neoadjuvant or adjuvant regimens will not be considered a line of therapy in locoregional recurrent or metastatic setting.

2.4 STUDY OBJECTIVES

Primary Objectives

Among MBC patients receiving palbociclib+LET according to its labeled indication as initial endocrine therapy for MBC, the research objectives are to:

1) Describe the demographic and clinical characteristics of patients
    a. Demographic characteristics will include age, race/ethnicity, body mass index, insurance status, state of residence at the date of MBC diagnosis, and palbociclib initiation. Employment status will be assessed to the extent documented in the

record. Overall duration of follow-up (months) from the initiation of palbociclib+LET will be presented.

b. Clinical characteristics will include year of breast cancer and MBC diagnosis, AJCC stage at initial diagnosis, sites of metastatic disease at MBC diagnosis and palbociclib+LET initiation (including nodal status), menopausal status at MBC diagnosis and initiation of palbociclib+LET, verification of HER2 and ER/PR status, ECOG performance status, comorbidities (based on Charlson comorbidity index listing) at initiation of palbociclib+LET, and treatments received in the neoadjuvant or adjuvant setting (chemotherapy, hormone therapy, surgery, radiation therapy).

2) Describe the frequency of laboratory monitoring during treatment

a. Note that complete blood count (CBC) monitoring and cardiac function monitoring will be assessed, but lab results/values will not be assessed under this objective.
b. Evaluate the extent of laboratory monitoring using CBC during the first three cycles of 1L treatment
c. Assess the frequency of cardiac toxicity monitoring using electrocardiogram, liver function panels, and electrolytes during the first three cycles of 1L treatment
    i. The frequency of assessment of cardiac monitoring by each method will be evaluated during the initial endocrine-based therapy for MBC

3) Describe treatment patterns in terms of palbociclib+LET dosing, cycles received, and post-discontinuation treatment regimens

a. Palbociclib dosing will include description of the starting dose, dose adjustment (increase and decrease, interruptions), time to dose adjustment for palbociclib, and rationale for dose adjustment (provider interpretation)
b. Duration of palbociclib in terms of the number of cycles completed prior to the discontinuation of initial treatment for MBC
c. Primary rationale for the discontinuation of palbociclib+LET per provider interpretation
d. Treatment patterns includes the distribution of regimens administered, by line, from MBC diagnosis through the end of the medical record
e. Treatment patterns also includes the sequence of treatments across lines, from MBC diagnosis through the end of the medical record

4) Describe the rate of objective disease response during initial endocrine-based therapy

a. Tumor response will be classified per provider report for each regimen received during MBC treatment
b. Tumor response will be classified under a primary response classification as complete response (CR), partial response (PR), stable disease (SD), progressive

disease (PD), and not evaluable (NE), and unknown which comprises any other status

c. Tumor response will be classified under a secondary response classification as matching the primary classification, but for patients with NE, responses classifiable as “Other Favorable” or “Other Unfavorable”

5) Describe PFS from the initiation of initial endocrine-based therapy

a. Proportion of patients who are persistent to initial endocrine-based therapy for MBC at 3, 6, 12, 18, and 24 months, with persistence defined as the duration of initial regimen until one of the following events occurs: a regimen change or switch, treatment discontinuation, disease progression, or death.

b. Landmark PFS at 3, 6, 12, 18, and 24 months

c. Proportion alive at 3, 6, 12, 18 and 24 months

CCI [redacted]

3 INTERIM ANALYSES

An interim analysis will be conducted when the data from the full complement (200 patients) treated with 1L palbociclib+LET have been collected and verified. The interim analysis will include all descriptive analyses of the palbociclib+LET cohort CCI [redacted] This will include reporting of demographic and clinical variables described in Section 4 and Section 5. CCI [redacted]

CCI [redacted]

CCI [redacted]

4 ANALYSIS SETS/ POPULATIONS

All patients will be selected by the patient's treating provider. CCI [redacted] Only patients meeting the selection criteria will be included and a patient eligibility screening questionnaire is included for each patient with programmatic checks to ensure that only qualified patients are included in the analysis set. CCI [redacted]

4.1 FULL ANALYSIS SET

The full analysis set includes all patients who after clinical and analytical quality control assessment are retained for analysis in the study. CCI [redacted]

CCI [redacted]

[redacted]

5 ENDPOINTS AND COVARIATES

The purposes of this analysis is to describe the demographics, clinical characteristics, treatment and monitoring patterns, and clinical outcomes including disease response and PFS for patients treated with 1L palbociclib+LET[redacted] There are four periods along the patient journey which will be characterized: at initial diagnosis of breast cancer until development of locoregional recurrent or metastatic disease (non *de novo* only), at initiation of therapy for locoregional recurrent or metastatic disease, during 1L treatment, and post discontinuation of 1L.

5.1 EFFICACY/ EFFECTIVENESS ENDPOINT(S)

The table below describes data elements to be abstracted by the provider ("Abstracted Data Points") and independent/exposure variables calculated from the abstracted data ("Calculated Variables"). Further description of the calculation of clinical outcomes including disease response and PFS is described below the table. Variables in ***bold italics*** will be evaluated as part of the analytical assessment of data quality. Variables that are in *underlined italics* will be used in the 10% data validation exercise. These variables, along with other characteristics that may be evaluate as part of the quality control assessment are summarized below the table.

Table 2. Data Points and Calculated Variables by Role/Time Period Showing Operational Definition

Variable	Role/Time Period	Operational definition
Patient demographics	Descriptive outcome, diagnosis of breast cancer, MBC, and initiation of 1L	**Abstracted Data Points:** site of treatment (academic vs. community), year of birth, payer, state of residence, ethnicity, weight, height **Calculated Variables:** body mass index

Variable	Role/Time Period	Operational definition
Clinical characteristics	Descriptive outcome, diagnosis of breast cancer, MBC, and initiation of 1L, visceral disease used as subgroup/matching variable	**Abstracted Data Elements:** weight, height, ER status, PR status, HER2 status, family history of breast cancer, date of diagnosis of advanced/metastatic disease, *AJCC stage*, node status, menopause status, ECOG-PS, sites of metastatic disease, comorbidities via Quan[13] adaptation of the Charlson comorbidity index (CCI) (see Appendix 10.1 for comorbid conditions), prior cardiac toxicities, hematologic events, electrolyte abnormalities **Calculated Variables:** age at advanced/metastatic diagnosis, age at initiation of endocrine-based therapy, time to advanced/metastatic disease***, de novo metastatic disease***, CCI, visceral disease at initiation of endocrine-based therapy
Neo/adjuvant treatment history	Descriptive outcome, receipt and duration of neo/adjuvant treatment used as subgroup/matching variable	**Abstracted Data Elements:** chemotherapy/hormonal therapy regimens received, date of discontinuation of adjuvant treatment, receipt/date of surgery **Calculated Variables:** ***disease free interval*** (time from discontinuation of adjuvant therapy to diagnosis of advanced/metastatic disease)
1L therapy treatment characteristics	Forms analysis set cohorts, duration of treatment is descriptive outcome	**Abstracted Data Elements:** drug and/or combination endocrine partner, *date of initiation*, date of discontinuation, ***total number of cycles received***, dose at initiation, dose reductions, dose increases, rationale for dose increase/decrease, treatment interruptions (e.g., drug holiday), rationale for treatment discontinuation (e.g., progression, toxicity, patient choice) **Calculated Variables:** duration of treatment with initial endocrine-based therapy
1L therapy laboratory monitoring	Descriptive outcome	**Abstracted Data Elements:** frequency of CBC, cardiac monitoring using electrolyte panel, liver function panel monitoring during first 3 cycles of therapy, date of first CBC, electrolyte panel, ECG, liver function panel **Calculated Variables:** Time to first test during 1L therapy

Variable	Role/Time Period	Operational definition
Clinical outcomes during initial endocrine-based therapy	Primary clinical outcomes, comparison outcome for palbociclib+LET CCI [redacted]	**Abstracted Data Elements:** *provider assessed response to therapy (CR, PR, SD, PD)*, date of best initial response (CR, PR, SD), date of disease progression, **Calculated Variables:** duration of stable disease
Advanced/metastatic treatment patterns following discontinuation of initial endocrine-based therapy	Descriptive Outcome	**Abstracted Data Elements:** drug regimens received post discontinuation of initial endocrine-based therapy (chemotherapy, switch to alternative endocrine), date of initiation and discontinuation of treatment regimens received **Calculated Variables:** total lines of therapy received in the metastatic setting
Status at last follow-up	Descriptive outcome, death used as part of PFS calculation	**Abstracted Data Elements:** date of last follow-up, receipt of hospice care, receipt of palliative care, date of death (if deceased), cause of death **Calculated Variables:** See section 5.1.5

5.2 RESEARCH ANALYTICS QUALITY CONTROL VARIABLES/OUTCOMES

- de novo metastatic disease
- disease free interval (discontinuation of adjuvant to initiation of 1L)
- number of cycles received in 1L
- proportion of patients who discontinued 1L therapy
- proportion of responses to variables with missing/unknown levels

5.3 10% SAMPLE QUALITY CONTROL VARIABLES

- AJCC stage
- date of initiation of 1l therapy
- provider assessed response to therapy (CR, PR, SD, PD) to 1L therapy

5.4 DISEASE RESPONSE TO THERAPY

For this analysis, beyond the variables considered in section 5, non time-to-event clinical outcomes of interest will include the objective response rate (ORR), which is defined as the sum of CR+PR and clinical benefit rate (CBR), which is defined as the sum of CR+PR+SD (lasting >24 weeks). Both the ORR and CBR will be evaluated according to the provider assessed response to therapy.

5.5 PROGRESSION RATE AND PROGRESSION-FREE SURVIVAL

Disease progression is taken to have occurred when a pathology report or radiological scan note indicates disease progression and/or there is a physician progress note consistent with that determination. Providers will be informed of these criteria and indicate the date of disease progression during initial endocrine therapy for MBC following that guidance.

5.6 SAFETY ENDPOINTS

Not applicable

6 HANDLING OF MISSING VALUES

The eCRF is designed in a way to minimize missing values as much as possible. In situations where the data is truly missing or has inconsistencies (e.g., dates do not follow a logical sequence of events), Cardinal Health will reach out to the providers of these records to validate these fields. In cases where fields cannot be validated, Cardinal Health will consult with Pfizer to determine if the variable should be encoded as unknown, removed or if the subject associated with this variable should be excluded from the study.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 DESCRIPTIVE ANALYSIS

All categorical or numeric non time-to-event variables collected from the chart data abstraction or calculated from said data will be analyzed using descriptive statistical techniques. For demographic continuous variables, the mean, standard deviation, median, and minimum/maximum will be calculated as appropriate. For categorical variables, frequencies and percentages will be provided. The number of missing or unknown observations will be described for both categorical and numeric variables. The 95% confidence internals will be provided as a measure of estimated precision when appropriate. The following characteristics will be described using in each cohort using the statistical techniques previously described: demographics, receipt of and treatment received for neo/adjuvant treatment, clinical characteristics at diagnosis (e.g., stage, nodal status, menopause status), and clinical characteristics at diagnosis of locoregional recurrent or metastatic/initiation of 1L treatment (e.g., comorbidities, ECOG-PS, menopause status, receipt of CBC/cardiac tests in 30 days prior to initiation of 1L). Other descriptive analyses will include assessing the time from diagnosis to the initial initiation of 1L, duration of adjuvant treatment, and duration of follow-up from initiation of 1L treatment.

In addition, during 1L treatment, the following will be described: dose reductions, dose increases, treatment interruptions, and number of palbociclib cycles completed. The following details the assessment of these outcomes. Response levels are those specified in the case report form for the study.

1. Frequency of initiation of 1L palbociclib at 125mg, 100mg, and 75mg

   CCI [redacted]

2. Frequency/proportion of patients with any dose reductions and any dose increase
3. Frequency of reported rationale(s) for dose reduction (toxicity, other) and dose increases (no response, suboptimal response, loss or response, disease progression, other)
4. Mean months from initiation of 1L treatment to first dose reduction, first dose increase
5. Frequency of any treatment interruption; mean number of treatment interruptions during 1L treatment
6. Frequency of reported rationale(s) for first treatment interruption (toxicity, no response, loss of response, disease progression, prepare for alternative treatment strategy, patient choice, other)
7. Mean time to first treatment interruption
8. Mean duration (days) of first treatment interruption

Treatment Discontinuation and Switching:

9. Frequency/proportion of patients who discontinued 1L at 3 month intervals (through 24 months)
10. Frequency of reported rationale(s) for discontinuation of 1L (scheduled duration of therapy completed, disease progression, toxicities/adverse events, patient request (not due to toxicity/adverse event/intolerability), pill burden/compliance, death, unknown, other)
    a. Frequency of reported rationale(s) for patient request to discontinue therapy (quality of life, difficulty in attending to activities of daily living, no longer wishes to receive treatment, return to work, caregiver burden, financial challenges, unknown, other)
11. Frequency/proportion of patients not initiating subsequent therapy
12. Distribution of regimens received in second-line among patients who received subsequent therapy

Finally, the following variables and outcomes will be described to evaluate disease response rates among each cohort during 1L treatment.

1. Frequency/proportion of patients with disease response assessed
    a. Frequency/proportion with disease response assessed but recorded response level not available in the medical chart

2. Frequency/proportion of patients experiencing a CR, PR, SD, PD among all patients (including patients for who response was not evaluable/available at the time of data cut off)
3. Frequency/proportion of patients experiencing objective disease response (CR or PR)
4. Frequency/proportion of patients experiencing clinical benefit (CR or PR or SD lasting >24 weeks)
5. Time to response assessment among patients with known response categorization

Outcomes (response rates) for therapies received following discontinuation of 1L treatment will also be reported

7.2 SURVIVAL ANALYSIS

Survival analysis, also called time to event analysis, will be used in the current research to estimate the time to treatment discontinuation, time to progression, and PFS in 1L. This method of analysis is employed when non-informative right-censoring occurs as is the case for this study since not all patients will have discontinued treatment, progressed or died by the end of the study period. The Kaplan-Meier method (product limit estimator) will be used to generate median estimates of time to progression and PFS if median time is reached within the population. Survival curves will also be generated. In addition to calculating the median survival estimate, the life-table method will be used to estimate these time to event outcomes at successive 3 month intervals through 24 months post initiation of 1L.

The following lists the measurements to be conducted using survival analysis techniques:

1. Median time to treatment discontinuation
    a. Proportion of patients (survival estimate and 95% confidence interval) who are still receiving 1L treatment at 3, 6, 12, 18, and 24 months post 1L initiation
    b. Event = any treatment discontinuation for any reason, censor = patients who are still on 1L therapy at data cut-off
2. Median time to progression
    a. Proportion of patients (survival estimate and 95% confidence interval) who are progression free at 3, 6, 12, 18, and 24 months
    b. Event = any treatment discontinuation for disease progression, censor = patients who are still on 1L therapy or who discontinued therapy for any reason other than disease progression at data cut-off
3. Median progression-free survival
    a. Proportion of patients (survival estimate and 95% confidence interval) who are progression free and alive at 3, 6, 12, 18, and 24 months

b. Event = any treatment discontinuation for disease progression or death, censor = patients who are still on 1L therapy or who discontinued therapy for any reason other than disease progression or death at data cut-off

4. Proportion of patients alive at 3, 6, 12, 18, and 24 months following 1L initiation

   a. Event = death, censor = date of last follow-up among patients who are not deceased

CCI [redacted]

[redacted]

7.4 OTHER MULTIVARIATE ANALYSES

CCI [redacted] Logistic regression methods will be used to estimate both odds of disease response and odds of clinical benefit. Cox proportional hazard models will be used to estimate the risk of treatment discontinuation and risk of progression at selected time interval or over the entire treatment interval. For the Cox proportional hazards model a robust variance estimator to account for the clustering within matched sets will be employed as stratified analysis has been shown to result in biased estimation of the marginal hazard ratio.[13,14] Covariates included in these models will be ones measured at treatment initiation or prior to treatment initiation, such as age continuous age or categorical age, ECOG-PS (0/1 vs ≥2), and sites of metastatic disease (bone only vs any visceral sites). Additionally, other covariates significant at the 0.20 alpha level for the univariate analyses may be included in the multivariable model, after which individual removal of clinically and statistically insignificant variables using backward selection will occur to allow for the most parsimonious multivariable model possible.

7.5 SAFETY ANALYSES

Not applicable

[redacted]

9 REFERENCES

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10 APPENDICES

10.1 QUAN ADAPTED CHARLSON COMORBIDITY INDEX WEIGHTING

Comorbidities	Points
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic ulcer disease	1
Hemiplegia or paraplegia	2
Renal disease	2
AIDS/HIV	6
Diabetes	
with chronic complication	2
without chronic complication	1
Liver Disease	
Moderate or severe	3
Mild	1