Non-Interventional Study Protocol
A5481082

POLARIS: Palbociclib in Hormone Receptor–Positive Advanced Breast Cancer: A Prospective Multicenter Non-Interventional Study

Statistical Analysis Plan

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TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC	Advanced Breast Cancer
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
CAN	Canada
CCI	Charlson Comorbidity Index
CI	Confidence Interval
DPA	Documentation for Planned Analysis
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research & Treatment of Cancer Quality of Life Questionnaire
ER	Estrogen Receptor
FAS	Full Analysis Set
FMHT	First MBC Hormonal Therapy
G8	G8 geriatric screening tool
HR	Hazard Ratio
HR+/-	Hormone Receptor-positive/negative
HER2	Human Epidermal growth factor Receptor 2
LOT	Line Of Therapy
MBC	Metastatic Breast Cancer
MOS	Medical Outcomes Study
NI	Non-Interventional
OS	Overall Survival
PD	Progressive Disease
PPAS	Per-Protocol Analysis Set
rwPFS	Real-World Progression-Free Survival
PR	Progesterone Receptor
QoL	Quality of Life
QoLAS	QoL Analysis Set
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious AE
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Standard Deviation
rwTR	Real-World Tumor Response
US	United States

2 AMENDMENTS FROM PREVIOUS VERSION(S)

- The five ADL change categories defined for changes in ADL from baseline have been removed, as not supported by the literature.
- Updated list of demographic and baseline characteristics variables.
- Updated the definitions of the “QoLAS Dataset” and “Palbociclib Hormonal Partner”

3 INTRODUCTION

This statistical analysis plan (SAP) describes in detail the planned analyses for the Pfizer protocol A5481082 amended on 02AUG2017 entitled "POLARIS: Palbociclib in Hormone Receptor Positive Advanced Breast Cancer: A Prospective Multicenter Non-Interventional Study."

Breast cancer remains the most common cancer in women worldwide, with 1.6 million new cases diagnosed and a half a million deaths reported annually. In the United States (US), an estimated 246,660 new cases of invasive breast cancer, and an additional 61,000 new cases of in situ breast cancer, are expected to be diagnosed in 2016.[1] Breast cancer is ranked the second highest cause of cancer death in women[1] and is the third highest cause of cancer death overall, behind lung cancer and colon/rectum cancer, with 40,450 estimated deaths in 2016. Breast cancer represents about 29% of all new cancer cases and 14% of all cancer deaths in women. From 2003 to 2012, breast cancer incidence rates were stable in white women and increased slightly, at a rate of 0.3% per year, in black women. While death rates declined over the same time period (by 1.9% in white women and 1.4% in black women), due to early detection and treatment, breast cancer still remains a major health issue in the US. Statistics for breast cancer in males are also notable: 2,600 new cases are expected to be diagnosed in 2016, with 440 estimated deaths.

According to latest figures from the Canadian Cancer Society, 1 in 8 Canadian women is expected to develop breast cancer in their lifetime, with 27,400 expected new cases in 2020. Breast cancer is the second most common cause of cancer death in Canadian women, accounting for 13% of all cancer deaths in women, and is the third most common cancer in Canada (CAN), accounting for 13% of all cancers and 5% of cancers among women. Consistent with data from the US, the breast cancer incidence rate in CAN stabilized from 2004 through 2010, and the death rate due to breast cancer has fallen from a peak of 41.7 deaths per 100,000 in 1987 to a projected rate of 23.4 deaths per 100,000 in 2016.

Approximately 80% of breast cancers expressed estrogen receptor (ER), progesterone receptor (PR), or both. Endocrine therapy is the mainstream treatment for the HR+ cancers. Currently, first line treatment in the ER+/human epidermal growth factor receptor (HER2) – advanced breast cancer (ABC) postmenopausal population typically includes endocrine therapies, such as letrozole, anastrozole, exemestane, fulvestrant, and tamoxifen with time to progression and prolongation of real-world progression-free survival (rwPFS) ranging from 5 to 15 months.[2-4] These treatment options are supported by clinical practice guidelines published by the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) as preferred first-line options in patients who are antiestrogen naïve or who are more than 2 years from previous antiestrogen therapy and do not have extensive visceral involvement.[2, 4] Single-agent treatment with an aromatase inhibitor or tamoxifen has shown limited clinical

benefit.[5, 6] The selective ER degrader fulvestrant has modest activity in this population of patients,[7, 8] and the development of effective therapies that can address resistance to endocrine therapy is of clinical importance.

In vitro evidence suggests that breast cancer that has developed resistance to prior endocrine therapy remains dependent on cyclin to promote proliferation.[9, 10] Palbociclib is an orally bioavailable small-molecule inhibitor of cyclin-dependent kinase (CDK)4 and CDK6, with a high level of selectivity for CDK4 and CDK6 over other cyclin-dependent kinases.[11] Palbociclib inhibits CDK4 and CDK6 in vitro, resulting in loss of RB1 phosphorylation. It has high activity in hormone receptor – positive breast-cancer cell lines and is synergistic in combination with endocrine therapies.[12]

In a phase 1/2 study, PALOMA-1, patients were randomized to a 1:1 ratio to receive palbociclib + letrozole or letrozole alone.[14] The median rwPFS was 20.2 months with palbociclib + letrozole and 10.2 months with letrozole alone (hazard ratio [HR] = 0.488; P = 0.0004). In terms of the safety profile, grade 3/4 neutropenia was significantly higher in patients receiving palbociclib + letrozole compared with letrozole alone (54% vs. 1%). Additionally, the rate of grade 3/4 leucopenia (19% vs. 0%) and fatigue (4% vs. 1%) were also higher with palbociclib + letrozole. No cases of febrile neutropenia or neutropenia-related infections were reported in the study.[13]

A confirmatory phase 3 study, PALOMA-2,[14] was conducted with 666 postmenopausal women without prior systemic therapy for ER+/HER2 – ABC. Patients were randomized to a 2:1 ratio to receive palbociclib + letrozole or placebo + letrozole. The median rwPFS was 24.8 months with palbociclib + letrozole and 14.5 months with placebo + letrozole (HR = 0.58; 95% confidence interval [CI] 0.46, 0.72, P < 0.000001). All grades of common adverse events (AEs) with palbociclib + letrozole vs. placebo + letrozole were neutropenia (79.5% vs. 6.3%), fatigue (37.4% vs. 27.5%), nausea (35.1% vs. 26.1%), arthralgia (33.3% vs. 33.8%), and alopecia (32.9% vs. 15.8%). Grade 3/4 neutropenia occurred in 54% of patients; other AEs were of grade 1 severity. Febrile neutropenia was seen only with palbociclib + letrozole (2.5%). Permanent discontinuation due to AEs occurred in 9.7% of patients receiving palbociclib + letrozole vs. 5.9% receiving placebo + letrozole. PALOMA-2 confirmed the significant clinical benefit and safety of palbociclib + letrozole in ER+/HER2 – ABC patients who had not received prior systemic therapy for their advanced disease.[14]

Another phase 3 study, PALOMA-3, was conducted with 521 patients with advanced HR+/HER2 – patients that had relapsed or progressed during prior endocrine therapy.[15] Patients were randomized to a 2:1 ratio to receive palbociclib + fulvestrant or placebo + fulvestrant. The median rwPFS was 9.2 months (95% CI, 7.5, upper limit not estimable) with palbociclib + fulvestrant and 3.8 months (95% CI 3.5, 5.5) with placebo + fulvestrant (HR for disease progression or death, 0.42; 95% CI, 0.32, 0.56; P < 0.001). The most common grade 3 or 4 AEs in the palbociclib + fulvestrant group were neutropenia (62%, vs. 0.6% in the placebo + fulvestrant group), leukopenia (25.2% vs.

0.6%), anemia (2.6% vs. 1.7%), thrombocytopenia (2.3% vs. 0%), and fatigue (2.0% vs. 1.2%). Febrile neutropenia was reported in 0.6% of patients in each treatment group. The rate of discontinuation due to AEs was 2.6% vs. 1.7%.[15]

Estrogen receptor – positive breast cancer is biologically heterogeneous. Although palbociclib clinical trial results are very promising, it is also recognized that not all patients may respond to palbociclib treatment, and palbociclib treatment does come with mechanism-based toxicities. CCI [redacted][16]

Palbociclib is a novel CDK4/6 inhibitor approved in the US and CAN in combination with certain endocrine therapies for HR+/HER2 – ABC. With the introduction of this first in a new class of drugs, it is important to understand palbociclib treatment patterns in routine clinical practice in the US and, as a result, the evolving treatment landscape of ABC. It is important to understand real-world practice patterns and patient-reported outcomes as clinical trial populations may not be representative of real-life populations of patients given the preselection criteria and specific focus on a single line of therapy (LOT). This study will provide prospective observational data in real-world setting to contribute to the knowledge of palbociclib in ABC disease management and the new ABC treatment paradigm, CCI [redacted]. It is also of value to understand patient quality of life and the utility of geriatric assessment screening tools in treatment outcome measures of older breast cancer patients.

STUDY DESIGN

Protocol A5481082 is a prospective non-interventional (NI) multicentre study being conducted in the US and Canada (CAN). The primary goal is to understand palbociclib prescribing and treatment patterns for patients with Advanced Breast Cancer (ABC) being treated in routine clinical practice in the US.

Approximately 1,500 patients will be enrolled – patient inclusion and exclusion criteria are itemized in Sections 8.2.1 and 8.2.2, respectively, of protocol A5481082 – across approximately 100 sites (community and academic) in the US and 10 sites in CAN. Study duration consists of observations of patients on palbociclib treatment and approximately 3 years of follow-up after each patient's end of treatment with palbociclib, or until patient withdrawal from the study or death.

Participation in this study is not intended to change the routine treatment patients receive, as determined by their prescribing physicians; all treatment decisions, type, and timing of disease monitoring are at the discretion of the treating physician and patient. Assessments include patient questionnaires and quality of life (EORTC QLQ-C30, G8 Screening Tool,

Activities of Daily Living [ADL] Questionnaire), site questionnaires, physician metastatic breast cancer (MBC) treatment selection survey, and CCI .

Baseline (or Visit 1) is defined as the date of study enrolment when informed consent is obtained and inclusion/exclusion criteria assessed. The Data Entry Schedule is included in Table 1 and the EORTC QLQ-C30 and Geriatric Assesments in Table 2.

Table 1: Data Entry Schedule

Data Collection and Entry[1] ►	Baseline	During Treatment with Palbociclib	Post Treatment with Palbociclib
	SOC Visit 1	SOC Visit 2 through End of Treatment with Palbociclib	Follow-up through End of Study[2]
Informed Consent & Inclusion/Exclusion Criteria	x		
Patient Demographics, Study Site Characteristics, Medical History, Baseline Concomitant Medications, Baseline Metastatic Disease Status	x		
Breast Cancer Diagnosis and Recurrence History	x		
Breast Cancer Treatment[3]	x[3]	x[3]	x[3]
Physician MBC Treatment Selection Survey[4]	x[4]	x[4]	x[4]
Performance Status (ECOG)	x	x	
Clinical Assessments[5]	x[5]	x[5]	x[5]
CCI			
Laboratory: CBC[7]	x[7]	x[7]	
Adverse Events and Serious Adverse Events[8]	x[8]	x[8]	

SOC = Standard of care; ABC = advanced breast cancer; CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; MBC = metastatic breast cancer; SAE = serious adverse event

1. Data is collected in accordance with normal standard of care visits, enter all data available per Data Entry Schedule into the electronic data capture system.
2. Follow up through End of Study: Enter data at SOC visits where each subsequent (post palbociclib treatment) MBC treatment regimen is prescribed and at end of study.
3. Breast cancer treatment: including surgery, radiation, systemic chemotherapy, hormone therapy, and/or targeted therapy, in both neoadjuvant/adjuvant and metastatic disease settings, prior to, during, and post palbociclib treatment; supportive care is also collected in the metastatic setting while on this study.
4. Physician MBC Treatment Selection Survey: Treating physicians will complete a treating physician MBC treatment selection survey that will capture the reason(s) for treatment choice at start of palbociclib therapy and at start of subsequent therapies.
5. Clinical assessments: overall clinical response as judged by treating physician, at intervals per standard of care schedule: imaging assessment, clinical progression, and clinical biomarkers.

CCI

7. CBC: Baseline and during palbociclib treatment, enter any CBC during the 1st 3 cycles, then enter Day 1 (or prior to start of a new cycle) CBC for the subsequent cycles as per standard of care.
8. AE/SAE reporting begins at the time of the patient's first dose of palbociclib or the time of the patient's informed consent if s/he is already exposed to palbociclib and up to 28 calendar days following the last administration of palbociclib.

Table 2: EORTC QLQ-C30 and Geriatric Assessments

Data Collection and Entry ►	Baseline SOC Visit 1	Through End of Treatment with Palbociclib
EORTC QLQ-C30[1]	x[1]	x[1]
G8 Screening Tool[2]	x[2]	x[2]
ADL: Activities of Daily Living[2]	x[2]	x[2]

ADL = Activities of Daily Living; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30

1. EORTC QLQ-C30 will be collected at baseline (before starting palbociclib) then monthly for the first 3 months of treatment with palbociclib, then every three months until the end of treatment with palbociclib.
2. G8 Screening Tool and Activities of Daily Living to be completed only for patients equal to or greater than 70 years of age at the time of study enrollment. G8 and ADL will be collected at baseline (before starting palbociclib) then monthly for the first 3 months of treatment with palbociclib, then every three months until the end of treatment with palbociclib. ADL to be completed by the patient or in conjunction with the appropriately delegated site staff, G8 to be completed by the treating physician or the appropriately delegated site staff.

STUDY OBJECTIVES

The objectives of this prospective NIS of palbociclib in ABC treatment are:

- Palbociclib prescribing and treatment patterns in routine clinical practice in ABC treatment;
- Clinical outcomes;
- MBC treatment sequence prior to, during, and after palbociclib ;
- Patient quality of life, as measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30); and,
- Geriatric assessments in patients ≥ 70 years of age at enrolment.

CCI [redacted]

4 INTERIM ANALYSES

The study will consist of several interim analyses and a final analysis. The frequency and timing of the interim analyses will be driven by the observations and events available and also strategic medical interest (e.g., congress research submission deadlines). Each interim analysis will include data on baseline characteristics for patients enrolled in the study as well as longitudinal endpoints for patients with sufficient follow-up. Interim analyses will include summaries of patient, physician, and site characteristics. The specific measures (e.g., changes in patient-reported outcomes score, time-to-event analyses) presented for each interim analysis will be determined by Pfizer and analysis contributors based on the longitudinal data available at the time each interim dataset is released. At the time of each interim analysis, summaries related to treatment regimen, prescribing patterns, and dosing may be conducted as needed for abstracts and manuscripts provided sample sizes are sufficient for estimation.

5 ANALYSIS SETS

FULL ANALYSIS SET

The full analysis set (FAS), also referred to as the Safety Analysis Set (SAS), or quality of life analysis set (QoLAS), is defined as all subjects enrolled in the study and received at least one dose of study medication. The FAS will be used in all analyses unless specified otherwise.

PER-PROTOCOL ANALYSIS SET

The per-protocol analysis set (PPAS) is a subset of the FAS and defined as all subjects enrolled in the study who a) received at least one dose of palbociclib, b) did not have any treatment-free interval (see Appendix 1 Data Derivation Details) and c) had no disease-free interval (see Appendix 1).

CCI [redacted]

[redacted]

SUBGROUPS

Key measures, such as baseline patient characteristics, comorbidities, prior breast cancer treatments, treatment regimens during and after palbociclib treatment, and clinical outcomes will be assessed for the FAS and by specific subgroups defined by palbociclib hormonal partner and up to two additional subgroups. Patients will be classified into one of two or more levels for each subgroup of interest.

Potential subgroups of interest include:

- Age at enrolment (≥ 70 years / < 70 years)
- Ethnicity (Hispanic or Latino / Not Hispanic or Latino)
- Receipt of prior endocrine treatment (yes / no)
- Eastern Cooperative Oncology Group (ECOG) performance status (0-1 / 2-4)
- Insurance type (public / private / uninsured)
- ABC/MBC diagnosis at enrolment (de novo / recurrent disease)
- Disease stage at initial diagnosis (stage 0-IIIA / stage IIIB-IV)
- Charlson Comorbidity Index (CCI) (0 / 1-2 / 3+)

- Type of regimens (endocrine only / chemotherapy only / endocrine therapy combined with target therapy)
- Disease-free interval (0-<12 months / 12-<24 months / 24-<36 months / 36+ months)
- Visceral disease at enrolment (yes / no)
- Menopause status (yes / no)
- Line of therapy (LOT) in the ABC/MBC setting (1st line, ≥2nd line]

6 ENDPOINTS

EFFICACY/EFFECTIVENESS ENDPOINTS

The clinical endpoints listed below will be assessed by line of therapy (LOT) (1st line, ≥2nd line) in the ABC/MBC setting and reported.

- Real-World Tumor Response (rwTR)
- Real-World Progression-Free Survival (rwPFS)
- Overall Survival (OS)

Although a comparison of treatment regimens is not the primary intent of this NI study design, some clinical endpoints of interest may be separately summarized by different treatment regimens.

SAFETY ENDPOINTS

Safety will be assessed by adverse events (AEs), adverse events of special interest (AESIs), SAEs, and results of standard laboratory tests.

PHYSICIAN-REPORTED ENDPOINTS

Physician responses to quality of life questionnaires – ECOG performance status and G8 Screening Tool – will be evaluated at baseline and post-baseline.

ECOG Performance Status
ECOG performance status is a 6-level item ranging from "0: Fully active, able to carry on all pre-disease performance without restriction" to "5: Dead." Physicians complete this assessment for patients at baseline and at every post-baseline standard of care visit.

G8 Screening Tool
The G8 Screening Tool consists of 7 items based on the Mini-Nutritional Assessment and a single item covering the patient's age. Specifically, the G8 assesses food intake, weight changes, mobility, neuropsychological problems, body mass index, prescription count, and health status compared to similarly aged patients. Points are associated to each item and index score is calculated by summing points. The index score ranges in value from 0-17. If any of the 8 items is missing, the total score is missing. See Appendix 1 Data Derivation Details for item point values.

Physicians complete the G8 at baseline (prior to starting palbociclib) for patients ≥70 years of age, and then for these same patients and then at 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, etc. (i.e., every three months until the end of treatment with palbociclib) post-baseline. Additional timepoints will be added based on sample size.

PATIENT-REPORTED ENDPOINTS

Patient responses to quality of life questionnaires – EORTC QLQ-C30 and ADL – will be evaluated at baseline and post-baseline.

EORTC QLQ-C30

The EORTC QLQ-30 is a 30-item questionnaire composed of 5 multi-item functional subscales (physical, role, cognitive emotional, and social functioning), 3 multi-item symptom scales (fatigue, nausea/vomiting, and pain), a global health/quality of life (QoL) subscale, and 6 single items assessing other cancer-related symptoms (dyspnea, sleep disturbance, appetite, diarrhea, constipation, and the financial impact of cancer). For functional and global QoL scales, higher scores represent a better level of functioning and are converted to a 0 to 100 scale. For symptom-oriented scales, a higher score represents more severe symptoms. Missing data will be imputed according to the EORTC guidelines, and questionnaires will be considered as missing if >50% of the items were missing.. See scoring algorithm in Appendix 1 Data Derivation Details.

Patients (regardless of age) complete the EORTC QLQ-C30 at baseline (prior to starting palbociclib) and then at 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, etc. (i.e., every three months until the end of treatment with palbociclib) post-baseline.

Activities of Daily Living

The Activities of Daily Living (ADL) is a subscale of the Medical Outcomes Study (MOS) Physical Health. It is applicable to patients ≥70 years of age. The MOS Physical Health Scale measures a broad range of physical functioning that include bathing, dressing, toileting, transfer, continence, and feeding activities. Items for each of the six activities are rated on a 3-point Likert scale measuring independence in performing the activitiy (i.e., no assistance needed, partial assistance needed, unable to do without assistance). No imputation will be performed for missing items.

Katz Index[17] will be used to present items in a hierarchy of severity or difficulty of performing each task and a total score will be summaried for the six items. Independence is defined as performing these tasks without supervision, guidance or personal assistance while dependence is defined as doing the tasks with supervision, guidance or personal assistance. See Appendix 1 Derived Data Details for scoring details.

Patients ≥70 years of age complete the ADL at baseline (prior to starting palbociclib), and then at 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, and so on (i.e., every three months until the end of treatment with palbociclib) post-baseline.

7 HANDLING OF MISSING VALUES

Given the prospective observational multi-site study design, missing data may occur, even though effort will be made to ensure consistent and complete data are collected. All available patient data will be used for analysis.

Date Imputations

For initial diagnosis date, date of prior therapy, date of prior radiation, or date of prior surgery:

- If the date of initial diagnosis has nonmissing month and year but the day is missing, the 15th will be inserted as the day.
- If the date of initial diagnosis has nonmissing year but the month and the day are missing, June 30th will be inserted.

For all other dates:

- If the variable is a stop or end date and day of the month is missing, the last day of the month will be imputed. All other dates with missing day of the month will be assigned the first day of the month.
- If the variables is a stop or end date and day and month are missing, 31 December will be imputed. All other dates with missing day and month will be assigned to 1 January.

Dates missing the year will be treated as completely missing.

Questionnaire Imputations

Missing data patterns will be explored using multivariable regression cross sectional analysis conducted at baseline and selected 6-month time points with completion of instrument (EORTC QLQ-30, G8, or ADL) coded as ‘1’ and non-completion of the same instrument coded as ‘0’.
Additional information on missingness (e.g. reasons for withdrawal) may be explored.
Scores associated with the EORTC QLQ-C30, G8, and ADL are addressed in section 8.9 Analyses Quality of Life Endpoints and Appendix 1 Data Derivation Details.

8 STATISTICAL ANALYSIS

This study has a convenience sample; thus, results may not be generalizable to the entire population with the disease. Due to the study's exploratory nature, study measures will be summarized descriptively. Furthermore, any p value reporting should be placed in a descriptive framework for hypothesis generation and any such inferential analysis is intended to guide further research.

All analyses will be conducted using SAS® version 9.4 or higher.

The intention is to analyze all available data. In the advent that COVID may cause gaps in subject data or require adjustments to statiscal methodologies, our intent is to address such issues if or as needed. Both ICON and Pfizer have internal guidances and recommendations on file to assist with decision-making with regards to COVID-related data issues and these will be consulted if or as needed.

GENERAL METHODS

For continuous variables, means, standard deviations (SD), medians, minimums, maximums, and missing will be reported. For discrete variables, frequencies and percentages will be reported. Missing or unknown categories for each variable also will be presented. Percentages will be calculated excluding missing or unknown values. 95% Confidence Intervals (CI) are two-sided.

All summaries will be performed for all patients in the corresponding analysis set and by treatment combination defined at study entry within the corresponding analysis set:

- Palbociclib + Letrozole or Anastrozole
- Palbociclib + Fulvestrant
- Palbociclib + Exemestane
- Other

The baseline record is defined as the last observed measurement prior to palbociclib administration. Change from baseline is defined as the post-baseline value minus the baseline value.

Time in days between two dates will be calculated using the formula most recent date minus earlier date plus 1. For time in months, the same formula for days will be applied but then divided by 30.4. For time in years, the same formula for days will be applied but then divided by 365.25.

Variable definitions are found in Appendix 1 Data Derivation Details.

DISPOSITION OF SUBJECTS

A subject disposition summary will be reported. Subjects' study completion date and reason for premature termination will be reported in listing format. Number of subjects with initial diagnosis and with recurrent diagnosis will be reported in table and listing format.

DEMOGRAPHIC AND BASELINE CLINICAL CHARACTERISTICS

Demographic and baseline characteristics variables will be summarized for the FAS. For continuous variables (i.e., age at study enrollment, weight, height, BMI), summary statistics will be generated. For categorical variables (sex, race, ethnicity, insurance provider), the frequency and percentage of subjects in each category will be presented.

The following disease-related baseline characteristics will be summarized:

- Paloma-3 disease-free interval
- Disease free interval following treatment for early stage disease
- Treatment-free interval
- ABC/MBC diagnosis
- Duration of ABC/MBC disease
- Age of diagnosis
- Disease type
- Disease stage
- Disposition of diagnosis
- Performed biopsy and associated mutations
- Diagnostic imaging performed and imaging method
- Sites of metastases
- Estrogen Receptor (ER)/Progesterone receptor (PR) status
- Human epidermal growth factor receptor 2 (HER2) status
- Visceral status
- ECOG performance status
- Line of therapy in the ABC/MBC setting (1st line, 2nd line, 2+ line)
- Menopause status

MEDICAL HISTORY AND CONCURRENT MEDICAL CONDITIONS

Medical history and concurrent medical conditions will be summarized and presented in tabular and listing format for the FAS.

In addition, the CCI score[17, 18] will be calculated. See Appendix 1 Data Derivation Details. Note cancer will not be included in the CCI calculation because it is the diagnosis of interest. CCI score at time of enrolment will be summarized and reported in tabular format.

MEDICATION HISTORY AND CONCOMITANT MEDICATION

Summarized information on medication history for the FAS will include:

- Prior therapy for initial diagnosis and the best response
- Prior therapy at ABC/MBC setting and the best response
    - Number of Lines of therapy
    - Therapy categories
    - Best response
- Prior chemotherapy
- Treatment free interval
- Prior radiation therapy
- Months from last prior radiation to first study dose
- Prior surgery or non-radiation procedures

All concomitant medications will be coded by therapeutic classification, subclassification, and medication using the World Health Organization Drug Dictionary (WHO Drug). A concomitant medication is defined as a medication that is ongoing as of Study Day 1, ends on or after Study Day 1, or starts on or after Study Day 1 and no more than 28 days after the last dose of study drug.

Concomitant medication of interest will be reported separately.

STUDY DRUG EXPOSURE

Overall palbociclib treatment will be summarized as below for the FAS overall and by LOT:

- Number of cycles of palbociclib received
- Length of palbociclib treatment (months)
- Treatment disposition: (still receive palbociclib, discontinued palbociclib)

Palbociclib prescribing and treatment patterns will also be explored by cycle. For each cycle, below will be summarized:

- Starting dose (if less than 125mg, present reason)
- Primary reason for selecting palbociclib for the first cycle
- Dose modification (type, dose received after modification, reason)

Treatment patterns following enrollment will be reported, which include only lines started at enrollment:

- Type of therapy received (such as chemotherapy, hormonal therapy, other therapy)
- Agent (drug) composition of the treatment regimen received
- Time from initiation of treatment to initiation of each subsequent lines of treatment

- Time from discontinuation of previous line to initiation of the subsequent line of treatment
- Time from the start to end of each treatment line (in months for the total duration). This measure will be presented overall and by the top four regimens received in the line.

The sequence of agents/combination regimens received for first-line treatment in the ABC/MBC setting and subsequent lines of treatment will be presented. The proportion of all patients with each unique sequencing pattern will be reported for the overall study sample. Type of therapy sequencing (e.g., endocrine only, chemotherapy only, endocrine therapy combined with target therapy) will also be presented in the same format.

CLINICAL OUTCOMES

rwTR, rwPFS, and OS will be assessed by LOT (1st line, ≥ 2nd line) in the ABC/MBC setting for the FAS. Based on the nonrandomized, observational nature of the study design, no clinical endpoints will be separately assessed and compared between specific treatment regimens.

Real-world tumor response (complete response, partial response, stable disease, progressive disease) is determined by physician based on imaging, biopsies, biomarkers, and/or clinical judgment. Response as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) criteria may not be available for all patients. rwTR will be derived as the best tumor response recorded from the palbociclib combination treatment start date until the first documentation of progressive disease. Only response assessments recorded on or before the start date of next subsequent line of treatment will be considered. The proportion of patients with a best response of complete response, partial response, stable disease, and progressive disease will be calculated and reported. Real-world response rate is defined as the propotion of patients with a best tumor response of complete response or partial response. Best tumor response, clinical benefit, and study end date are defined in Appendix 1 Data Derivation Details.

rwPFS will be estimated by LOT in the ABC/MBC setting. rwPFS is defined as time (months) from initiation of the palbociclib combination treatment to the earliest of clinician-documented progression or death due to any cause, whichever occurs first. Patients absent of the above events will be censored at the last date of response assessment without progressive disease.

OS will be estimated by LOT in the ABC/MBC setting. OS is defined as time (months) from initiation of the palbociclib combination treatment to date of death due to any cause. Patients do not have a documented death will be censored at last available visit date known to be alive.

Follow-up time will be calculated as time (months) from initiation of the palbociclib combination treatment to date of death or last available visit date. Median follow-up time and range (minimum, maximum) will be provided overall and by LOT.

Time-to-event outcomes (i.e., rwPFS, OS) will be analyzed using the Kaplan-Meier method and estimated survival curves will be displayed when appropriate. The number of patients at risk over time will be presented. A summary table will include number of patients with events, number of patients censored, and Kaplan-Meier quartiles (when estimable) accompanied by two-sided 95% confidence intervals (CIs). Based on the Kaplan-Meier life table, Survival function estimates at the specific time points (eg, 6, 12, 18, 24, 30 and 36 months) will also be reported along with two-sided 95% CIs.

Cox proportional hazards models may be developed for each time-to-event outcome when appropriate. These models would include covariates such as age, comorbidities, and hormonal partner. If performed, the validity of the proportional hazards assumption will be assessed using plots of scaled Schoenfeld residuals versus time as well as score tests for each covariate in each model. If necessary, alternative Cox modeling approaches (e.g., parametric models, restricted mean survival time, stratification, time-varying covariates) will be considered if there is evidence of nonproportional hazards. Hazard ratios for each model term, along with two-sided 95% CIs, will be computed and displayed in a table for each covariate in the final model for each outcome.

SAFETY ANALYSES

8.8.1 Adverse Events

All safety analyses will be completed following Pfizer safety analysis standards, including descriptive statistics on all safety endpoints for the FAS. AEs will be monitored throughout the study duration. If the type and/or number of AEs warrants further examination, interim analyses will be conducted to determine whether those experiencing AEs are systematically different from other study participants. If the percentage of patients withdrawing from the study exceeds 25%, interim analyses will be conducted to examine whether systematic differences exist between those withdrawing from the study and those that continue with palbociclib treatment. Descriptive statistics comparing women and men who complete follow-up with those who withdraw from the study will also be completed to determine whether there are any systematic (demographic, clinical) differences between these such defined groups.

Descriptive statistics will be presented for all AEs and will be examined by AE grade. The incidence of all-cause and treatment-related AEs and SAEs separately will be reported. Specifically, a summary of incidence will be presented for the following variables:

- Patients evaluable for AEs
- Number of AEs
- Patients with AEs

- Patients with SAEs
- Number of SAEs
- Patients with Grade 3 or 4 AEs
- Patients with Grade 5 AEs
- Patients permanently discontinued study associated with AEs
- Patients permanently discontinued study associated with SAEs
- Patients permanently discontinued treatment associated with AEs
- Patients permanently discontinued treatment associated with SAEs
- Patients temporarily discontinued treatment associated with AEs
- Patients temporarily discontinued treatment associated with SAEs
- Patients with dose reduction associated with AEs
- Patients with dose reduction associated with SAEs
- Deaths

8.8.2 Clinical Laboratory Evaluation

Clinical laboratory variables will be summarized using descriptive statistics for baseline, post-baseline, and change from baseline to post-baseline values.

All lab parameters will be summarized by worst grade/value by cycle in addition to overall worst grade/value. Lab cycles are windowed as a cycle's start date until the next cycle's start date. See Appendix 2 Visit Windowing.

Table 3: Lab Unit Conversions

Lab Test	Standard Unit	%	g/dL	/ul	'K/mol' or 'x10^3/moL'
HGB	g/L		Value*10		TBD
Lymphocytes	10^9/L	(Value*WBC)/100		value*0.001	
Neutrophils	10^9/L	(Value*WBC)/100		value*0.001	
Platelets	10^9/L			value*0.001	
WBC	10^9/L			value*0.001	

The following units were considered equivalent to 10^9/L: '10**3/uL', '10*3/UL', 'x10^3/mm^3', 'x10^3/microL', 'K/UL', 'x10^9/L', 'K/mm3', '10*9/L', 'K/mol', 'x10^3/moL'

Table 4: CTCAE Grading

Lab Test	Normal		CTCAE Grade			
			1	2	3	4
HGB	≥ LBLLN and ≤ LBULN	**High**	> 0 – 1.2412 mmol/L above LBULN	>1.2412 – 2.4824 mmol/L above LBULN	> 2.4824 mmol/L above LBULN	
		Low	< LBLLN - 6.2 mmol/L	< 6.2 - 4.9 mmol/L	< 4.9 mmol/L	
Lymphocytes	≥ LBLLN and ≤ 4.0	**High**		4 < to ≤ 20	> 20	
		Low	0.8 ≤ to < LBLLN	0.5 ≤ to < 0.8	0.2 ≤ to < 0.5	< 0.2
Neutrophils	≥ LBLLN	**Low**	< LBLLN - 1.5 X 10^9/L	< 1.5 - 1.0 X 10^9/L	< 1.0 - 0.5 X 10^9/L	< 0.5 X10^9/L
Platelets	≥ LBLLN	**Low**	< LBLLN - 75.0 X 10^9/L	< 75.0 - 50.0 X 10^9/L	< 50.0 - 25.0 X 10^9/L	< 25.0 X 10^9/L
WBC (leukocytes)	≥ LBLLN and <100 X 10^9/L	**High**			>100 X 10^9/L	
		Low	< LBLLN - 3.0 X 10^9/L	< 3.0 - 2.0 X 10^9/L	< 2.0 - 1.0 X 10^9/L	< 1.0 X 10^9/L

ANALYSES OF QUALITY OF LIFE ENDPOINTS

All analyses will be conducted using the QoLAS. Where noted, the following binary categorizations will apply: age at baseline (<70 years and and ≥70 years), LOT (1 line and ≥2 lines), ECOG performance status (0 and 1-5), any dose modifications (yes and no), and SAE status (none and ≥1). Also, binary categorizations for ADL (all activities "No Assistance Needed" and other) and G8 index score (≤14 and >14) will be created.

8.9.1 EORTC QLQ-C30

EORTC QLQ-C30 scores and subscores will be summarized at baseline and each post-baseline visit. Paired t-test p-values will be reported. Change from baseline at each post-baseline visit will be summarized if both values are nonmissing. The EORTC QLQ-C30 scores will be compared with country population norms as part of this analysis.

Furthermore, repeated-measures models with unstructured covariance may be considered to estimate average change in global health status (as measured by the EORTC QLQ-C30) from baseline at each post-baseline timepoint. If such models will be performed, time from baseline will be included as a categorical covariate. For each outcome measure, model-based predicted values (least squares means) may be presented along with 95% CIs for each time point.

A descriptive analysis of EORTC QLQ-C30 scores and subscores will be conducted by the following categorizations: age at baseline, LOT, ECOG performance status, any dose modifications, and by SAE status. Two-sample t-test p-values will be reported for category comparisions.

In addition, differences in EORTC QLQ-C30 "worsening" (see definition in Appendix 1 Derived Data Details) percentages between categorizations for age at baseline and LOT at post-baseline timepoints. Counts and percentages will be reported along with 95% CIs (based on Wilson's Score as Modified by Newcombe)[19] and chi-square p-values.

8.9.2 Activities of Daily Living

Activities of Daily Living (ADL) is assessed using a six-item ADL limitations measure that inventoried whether participants had difficulty bathing, dressing, toileting, feeding, with transfer, and incontinence.[20, 21] Respondents selected 1 (unable to do without assistance), 2 (partial assistance needed), or 3 (no assistance).

For each of the 6 activities, counts and percentages will be reported by response at baseline and each post-baseline timepoint. In addition, a summary score using Katz Index will also be presented.

Change from baseline in total score at each post-baseline visit will be summarized if both values are nonmissing. Furthermore, repeated-measures models with unstructured covariance may be considered to estimate average change in ADL summary score from baseline at each post-baseline timepoint. If performed, the model with time since baseline will be included as a categorical covariate. For each outcome measure, model-based predicted values (least squares means) may be presented along with 95% CIs for each time point.

ADL binary categorizations may be paired at baseline and each post-baseline timepoint and, if performed, p-values based on McNemar's test will be reported.

8.9.3 G8 Screening Tool

Physician responses to the G8 items and index score will be summarized at baseline and each post-baseline timepoint.

G8 binary categorizations may be paired at baseline and each post-baseline timepoint, and, if performed, p-values based on McNemar's test will be reported.

Change in index score from baseline at each post-baseline visit will be summarized if both values are nonmissing. Furthermore, repeated-measures models with unstructured covariance may be considered to estimate average change in G8 index score from baseline at each post-baseline timepoint. If so, time from baseline will be included as a categorical covariate. For each outcome measure, model-based predicted values (least squares means) may be presented along with 95% CIs for each time point.

8.9.4 ECOG Performance Status

ECOG Performance Status will be summarized by any dose modification category and SAE status.

Categorized ECOG performance status will be examined with ADL category and G8 category at baseline and each post-baseline timepoint. Along with frequencies and percentages, Fisher's exact test p-value will be reported. Furthermore, ECOG performance status may be examined with ADL total score and G8 index score using Pearson correlation coefficients and Spearman's rank coefficients at baseline and each post-baseline timepoint..

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[redacted]

8.9.6 Neutropenia/Lab monitoring pattern

An agreed upon Documentation for Planned Analysis (DPA) will detail the expected analyses prior to execution. Appropriate statistical methodology will be applied to the analyses.
Both Neutropenia and Lab Monitoring Patterns are exploratory analyses to be conducted to explore emerging patterns. The primary exploration will focus on the timepoints during treatment with palbociclib overall and by LOT, evaluated by treatment partner.

In addition to neutrophil counts, palbociclib dosing, palbociclib dose adjustment, MD reported AE of interest, and xx% neutropenia, neutrophil count decrease, by grade; Neautropenia analysis for trend identification between the following will be assessed:

- Correlations of neutropenia value and grade to dosing and dose adjustment
- Neutropenia grades(1/2 vs 3/4) and median by LOT
- Neutropenia grades and median and clinical outcomes: rwPFS
- Neutrophil mean, median, during 1st month, 3 months, 6 months, 12 months, 18 months, 24 months, 36 months, …

Lab monitoring pattern analysis will include CBC lab testing frequency over palbociclib treatment course, xx% for neutropenia at predetermined time points.

APPENDICES

APPENDIX 1: DERIVED DATA DETAILS

Study End Date: the earliest of study withdrawal date or last contact visit date

Study Duration: defined in days as study end date minus baseline date +1.

Study Day: post-baseline visit or event date minus baseline date +1. For pre-baseline visits or events, study day is defined as pre-baseline visit or event date minus baseline date. Note there is no study equal to 0.

Age at baseline: defined in years as baseline date minus date of birth +1 divided by 365.25.

Duration of disease: defined in days from initial diagnosis date to study enrollment date.

Duration of ABC/MBC disease: defined in days from ABC/MBC diagnosis date to study enrollment date.

Disease-free interval: time from the end of adjuvant/neoadjuvant treatment to the first disease recurrence.

Paloma-3 disease-free interval: defined in days as the time between first diagnosis of breast cancer and onset of metastatic disease or disease recurrence.

Treatment-free interval: defined in days as the time from last dose of prior chemotherapy to first MBC therapy or first study dose whichever occurred earlier.

Line of Therapy (LOT):
Clinical outcome endpoints will be summarized by LOT which is defined based on the number of therapies taken after initial diagnoses of ABC or MBC, but before palbociclib treatment start:

- 1^{st} line: patients had no LOT in the ABC/MBC setting before palbociclib initiation
- 2^{nd} line: patients had one LOT in the ABC/MBC setting before palbociclib initiation
- 2^{+} line: patients had >1 LOT in the ABC/MBC setting before palbociclib initiation

Best Tumor Response: best overall tumor response recorded from palbociclib treatment start until first documentation of progressive disease. Only response assessments recorded on or before the start date of next subsequent line of treatment will be considered.

Clinical Benefit: a best overall tumor response of complete response or partial response at any time, or stable disease for at least 24 weeks post-study treatment initiation. Only response assessments recorded on or before the start date of next subsequent line of treatment will be considered.

Overall Survival (OS): is defined as time (months) from initiation of the palbociclib combination treatment to date of death. due to any cause.

First Hormonal Therapy After Stage III or IV Diagnosis: the first recorded MBC or adjuvant hormonal therapy after initial diagnosis of stage IIIb or IV MBC or ABC.

Palbociclib Hormonal Partner: the concurrent hormonal therapy recorded while on Palbociclib. If the patient took both LETROZOLE and ANASTROZOLE then the first hormone partner (chronologically) is assigned.

Time from Initiation of Treatment to Initiation of Each Subsequent Line of Treatment: defined in days by subtracting the date of treatment initiation from the date of initiation of each subsequent treatment line and adding 1.

Time from Discontinuation of Previous Line to Initiation of the Subsequent Line of Treatment: defined in days by subtracting the initiation date of the previous line from the initiation date of the subsequent line and adding 1.

Time from the Start to End of Each Treatment: defined in months by subtracting the discontinuation date from the initiation date for each treatment line, adding 1, and then dividing by 30.4.

Charslon Comborbidity Index:
Assign a point score to each condition per Table 5 below. Point scores are then summed within patient to generate an overall score of disease burden.

Table 5: List of Comorbidities Collected at Time of Enrolment

Condition	Point Score
Charlson Comorbidity Index conditions:	
Cerebrovascular disease	1
Chronic pulmonary disease	1
Congestive heart failure	1
Connective tissue disease	1
Dementia	1
Diabetes with end organ damage	2
Diabetes without end organ damage	1
Depression	1
Hemiplegia or paraplegia	2
History of myocardial infarction	1
HIV/AIDS[a]	6
Hypertension	1
Mild liver disease	1
Moderate to severe liver disease	3
Use of warfarin	1
Moderate to severe renal disease	2
Peptic ulcer disease	1
Peripheral vascular disease	1
Skin ulcers/cellulitis	2
Other specific comorbidities	
Leukemia	N/A
Lymphoma	N/A
Neutropenia	N/A
Anemia	N/A
Other comorbidities not listed above	N/A
No comorbidities	N/A

[a] AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus.

ECOG Performance Scale:
Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

Grade	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

EORTC QLQ-30 Scoring:
15 scales and items are calculated per Table 6 below.

Table 6: EORTC QLQ-30 Scoring Instructions

Scale/Item Label	Scale Name	Item Number	Raw Score (RS)[a]	Score
Global health status/QoL	QL2	29, 30	$(I_{29} + I_{30}) / 2$	[(RS – 1) / 6] * 100
Physical functioning	PF2	1 to 5	$(I_1 + I_2 + I_3 + I_4 + I_5) / 5$	[1 – (RS - 1) / 3] *100
Role functioning	RF2	6, 7	$(I_6 + I_7) / 2$	[1 – (RS - 1) / 3] *100
Emotional functioning	EF	21 to 24	$(I_{21} + I_{22} + I_{23} + I_{24}) / 4$	[1 – (RS - 1) / 3] *100
Cognitive functioning	CF	20, 25	$(I_{20} + I_{25}) / 2$	[1 – (RS - 1) / 3] *100
Social functioning	SF	26, 27	$(I_{26} + I27) / 2$	[1 – (RS - 1) / 3] *100
Fatigue	FA	10, 12, 18	$(I_{10} + I_{12} + I_{18}) / 3$	[(RS – 1) / 3] * 100
Nausea and vomiting	NV	14, 15	$(I_{14} + I_{15}) / 2$	[(RS – 1) / 3] * 100
Pain	PA	9, 19	$(I_9 + I_{19}) / 2$	[(RS – 1) / 3] * 100
Dyspnea	DY	8	I_8	[(RS – 1) / 3] * 100
Insomnia	SL	11	I_{11}	[(RS – 1) / 3] * 100
Appetite loss	AP	13	I_{13}	[(RS – 1) / 3] * 100
Constipation	CO	16	I_6	[(RS – 1) / 3] * 100
Diarrhoea	DI	17	I_7	[(RS – 1) / 3] * 100
Financial difficulties	FI	28	I_{28}	[(RS – 1) / 3] * 100

[a] "I" indicates item response value. Raw score (RS) is the average of all nonmissing item values if at least ½ the item values comprising the scale are nonmissing. For instance, if I_3 and I_5 are missing but the other 3 item values comprising PF2 are nonmissing, RS is calculated as $(I_1 + I_2 + I_4) / 3$.

EORTC QLQ-30 Categories:

(1) Worsening is defined as a change from baseline of at least a 10-point decrease in score on the functioning domains and global quality of life and at least a 10-point increase in score on the symptom items.

(2) Improving/Maintaining is defined otherwise.

G8 Screening Tool[22-24]

An index (or total) score is calculated by assigning a score to each item per Table 7 below and summing all scores within patient. If any items are missing, the index score is missing. The score ranged from 0 (heavily impaired) to 17 (not at all impaired).

Table 7: G8 Screening Tool Index Score Calculation

	Items	Possible responses (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss >3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
E	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
F	BMI? (weight in kg)/(height in m^2)	0 = BMI <19
		1 = BMI 19 to <21
		2 = BMI 21 to <23
		3 = BMI ≥23
H	Takes more than three prescription drugs per day?	0 = yes
		1 = no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
Age		0: >85
		1: 80–85
		2: <80
	Total score	0–17

Activities of Daily Living (ADL) Total Summary Scores and Categories:

The activity uses a 3-point Likert scale measuring independence in performing the activitiy (i.e. bathing, dressing, toileting, etc.). “Unable to do without Assistance” is assigned a score of 1, “Partial Assistance Needed” is assigned a score of 2, and “No Assistance Needed” is assigned a score of 3.

The total/summary score ranges between 6 to 18, where a score of 6 indicates a very dependent patient and a score of 18 represents an independent patient.

All 6 items must be available to yield a summary score.

APPENDIX 2: LAB VISIT WINDOWING

Visit	Visit Day	Window of Days	
		non-lab domains	CBC Labs
Baseline	1	<=1	
Day 15	15	n/a	2-18
Day 21	21	n/a	19-25
Day 28	28	n/a	26-45
Month 1	30	2-45	n/a
Month 2	60	46-75	
Month 3	90	76-135	
Month 6	180	136-225	
Month 9	270	226-315	
Month 12	360	316-405	
Month 15	450	406-495	
Month 18	540	496-585	
Month 21	630	586-675	
Month 24	720	676-765	
Month 27	810	766-XX	

If multiple records are assigned per analysis visit, the latest record will be selected for reporting.

An alternate presentation of lab data will display by Cycle. Cycle *x* is defined as any lab record between Cycle *x* start date until Cycle *x+1* start date.

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