NON-INTERVENTIONAL STUDY PROTOCOL

A5481090

TREATMENT PATTERNS AND CLINICAL OUTCOMES AMONG PATIENTS RECEIVING PALBOCICLIB COMBINATIONS FOR HR+/HER2- ADVANCED/METASTATIC BREAST CANCER IN REAL WORLD SETTINGS

Statistical Analysis Plan
(SAP)

Revision	Effective Date	Summary of Revisions
2.0	01.10.2018	Addition of new client lead and additional markets in which the research is being conducted
3.0	19.12.2018	Addition of clarifying text requested by medical staff
4.0	04.10.2019	Updated stratifications

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Authors: PPD

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Addition of new client lead and additional markets in which the research is being conducted.

2. INTRODUCTION

Breast cancer is the most common diagnosed cancer and the most common cause of death in females worldwide. There were 1.67 million new cases of breast cancer diagnosed globally in 2012, which equated to 12% of all diagnosed cancers. Across the world 522,000 women died of the disease the disease in 2012, which represented 15% of female deaths from cancer.[1] There is a huge worldwide variation in breast cancer survival rates, ranging from 80% or more in North America, Sweden and Japan to 60% in middle-income countries and as low as 40% in low-income countries.[2] Breast cancer survival rates have increased over the last 50 years, as relative survival increased from 75.2% in 1975 to 90.6% in 2008.[3] The 5 year survival rate for women with stage 0/I breast cancer is near to 100%, compared to that of stage II and III, which are 93% and 72% respectively. Women who are diagnosed with metastatic or stage IV breast cancer have a much lower 5 year survival rate of 22%.[4]

Over the past few decades, hormonal therapies such as letrozole, anastrazole, and fulvestrant have emerged as the preferred treatment for HR+ breast cancers. Following the success of the phase II PALOMA-1 trial, the FDA granted accelerated approval of the CDK4/CDK6 inhibitor palbociclib that causes cell cycle arrest to be used in combination with letrozole to treat HR+/HER2- advanced/metastatic post-menopausal breast cancer. The PALOMA-1 trial demonstrated median progression-free survival of 20.2 months for post-menopausal patients with advanced/metastatic HR+/HER- breast cancer receiving letrozole in combination with palbociclib vs. 10.2 months in patients receiving letrozole and placebo.[5] The follow up phase III PALOMA-2 trial demonstrated median progression free survival of 24.8 months for post-menopausal patients with HR+/HER- advanced/metastatic breast cancer (ABC/MBC) receiving letrozole in combination with palbociclib vs. 14.5 months in patients receiving letrozole and placebo.[6] The label has since been expanded to include any aromatase inhibitor in this indication.[7]

In October 2016, palbociclib was granted approval to be used in combination with fulvestrant. This was following the success of the phase III PALOMA-3 trial, conducted in patients with advanced/metastatic HR+/HER- breast cancer that had relapsed or progressed during endocrine therapy. The PALOMA-3 trial demonstrated a median progression-free survival of 9.2 months in those receiving fulvestrant in combination with palbociclib vs. 3.8 months in patients receiving fulvestrant with placebo.[8] Palbociclib was approved by the EMA in November 2016 to be used in combination with an aromatase inhibitor or with fulvestrant in patients who had previously received endocrine therapy.[9]

As a result of the recent approval of palbociclib, there is scarce information regarding how and when palbociclib combination is prescribed in routine clinical practice, palbociclib treatment patterns, the outcomes associated with palbociclib use and the characteristics of palbociclib responders. Therefore, real world data on the characteristics, treatment patterns and clinical outcomes among patients receiving palbociclib combinations to treat HR+/HER- ABC/MBC will provide valuable insight to help inform treatment decisions.

2.1. Study Design

This study will be conducted as a retrospective physician based medical record review of patients who have received palbociclib combination in line with locally approved indications. In some countries data may be collected from patients receiving palbociclib combinations before the local reimbursement date, however patients must still be receiving palbociclib combinations in line with the approved indication. The study will comprise of a medical record review conducted in the **US, Canada, Argentina, Italy, UK, France, Germany, Belgium, Switzerland, Spain, Netherlands, Portugal and Japan**. The study design is outlined in Figure 1. The study has been previously conducted in the US, Argentina, Canada with an additional 'interim' record review conducted in Germany (with a minimum of 3 month follow up) whereby no long-term clinical outcomes were collected. The core German study is now completed with clinical outcome data.

Data collection will be online via electronic data capture using electronic case report form (eCRF). Eligible physicians will be invited to complete an eCRF for up to 14 patients that meet the study criteria. Each eCRF will take around 25 minutes to complete. Patient eligibility will be confirmed by treating physicians. In order to allow for a sufficiently long observational window, treating physicians will be asked to go back to a specific point in time, the index date, and sequentially select the medical records of the next 'n' patients who meet the inclusion criteria. The 'index date' will be defined as 60 days after the physician first prescribed palbociclib + partner therapy following the availability of specific indication in the market (eg, If palbociclib + letrozole was available Feb 1, 2015 in the US and the physician initiated a patient on palbociclib+ letrozole the next day, the index date will be April 2, 2015). The index date will differ for the specific indications/combination partners if approved on different dates.

Study materials (ie, the CRF) will be subject to pilot testing with physicians followed by interviews to discuss the length, feasibility, ease of understanding and use, and the relevance to the objectives.

2.1.1. Core Medical Record Review

The core medical record review will capture data from approximately 2874 patients on demographics, clinical characteristics, disease history, treatment history, palbociclib dosing, clinical outcomes and post-palbociclib combination therapy treatment data. The study will be descriptive in nature therefore no control or comparator groups will be included.

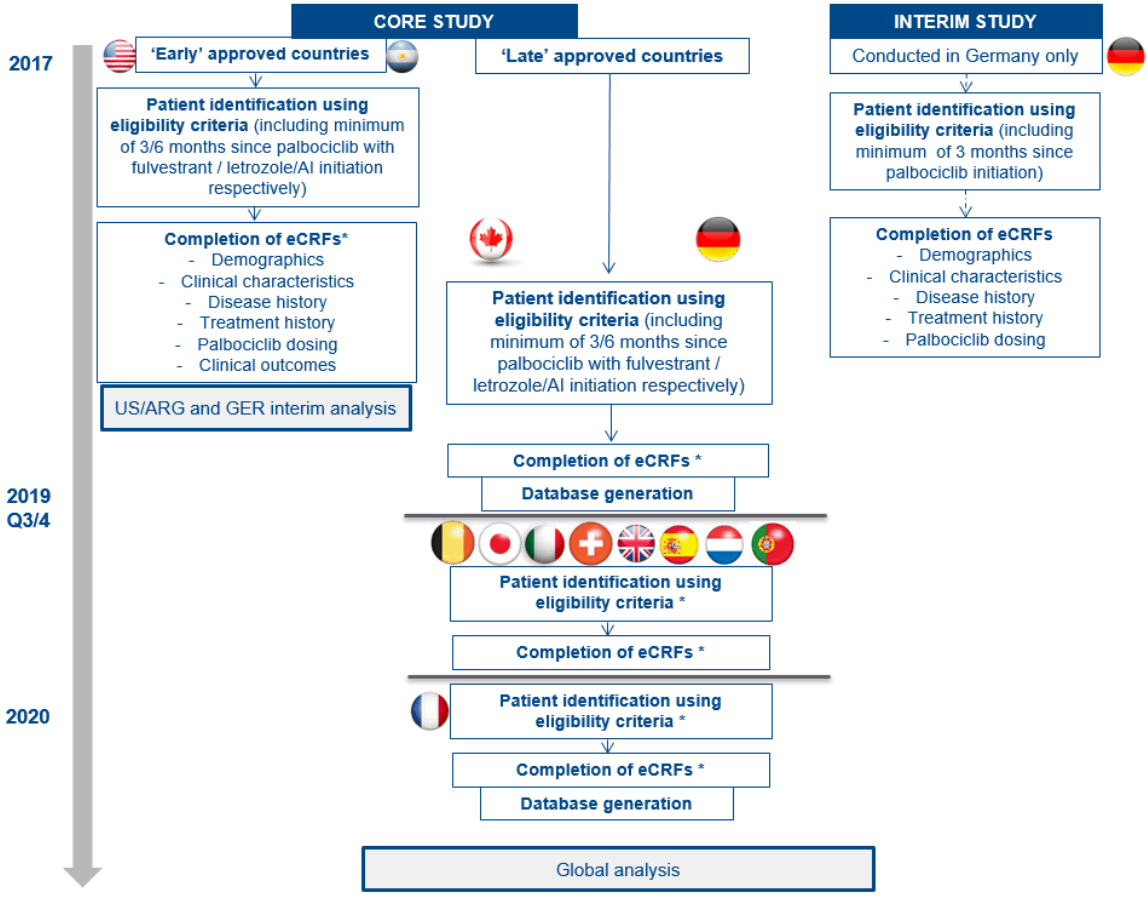
The core medical record review has already been conducted in the US and Argentina in 2017 and for Germany (core) and Canada in Q3 2019. Palbociclib has only been recently approved for use in the EU, therefore, additional European data collection in Belgium, Italy, Spain, Netherlands, Portugal and the UK for the core medical record review will commence in Q4 2019. Similarly, data collection for Switzerland and Japan will commence Q4 2019, depending on the date of approval of palbociclib in each individual country. Data collection in France is due to commence later in 2020 to allow sufficient follow-up period following the palbociclib early access program (index date for patient eligibility in France post-01 Jan 2018). In some countries data may be collected from patients receiving palbociclib

combinations before the local reimbursement date, however patients must still be receiving palbociclib combinations in line with the approved indication.

2.1.2. German Interim Medical Record Review

A German interim medical record review was conducted in Germany in October 2017. This interim medical record review allowed for the collection of a number of baseline characteristics data. This study had the same methodology as the core study and an almost identical eCRF, capturing demographics, clinical characteristics, disease history, treatment history and palbociclib dosing for patients receiving palbociclib combination treatment in line with the approved indications. However, appropriate sections from the CRF relating to clinical outcomes associated with palbociclib combination were omitted from the interim eCRF (ie, ORR, CRF, progression free rates and survival rates). A further full core medical review will be conducted in Germany in April 2019 in line with the methodology outline in Section 2.1.1.

Figure 1. Study Design Depicting the Proposed Time Frame for the Medical Record Reviews



3. STUDY POPULATION

Upon study completion, data will be collected from 13 countries with approximately 15-60 physicians (oncologists/gynecologists)[1] recruited per country. Each physician will complete between 3-14 eCRFs (country and sample size dependent). Data will be collected retrospectively at a single point in time from patient medical records.

Initial screening questions/recruitment criteria will ensure the relevant physicians are selected. In addition during physician recruitment a representative geographical split and private/public practice split will be sought where possible to ensure a representative sample.

To be eligible, physicians must have treated or be treating two or more HR+/HER2- ABC/MBC patients who meet the eligibility criteria for the study. This will ensure that recruited physicians will be able to complete the minimum number of eCRFs required to participate in the study. Once physicians have been recruited, they must go back to a specific index date, defined in Section 2.1, and select the next "n" number of eligible patient records from patients who have been treated with a palbociclib combination. The consecutive approach to recruitment will be stressed to each participating physician to limit selection bias. Physicians will confirm patient eligibility.

Patient records must meet the following criteria to be eligible for the medical record reviews. They must be female, over 18 years of age and they must have been diagnosed with HR+/HER2- ABC/MBC. Patients must have received palbociclib combination in line with country/regional approved indications. For the core medical record review, palbociclib and letrozole/aromatase inhibitor combination therapy (depending on labeled indication per country) must have been initiated a minimum of 6 months prior to date of medical record review, and palbociclib and fulvestrant must have been initiated a minimum of 3 months prior to date of medical record review. This will permit the capture of meaningful clinical outcomes data. For the German interim medical record review, palbociclib was required to have been initiated a minimum of 3 months prior to data collection regardless of partner therapy.

The eligibility criteria for the medical record reviews are as follows:

Physician inclusion criteria

- Oncologist or gynecologist;
- Responsible for treating ≥2-6 (depending on country) ABC/MBC patients who meet the eligibility criteria;
- Agrees to participate in the study and complete the CRFs.

[1] Breast surgeons/general surgeons/gastro-surgeons may also be included as relevant treaters in Japan.

Patient inclusion criteria

- ≥18 years old;
- HR+/HER- breast cancer diagnosis with confirmed metastatic or advanced disease;
- Received palbociclib plus letrozole/aromatase inhibitor or palbociclib plus fulvestrant in line with the licenced indication(s);
- No prior or current enrolment in an interventional clinical trial for ABC/MBC;
- Minimum of three months of follow up data since palbociclib with fulvestrant initiation, or minimum of six months of follow up data since palbociclib with letrozole/aromatase inhibitor initiation (core medical record review);
- Minimum of three months of follow up data since palbociclib initiation (German interim medical record review only);
- Inoperable or recurrent breast cancer (Japan only).

In order to ensure that sufficient data is captured for each indication, indication soft quotas will be enforced. This will be determined on a country by country basis.

3.1. Study Objectives

Primary Objectives

1. To describe the demographic and clinical characteristics of patients who have received palbociclib combination treatments in line with locally approved indications.
2. To summarize adjuvant therapies received for the treatment of early or locally advanced breast cancer (Stages 0-IIIa).
3. To describe treatments received in the advanced/metastatic setting, before and after palbociclib combination use.
4. To describe dosing and dose changes, interruptions, delays, and discontinuations associated with palbociclib use in clinical practice.
5. To describe supportive therapies received by patients while receiving palbociclib combination treatments.
6. To determine clinical outcomes including:
    - Proportion of patients who are progression free at quarterly intervals (eg, 3, 6, 12, 18 months);
    - CCI [redacted]

- Objective response rate (ORR);
- Clinical benefit rate (CBR) – if feasible;
- Proportion of patients alive 1 and 2 year post palbociclib combination initiation (depending on availability of follow-up data);
- Best response (complete response, partial response, stable disease, disease progression);
- Time to death.

CCI [redacted]

[redacted]

4. ANALYSIS SETS/POPULATIONS

4.1. Full Analysis Set

Only patients who meet the completed inclusion and exclusion criteria described in Section 3.0 and for whom a core medical record review was conducted will be included in the full analysis set (FAS).

4.2. Interim Analysis Set

Only patients who meet the completed inclusion and exclusion criteria described in section 3.0 and for whom an interim medical record review was conducted (Germany only) were included in the interim analysis set (IAS). The interim analysis did not derive the clinical outcomes variables outlined in Section 5.5 (including CCI [redacted], progression free survival and clinical benefit rate).

4.3. Stratifications and Subgroups

Stratifications will be conducted to assess differences in outcomes by line of therapy, demographics, treatments clinical characteristics or 'responders' and 'non-responders' to treatment, however these will be only descriptive in nature. Responders and non-responders will be defined according to the best recorded response to palbociclib treatment.

For wave 1 countries already conducted (US, Argentina and Germany (interim)) additional stratifications included:

- Disease stage at initial diagnosis (ABC vs mBC);
- Combination partner (AI/letrozole vs fulvestrant);
- Treatment sequence (line of therapy: AI 1st line, fulvestrant 1st – 3rd line);

- Age (up to 65, greater than 65 years);
- Metastases, visceral vs. non-visceral disease.

Additional ad hoc stratifications were completed for the US 2017 analysis, as below:

- Age classification by indication (up to 65, >65);
- ECOG at palbociclib initiation for all patients and by indication;
- Palbociclib starting dose 125 mg vs not 125 mg for all patients and by indication;
- Disease progression with initial control vs without initial control;
- Visceral status (mBC only) by indication;
- Alternative classification of metastases by indication (bone metastases only, visceral disease only, bone and visceral, neither (other)).

For analysis of the wave 2 countries (Germany (core), Canada, UK, Italy, France, Belgium, Switzerland, Japan, Spain, Netherlands and Portugal), the following stratifications are requested (dependent of sample size):

- Combination partner (AI/letrozole vs fulvestrant);
- Treatment sequence (line of therapy: AI 1st line, fulvestrant 1st – 3rd line);
- Age <50, ≥50 years old;
- Age <65, ≥65 years old;
- Age <75, ≥75 years old;
- Starting dose 125 mg vs. non 125 mg.

For clinical outcomes variables only:

- Prior chemotherapy by palbociclib indication (AI/letrozole vs fulvestrant);
- Menopause status (peri- or post- menopausal);
- Disease stage at initial diagnosis (ABC vs mBC).

For treatment patterns variables only, the following stratifications may include:

- Academic vs. community institution.

5. VARIABLES

5.1. Physician Characteristics

To be obtained directly from the physician at enrolment:

- Specialty (eg, Surgical Oncologist, Medical or Clinical Oncologist);
- Year of qualification;
- Practice setting (vary according to country);
- Geographic location (vary according to country);
- Number of patients treated receiving palbociclib in line with approved indications;
- Date of initiating first patient on palbociclib (split by indication).

5.2. Patient Characteristics

To be abstracted directly from the medical records:

- Dead/alive at date of record abstraction;
- Time since death (if applicable);
- Ethnicity;
- Age at palbociclib initiation;
- Menopause status;
- Type of menopause (natural or induced);
- Insurance plan (vary according to country eg, Medicare, Medicaid, Commercial, None).

To be Derived:

- Age at initial breast cancer diagnosis;
- Age at ABC/mBC diagnosis.

5.3. Clinical Characteristics

To be abstracted directly from the medical records:

- Date of initial breast cancer diagnosis;
- Stage at initial breast cancer diagnosis;

- Date of ABC/mBC diagnosis;
- Stage of ABC/mBC diagnosis (eg, locoregionally advanced or metastatic);
- Site of metastases at metastatic diagnosis;
- Degree of involvement of metastases (eg, single vs. multiple lesions);
- Patient's performance status at initiation of palbociclib, as scored using the Eastern Cooperative Oncology Group scale or Karnofsky scale;
- Patient's current performance status, if applicable;
- Family history of breast cancer;
- Biomarker status (BRCA, Androgen receptor, ESR1 mutation);
- Comorbidities diagnosed in the 12 months prior to palbociclib initiation.

To be Derived:

- Time from initial breast cancer diagnosis to ABC/mBC diagnosis.

5.4. Prior Treatment for Early Breast Cancer

To be abstracted directly from the medical records:

- Category of treatment received (eg, surgery, radiotherapy, neoadjuvant treatment, adjuvant chemotherapy, adjuvant endocrine therapy);
- Adjuvant endocrine therapy start and end dates;
- Reason for stopping adjuvant endocrine therapy (eg, regimen complete, disease recurrence, patient preference, side effects/toxicity, other).

To be Derived:

- Duration of adjuvant endocrine therapy;
- Disease Free Interval, defined as time from regimen completion of adjuvant therapy to diagnosis of ABC/mBC.

5.5. Treatment Patterns for Advanced or Metastatic Breast Cancer

To be abstracted directly from the medical records:

- Number of lines of therapy received for ABC/mBC at the time of medical record abstraction;

- Treatment(s) received in each line of therapy;
- Start and stop dates of each treatment within each line of therapy;
- Receipt of palbociclib therapies, by combination partner;
- Reason for regimen end (eg, disease progression, disease progression following initial control/response, Disease progression without initial control/response, Treatment cost, pill burden/compliance, side effects/toxicity, patient request, other);
- Date of disease progression for each regimen (if applicable).

To be derived:

- Time from initial breast cancer diagnosis to palbociclib initiation;
- Time from advanced/metastatic diagnosis to palbociclib initiation;
- Duration of each line of therapy;
- Duration of ongoing and discontinued palbociclib treatment;
- Distribution of therapies received post palbociclib discontinuation;
- Line of therapy that palbociclib is received (T);
- Treatments received in the line of therapy prior to palbociclib (T-1);
- Treatments received in the line of therapy post palbociclib (T+1).

Palbociclib dosing characteristics

To be abstracted directly from the medical records:

- Palbociclib starting dose;
- Reasons for starting at a dose lower than 125 mg/day;
- Number of palbociclib dose changes;
- Details of each dose change (eg, dose increase, dose decrease, dose interruption, cycle delay);
- Date of dose change;
- Reason for dose change (eg, side effects/toxicity, lack of response);
- Status of combination partner therapy at dose change (eg, if continued or stopped).

To be derived

- Time from palbociclib initiation to first dose change;
- Duration of dose interruption;
- Duration of cycle delays.

Supportive therapies received during palbociclib treatment

To be abstracted directly from the medical records:

- Supportive therapies received during palbociclib treatment.

Clinical Outcomes

To be abstracted directly from the medical records:

- Initial response recorded;
- Time from palbociclib initiation to initial response;
- Frequency with which response to palbociclib was assessed;
- Proportion with complete response;
- Proportion with complete response defined by radiological evidence;
- Proportion with partial response defined by radiological evidence;
- Time from palbociclib initiation to complete response;
- Proportion with partial response;
- Time from palbociclib initiation to partial response.

To be derived

- Objective response rate defined as the proportion of patients achieving complete or partial response on palbociclib;
- Clinical benefit rate defined as the proportion of patients achieving complete or partial response, or stable disease >=24 weeks on palbociclib. Stable disease will be defined as no evidence of complete or partial response, and no progression on palbociclib therapy for 24 weeks or greater;
- Proportion with stable disease >=24 weeks on palbociclib;

[redacted]

- Progression free survival (if applicable) defined as the time from the start of palbociclib to the first subsequent progression or death;
- Time to death, defined as the time from the start of palbociclib to death;

[redacted]

- Progression free at 3, 6, 12, 18, 24 months defined as the proportion of patients who have no documented progression at defined time points;
- Survival at 12, 18, 24 months defined as the proportion of patients who are not deceased at defined time points.

5.6. Safety Endpoints

No safety endpoints are being collected for this study.

6. HANDLING OF MISSING VALUES

Subjects with missing values for a particular endpoint will not contribute to the analysis of that endpoint. Missing data will not be imputed.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1. Data Management

All data and project files will be stored on Adelphi Real World's network which has fail-safe/backup and archive protection.

Stata/SE 14.2 (or higher) on the Windows platform will be used for all analyses.

All statistical tasks are retained in written code (i.e. no menu commands will be utilised), and an overall structure to the code is planned to meet the following requirements:

- All data manipulation steps/analyses performed must be transparent and fully reproducible;
- Analyses should be programmed in sections for ease of interpretation;
- Where possible, programming code should not be hard coded to specific folders/directories;
- Code should be easy to understand to a competent statistician familiar with the programme used.

The starting point for the code will be opening the extracted database export and then a run of any variable cleaning/creation/manipulation commands before analysis steps are taken.

Headings and explanatory comments will be included with the programming code to make clear the purpose of each section. The comments will make it possible for another statistician, skilled in the package used, to fully understand both the programming code and the justifications behind it.

Saving programming code allows for replicability of the analyses at a later date.

7.2. Statistical Methods

Based on the descriptive nature of the study, all study measures will be summarized descriptively through the tabular and graphical display of mean values, standard deviations, and ranges for continuous/numeric variables of interest. For categorical variables, frequency distributions (n, %) will be displayed. Missing and unknown categories for each variable also will be presented. Percentages will be calculated excluding missing values. All endpoints will be calculated for the overall population and by the stratification variables listed in Section 4.3 (sample sizes permitting).

To show how one treatment line moves to the next, adjacent treatment combinations will be cross-tabulated (showing frequencies), eg, treatments received in the line prior to palbociclib (T-1) will be cross-tabulated with treatment line at which palbociclib was received (T), T will be crossed by treatments received at the line following palbociclib (T+1) and T+1 will be crossed by treatments received at the second line following palbociclib (T+2.)

For each of the 4 lines, whether or not that line is still ongoing or not will be described (this excludes T-1 as that line cannot be ongoing). For those not still ongoing (ie, the line has ended), the reason for ending will be described.

Time-to-event outcomes (ie, time to treatment start, time to dose reduction, treatment duration, CCI [redacted], PFS, death) will be described using the Kaplan-Meier method. In addition to reporting median event times for these measures, time-dependent event rates (eg, proportion of patients without event at various time points from a starting point of interest) will also be reported based on lifetables derived from the Kaplan-Meier analyses. All analyses will be conducted using Stata (version 14.2 or higher) statistical software and IBM SPSS Survey Reporter.

The outlined statistical methods anticipate that the selected sample is randomly drawn from normally distributed populations. However, this study will employ a convenience sample; thus, results may not be generalizable to the entire universe of patients receiving palbociclib.

7.2.1. Definitions of Clinical Outcomes

Objective Response Rate (ORR)

Objective response rate defined as the proportion of patients achieving complete or partial response on palbociclib combination therapy.

Clinical Benefit Rate (CBR)

Clinical benefit rate is defined as the proportion of patients achieving complete or partial response, or stable disease >=24 weeks on palbociclib combination therapy. Stable disease will be defined as no evidence of complete or partial response, and no progression on palbociclib therapy for 24 weeks or greater.

CCI [redacted]

Progression Free Survival (PFS)

Progression Free Survival is defined as the time from palbociclib combination treatment initiation until the earliest of (1) clinician-documented progression while on palbociclib (2) death, (3) start of a new therapy line after final palbociclib dose if the reason for discontinuation of palbociclib was disease progression, or (4) last available follow-up. Patients who did not experience a progression event (items 1, 2 and 3) will be censored at date of last available follow-up. PFS (in months) will be calculated as (first event date - palbociclib initiation date + 1)/30.4.

PFS will be analysed using a Kaplan-Meier (KM) survivor function. A table will show the survivor rate at 3 month intervals and will also show the 3 month incremental survivor rate, ie, the survivor rate from the start of that 3 month interval rather than from time zero. The median survival (if the median is reached) and a KM chart will also be shown. Time zero will be taken at the point of palbociclib initiation.

CCI [redacted]

8. LIST OF TABLES AND TABLE SHELLS

A list of tables is presented below. Full table shells can be found in Appendix 1

Table 1. Characteristics of Participating Physicians

Table 2. Demographic Characteristics of Study Population

Table 3. Clinical Characteristics of Study Population

Table 4. Characteristics of Initial Breast Cancer Diagnosis and Early Stage Disease Treatment

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Table 6. Time from Initial Breast Cancer and ABC/mBC Diagnosis to Initiation of Palbociclib

Table 7. Number of Lines of Therapy Received for ABC/mBC

Table 8. Patient and Treatment Characteristics for First Line ABC/mBC Therapy

Table 9. Patient and Treatment Characteristics for Second Line ABC/mBC Therapy

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Table 12. Patient and Treatment Characteristics for Palbociclib Treatment

Table 13. Treatment Regimens Prescribed Pre- and Post- Palbociclib Treatment

Table 14. Palbociclib Dose Changes

Table 15. Supportive Therapies Received During Palbociclib Treatment

Table 16. Recorded Response to Palbociclib Treatment

Table 17. Clinical Outcomes Associated with Palbociclib Treatment

9. REFERENCES

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Appendix 1. Table of Variables

Table 1. Demographics and Clinical Characteristics

Variable	Role	Data source(s)	Operational definition
Demographics			
Age when palbociclib was initiated	Primary objective 1	CRF B1	
Menopause natural or induced	Primary objective 1	CRF B2a	
Menopause induced surgically or LHRH	Primary objective 1	CRF B2b	
Ethnic origin	Primary objective 1	CRF B3	
Family history of breast cancer	Primary objective 1	CRF B4	
Biomarker result	Primary objective 1	CRF B5	Multiple responses – BRCA1, BRCA2, Androgen receptor, ESR1 mutation
Insurance type	Primary objective 1	CRF B8	
Concomitant conditions	Primary objective 1	CRF C1	Multiple responses allowed
Clinical characteristics			
ECOG at palbociclib initiation	Primary objective 1	CRF C2a	
ECOG (at time of data collection)	Primary objective 1	CRF C2a	
Karnofsky at palbociclib initiaion	Primary objective 1	CRF C2b	
Karnofsky (at time of data collection)	Primary objective 1	CRF C2b	
Vital status	Primary objective 1	CRF BQ6	
Stage at initial breast cancer diagnosis	Primary objective 1	CRF D2	
Time to advanced breast cancer diagnosis	Primary objective 1	CRF E1a, D1	

Variable	Role	Data source(s)	Operational definition
Stage at advance diagnosis	Primary objective 1	CRF E1b	Only too be derived if CRF D2 is Stage 0, I, II, or IIIa
Sites of metastases at advanced diagnosis	Primary objective 1	CRF E2	Multiple responses allowed
Burden of metastases at advanced diagnosis	Primary objective 1	CRF E2	

Table 2. Early Breast Cancer Treatment History

Variable	Role	Data source(s)	Operational definition
Adjuvant therapies received	Primary objective 2	CRF F1	Multiple responses allowed – class level
Duration of adjuvant endocrine therapy	Primary objective 2	CRF F2	
Reason for stopping adjuvant endocrine therapy	Primary objective 2	CRF F2	
Disease free interval	Primary objective 2	CRF F2 , E1a	Time from regimen completion of adjuvant therapy to diagnosis of ABC/mBC

Table 3. Advanced/metastatic Breast Cancer Treatment

Variable	Role	Data source(s)	Operational definition
Line that palbociclib is introduced	Primary objective 3	CRF G2	This line number will be used for the subsequent variables that are relative to palbociclib initiation, eg, if palbociclib is initiated at line 2 then prior will be at line 1 and post will be at line 3, etc.

Variable	Role	Data source(s)	Operational definition
Time to palbociclib initiation	Primary objective 3	CRF G2b	
Treatments received when palbociclib was initiated (T)		CRF G2a	Multiple responses allowed. Each treatment will be listed separately
Treatment combination at T	Primary objective 3	CRF G2a	Mutually exclusive treatment combinations
Is that line still ongoing?	Primary objective 3	CRF G2c	
If not, what was the reason for ending?	Primary objective 3	CRF G2d	
Treatments received in the line prior to palbociclib initiation (T-1)			Multiple responses allowed. Each treatment will be listed separately
Treatment combination at (T-1)	Primary objective 3	CRF G2a	Mutually exclusive treatment combinations
Reason for ending T-1	Primary objective 3	CRF G2d	
Treatments received in the line post palbociclib initiation (T+1)			Multiple responses allowed. Each treatment will be listed separately
Treatment combination at (T+1)	Primary objective 3	CRF G2a	Mutually exclusive treatment combinations
Is that line still ongoing?	Primary objective 3	CRF G2c	
If not, what was the reason for ending?	Primary objective 3	CRF G2d	
The 2nd set of treatments received in the line post palbociclib initiation (T+2)			Multiple responses allowed. Each treatment will be listed separately

Variable	Role	Data source(s)	Operational definition
The 2nd treatment combination at (T+2)	Primary objective 3	CRF G2a	Mutually exclusive treatment combinations
Is that line still ongoing?	Primary objective 3	CRF G2c	
If not, what was the reason for ending?	Primary objective 3	CRF G2d	
Number of treatment lines received	Primary objective 3	CRF G2a	
Duration of each line of therapy	Primary objective 3	CRF G2b/c	
Duration of ongoing palbociclib treatment	Primary objective 3	CRF G2b/c	
Duration of discontinued palbociclib treatment	Primary objective 3	CRF G2b/c	
Frequency that tumour response is assessed	Primary objective 6	CRF I1a	
Date of disease progression for each regimen (if applicable)	Primary objective 6	CRF G2e	

Table 4. Palbociclib Dosing Details

Variable	Role	Data source(s)	Operational definition
Initial dose	Primary objective 4	CRF H1	
Reasons for starting dose lower than 125 mg/day	Primary objective 4	CRF H1b	
Number of dose changes	Primary objective 4	CRF H2	
Number of dose changes	Primary objective 4	CRF H3	Including zeros, ie, no changes stated in CRF H2
Any dose reductions?	Primary objective 4	CRF H3b	
Any dose increases?	Primary objective 4	CRF H3b	

Variable	Role	Data source(s)	Operational definition
Any dose interruptions?	Primary objective 4	CRF H3b	
Dose resumed	Primary objective 4	CRF H3b	
Number of interruptions	Primary objective 4	CRF H3b	Including zeros, ie, no interruptions
Duration of interruptions	Primary objective 4	CRF H3a	
Any cycle delays?	Primary objective 4	CRF H3b	
Duration of cycle delays	Primary objective 4	CRF H3a	
Reasons for dose change	Primary objective 4	CRF H3c	Multiple responses allowed. Reduce to patient level, ie, if "lack of response" is ticked for any dose changes then "lack of response" is considered ticked
Status of combination partner therapy when dose is changed	Primary objective 4	CRF H3d	
Time from palbociclib initiation to first dose change	Primary objective 4	CRF H3a	

Table 5. Supportive Therapies Whilst Receiving Palbociclib

Variable	Role	Data source(s)	Operational definition
All supportive therapies received whilst receiving palbociclib	Primary objective 5	CRF H4	Multiple responses allowed

Table 6. Clinical Outcomes

Variable	Role	Data source(s)	Operational definition
CCI [redacted]	[redacted]	[redacted]	[redacted]
Progression free survival	Exploratory objective	CRF G2e	Defined as the time from the start of palbociclib to the first subsequent progression or death. The treatment grid in section G will be used to determine in which treatment line that this occurs.
Progression free at 6, 12, 18, 24 months of treatment	Primary objective 6	CRF G2e	Proportion of patients who have not displayed progression at defined time points.
Did the patient achieve complete response whilst receiving palbociclib?	Primary objective 6	TBC	
Time to complete response	Primary objective 6	TBC	
Did the patient achieve partial response whilst receiving palbociclib?	Primary objective 6	TBC	
Time to partial response	Primary objective 6	TBC	
Objective Response Rate	Primary objective 6	CRF I1d/I1e	Proportion of patients who achieve CR/PR at CRF I1d/Ile.

Variable	Role	Data source(s)	Operational definition
Time to Death	Primary objective 6	CRF B7	This will be the time from the start of palbociclib to death. This will only include patients for whom death has been recorded.
CCI [redacted]	[redacted]	[redacted]	[redacted]
Survival at 12, 18, 24 months	Primary objective 6	AQ2, BQ7	Proportion of patients who have not died at defined time points.