Non-Interventional Study Protocol
A5481155

Patient Characteristics, Treatment Patterns, and Clinical Outcomes in Patients Diagnosed with HR+/HER2- Advanced/Metastatic Breast Cancer Receiving Palbociclib + Aromatase Inhibitor (AI) Combination Therapy as First-Line Treatment

Statistical Analysis Plan
(SAP)

Amendment 1

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

Included the initiation of 2nd line of therapy as a censoring event in the definition of progression-free survival. This was inadvertently omitted from the SAP and was identified after an author review of the definition provided in the manuscript draft.

2 INTRODUCTION

Note: in this document, any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

This study is designed to examine real-world use of palbociclib and aromatase inhibitor combination therapy in both male and female patients with A/MBC as first-line treatment.

All patients initiating palbociclib + an AI from the Syapse Learning Health Network dataset who meet the inclusion and exclusion criteria and initiated palbociclib combination therapy between February 2015 and July 2019 will be evaluated. This study is designed to describe patient characteristics, treatment patterns, and clinical effectiveness outcomes in a cohort of patients diagnosed with HR+/HER2- A/MBC who were treated with palbociclib combination with AI in the US community oncology setting.

2.1 Study Design

This is an observational, retrospective cohort study. Eligible patients will be identified from the Syapse Learning Health Network database and medical chart review will be conducted by Syapse Certified Tumor Registrars (CTRs). All study data are secondary data and will have been collected retrospectively from existing clinical data originally collected as part of routine care. This single-arm descriptive analysis will describe the patient characteristics, clinical attributes and treatment patterns of A/MBC patients with HR+/HER2- disease, who were treated with palbociclib + AI as first-line therapy. Additionally, clinical effectiveness outcomes for these patients will be evaluated between Feb 2015 and July 2019.

Study population

The study will include adult patients 18 years or older, diagnosed with HR+/HER2- A/MBC who initiated palbociclib combination therapy with AI as the first-line therapy on or after 03 February 2015 up to and including 31 July 2019. Patients for this study will be identified from the Syapse Learning Health Network database.

Preliminary analysis identified up to 1,074 patients with evidence of key primary inclusion criteria: breast cancer diagnosis and palbociclib treatment. Three to four hundred patients are expected to fulfil complete study inclusion criteria. Given the inclusion criterion requiring a qualifying treatment identification period between 03 February 2015 through 31 July 2019, and assuming a data cutoff date of 01 February 2020, the minimum follow-up available is therefore 6 months.

Data source

Patients will be identified and data will come from the Syapse Learning Health Network database which includes both inpatient and outpatient clinical and molecular data captured through manual abstraction and interoperative data feeds from a number of health system source systems, including:

- *Electronic medical record (EMR), including inpatient, outpatient oncology, ambulatory, surgical, etc.*
- *Electronic data warehouse (EDW)*
- *Laboratory information system (LIS)*
- *Picture archiving and communication system (PACS)*
- *Hospital based cancer registries*
- *Computerized physician order entry (CPOE)*

    - *Additionally, Syapse augments health system data with the Surveillance, Epidemiology, and End Results (SEER) national cancer registry, other regional registries, the Social Security Death Index (SSDI), digitized obituary data. In order to capture complete and accurate vital status and dates of death, Syapse brings together data from multiple sources to create a composite view of patients' mortality (including EHR, hospital registry, manual abstraction, digital obituaries (such as tributes.com and legacy.com), Social Security Death Index, and SEER). Syapse is in the process of validating the completeness and accuracy of the Syapse mortality composite score versus the National Death Index (NDI), a centralized database of death records. Initial analysis shows that the combined Syapse Data Sources are very accurate. More detailed information forthcoming in the data management document.*

Treatment/cohort labels

Data from patients with only one treatment group labelled as palbociclib + AI are explored in this retrospective study.

2.2 Study Objectives

Primary Objectives:

1) *Among patients with HR+/HER2- A/MBC receiving palbociclib combination therapy with AI as first-line therapy:*
    a. *Describe demographic and clinical characteristics.*
        - *Demographic characteristics will include age, sex, race, insurance status, menopausal status, and region of residence at A/MBC diagnosis.*

- *Clinical characteristics will include variables such as, stage of initial diagnosis, histology, Eastern Cooperative Oncology Group (ECOG) performance status (where ECOG score unavailable, Karnofsky performance status will be converted to corresponding ECOG score) and comorbid disease burden utilizing the Charlson Comorbidity Index, HER2 and estrogen receptor (ER)/ progesterone receptor (PR) status, BRCA status, number and sites of distant metastasis at A/MBC diagnosis (visceral (defined as liver, lung, peritoneum, and pleural nodules), non-visceral, bone only); modalities of treatment received prior to A/MBC diagnosis (chemotherapy, hormone therapy, surgery, radiation therapy)* documentation of endocrine sensitivity and endocrine resistance if hormone therapy was received in the adjuvant setting, *time to metastasis (time between initial and metastatic diagnosis) and disease free interval (time between completion of adjuvant therapy and diagnosis of A/MBC).*

b. Describe treatment patterns.

- *Distribution of regimens from the diagnosis of A/MBC through the end of the record.*
- *Sequence of regimens across lines, through the end of the record of systemic therapy.*
- *Description of the dosing will include the starting dose, end dose, dose adjustment (dose increase and dose reduction), type of dose adjustment (dose modification, schedule changes, dose delay, or hold) discontinuation, reason* (including progression, end of planned therapy, insurance changes, schedule change, dose delay, hold, cost, patient refusal, toxicity), *and time to dose adjustment (discontinuation).*

2) Among patients receiving palbociclib + AI as first-line therapy, examine clinical effectiveness outcomes including:

a. Real-world progression-free survival (rwPFS) will be assessed for the first-line therapy.

b. *Real-world overall survival (rwOS) will be assessed from the start of the first-line therapy.*

c. *Real-world time to next therapy (rwTTNT) will be assessed from the start of the first-line therapy.*

d. *Real-world time to treatment discontinuation (rwTTD) will be assessed from the start of the first-line therapy.*

e. Real-world time to chemotherapy (rwTTC) will be assessed from the start of the first-line therapy.

f. *Real-world time to dose adjustment (rwTTDA) will be assessed from the start of the first-line therapy.*

3 HYPOTHESES AND DECISION RULES

Not Applicable

4 ANALYSIS SETS/POPULATIONS

Analysis population will be all patients identified from the Syapse Learning Health Network database who meet the following inclusion and exclusion criteria-

Inclusion criteria

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

1. *Female or male sex.*
2. *Diagnosis (confirmed by clinical review) of A/MBC, defined as breast cancer at stage IIIB, stage IIIC, stage IV or identified as having distant metastasis.*
3. *Age ≥ 18 years at A/MBC diagnosis.*
4. *Initiated palbociclib in combination with an AI as first-line therapy after A/MBC diagnosis on or after 03 February 2015 through 31 July 2019. Note that the date of the start of the inclusion period reflects the month of palbociclib US FDA approval.*
5. *Evidence of ER or PR positive disease, or absence of any indication of ER and PR negative disease closest to A/MBC diagnosis (ie patients are eligible without affirmative indication of ER/PR+ status as long as ER/PR- indication is not present).*
6. *Evidence of HER2 negative disease, or absence of any indication of HER2 positive disease closest to A/MBC diagnosis (ie patients are eligible without affirmative indication of HER2- status as long as HER2+ indication is not present).*

Exclusion criteria

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

1. Enrollment in an interventional clinical trial for A/MBC during the study observation period.

2. Evidence of prior treatment with any CDK4/6 inhibitor in the adjuvant setting (i.e. a CDK4/6 inhibitor is administered (start date) > 30 days prior to the A/MBC diagnosis date).

3. Evidence of another primary cancer within 3 years prior to the initial line containing palbociclib.

5 ENDPOINTS AND COVARIATES

Primary Endpoints-

1. To summarize the demographic and clinical characteristics.
   Demographic characteristics will include

- Year of initial, metastatic and AMBC diagnoses;
- age at initial diagnosis, A/MBC diagnosis, start of palbociclib treatment and death;
- sex;
- race;
- ethnicity
- insurance status;
- menopausal status;
- region of residence at A/MBC diagnosis.

Clinical characteristics will include

- stage of initial diagnosis;
- histology;
- Eastern Cooperative Oncology Group (ECOG) performance status (where ECOG score unavailable, Karnofsky performance status will be converted to corresponding ECOG score);
- prior surgery (and type);
- prior radiation therapy (and type);
- comorbid disease burden (see Section 9.2);
- Charlson comorbidity index
- Sites of metastasis – visceral (liver, lung, peritoneum and pleural nodules), non-visceral, bone only
- Number of metastatic sites
    - Number of lesions in the site
    - Disease burden in the liver, lungs, bone
- time to metastasis (time between initial and metastatic diagnoses)
- HER2 and estrogen receptor (ER)/ progesterone receptor (PR) status;
- BRCA status
- modalities of treatment received prior to A/MBC diagnosis (chemotherapy, hormone therapy, surgery, radiation therapy);
    - Documentation of endocrine sensitivity and endocrine resistance if hormone therapy received in adjuvant setting
- disease free interval (time between completion of adjuvant therapy and diagnosis of A/MBC).

2. To summarize treatment patterns.

   Treatment patterns will be evaluated by the review of

   - the distribution of regimens;
   - sequence of regimens across the lines;
   - description of dosing which will include the starting dose, end dose, dose adjustment (dose increase and dose reduction), type of dose adjustment (dose modification, schedule changes, dose delay or hold), discontinuation reason (including death, progression, end of planned therapy, insurance changes, schedule change, dose delay, hold, cost, patient refusal, toxicity), and time to dose adjustment

3. To summarize the effectiveness outcomes of treatment-
   a. Real-world progression-free survival (rwPFS) for the first-line therapy at time points 3, 6, 12, 18, 24, 30, and 36 months;
   b. Real-world overall survival (rwOS) from the start of the first-line therapy at time points 6, 12, 18, 24, 30, and 36 months.
   c. Real-world time to treatment discontinuation (rwTTD) from the start of the first-line therapy at time points 3, 6, 12, 18, 24, 30, and 36 months.
   d. Real-world time to next treatment (rwTTNT) from the start of the first-line therapy at time points 3, 6, 12, 18, 24, 30, and 36 months.
   e. Real-world time to chemotherapy (rwTTC) from the start of the first-line therapy at time points 3, 6, 12, 18, 24, 30, and 36 months.
   f. Real-world time to dose adjustment (rwTTDA) from the start of the first-line therapy at time points 3, 6, 12, 18, 24, 30, and 36 months.

5.1 Definitions/Derivations for Demographic, Clinical characteristics, treatment pattern and Efficacy/Effectiveness Endpoint(s)

- Age at initial diagnosis, A/MBC diagnosis, at start of palbociclib treatment and death. - They will be categorized into age categories: <50, 50-64, 65 –74, ≥75 years.
- Time to metastasis- It is defined as months between initial and metastasis diagnoses. It will be categorized into ≤12 months, 13-24 months, 25-36 months,>36 months and de novo metastatic.
- Disease Free Interval (DFI)- It is defined as months from the end of adjuvant therapy to the date of disease recurrence. It will be categorized into ≤12 months, 13-24 months, 25-36 months,>36 months and Unknown.
- Line of therapy- The line number (1; 2; 3; etc.) in the A/MBC setting will be assigned based on Syapse line of therapy algorithm.
- Regimen medication(s)- Systemic therapies included in line regimen defined by Syapse line of therapy algorithm.
- Time to first dose change- It is defined as days from palbo dose 1 start date to palbo dose 2 start date, if applicable.
- Number of dose changes- Number of dose reduction(s) and number of dose increases over the calendar time (quarter since February 2015) and over treatment cycle since palbo dose 1 start date.
- Real-world Overall Survival (rwOS)- It is defined as length of time from the start of palbociclib + AI treatment to the earliest of the following: date of death, date of last contact, or the end of study period
- Real-world progression free survival (rwPFS)- It is defined as length of time from the start of palbociclib + AI treatment to the earliest of the following: clinician-assessed progression event (sources include medical oncology consult/note, radiation oncology note and discharge summary), date of death, date of initiation

of the 2nd line for patients with >1 line of therapy, date of last contact, or end of study period.

- Real world time to treatment discontinuation (rwTTD)- It is defined as length of time from the start of palbociclib + AI treatment to the earliest of the following: date the patient discontinues first-line treatment, date of death, last known usage of first-line treatment, or end of study period.
- Real world time to next treatment (rwTTNT)- It is defined as length of time from the start of palbociclib + AI treatment to the earliest of the following: subsequent line of therapy initiation, date of death, date of last contact, or end of the study period.
- Real world time to chemotherapy (rwTTC)- It is defined as length of time from the start of palbociclib + AI treatment to the earliest of the following: the day before the start of subsequent chemotherapy for patients with evidence of chemotherapy, or date of death for any reason. Or, where censored, the latest of date of last contact, or end of the study period.
- Real world time to dose adjustment (rwTTDA)- It is defined as length of time from the start of palbociclib + AI treatment to the earliest of the following: date of first-line treatment dose adjustment, date of death, date of first-line treatment discontinuation, date of last contact or end of study period.

5.2 Safety Endpoints

Not Applicable.

5.3 Other endpoints

Not Applicable.

6 HANDLING OF MISSING VALUES

In general, data that are absent/not found will not be imputed but will be categorized and reported as not documented.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 Statistical methods

Descriptive analyses: For categorical variables (eg region, race, and stage at initial diagnosis), data will include the frequency (number of cases) and percentage (%) of total patients observed in each category; for continuous variables (eg age and time from initial breast cancer diagnosis to metastatic diagnosis), variables will be presented as the mean, standard deviation (SD), median, 25th and 75th percentiles and ranges (minimum and maximum) in some cases. The calculation of percentages will always include the missing category in the case of missing values. Continuous variables may be categorized into intervals, with the distribution of patients (N, %) provided.

Kaplan-Meier curves and landmark analyses will be performed to estimate rwPFS, rwOS, rwTTD, rwTTC, rwTTDA and rwTTNT. Specifically, landmark time points are; 3, 6, 12, 18, 24, 30, and 36 months for rwPFS and 6, 12, 18, 24, 30, and 36 months for rwOS. For rwTTD and rwTTNT, landmark time points are; 3, 6, 12, 18, 24, 30, and 36 months. Ninety-five percent confidence intervals on the median rwPFS, rwOS, rwTTD, rwTTNT, rwTTC and rwTTDA will be reported.

Cox proportional hazard models may include age categories, race, ECOG performance, menopausal status, stage at initial diagnosis, time from initial diagnosis to metastatic diagnosis, metastatic status (De novo, versus number of metastatic sites), number of disease sites (1, 2, ≥3), prior endocrine therapy, prior chemotherapy, prior surgery, prior radiation therapy, bone-only disease, presence of visceral disease, and presence of brain metastases as appropriate based on availabilities of the data and sample sizes. Potential interactions may be examined using survival trees for time to events.

All data analysis will be executed using statistical software R version 3.6.1 or later.

7.2 Statistical Analyses

Objective1:

a. To describe the demographic and clinical characteristics for patients diagnosed with HR+/HER2- A/MBC.
   The numbers of breast cancer patients in the Syapse database meeting the eligibility criteria will be presented in an attrition table.
   Demographic and clinical characteristics variables that will be reported include age, sex, race, insurance status, menopausal status, and region of residence at A/MBC diagnosis, stage of initial diagnosis, histology, Eastern Cooperative Oncology Group (ECOG) performance status (where ECOG score unavailable, Karnofsky performance status will be converted to corresponding ECOG score) and comorbid disease burden, HER2 and estrogen receptor (ER)/ progesterone receptor (PR) status, BRCA status, number and sites of distant metastasis at A/MBC diagnosis; modalities of treatment received prior to A/MBC diagnosis (chemotherapy, hormone therapy, surgery, radiation therapy), disease free interval (time between completion of adjuvant therapy and diagnosis of A/MBC) and follow-up time in the study. Descriptive analysis methods as detailed in Section 7.1 will be used for summarizing these parameters as appropriate.

b. To describe the treatment patterns for patients diagnosed with HR+/HER2- A/MBC.
   Treatment patterns generally include the record of all systemic anti-cancer therapies received from the index date through the end of the study period.

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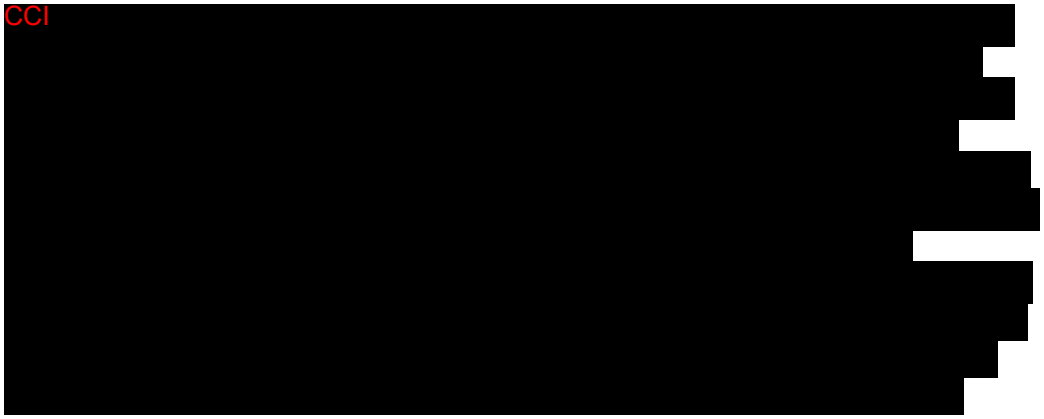

Description will include each of the following.

- Distribution of regimens, with the frequency and percentage of patients receiving each regimen within each line from the diagnosis of A/MBC through the end of the record.
- Description of sequence of regimens across lines, which shows how individual regimens were sequenced across lines through the end of the record of systemic therapy. Description will include the frequency and percentage of patients who received each specific sequence of treatments.
- Description of the dosing will include the starting dose, end dose, dose adjustment (dose increase and dose reduction), type of dose adjustment (dose modification, schedule changes, dose delay or hold), discontinuation reason (including death, progression, end of planned therapy, insurance changes, schedule change, dose delay, hold, cost, patient refusal, toxicity), and time to dose adjustment.

Objective2:
To examine clinical effectiveness for patients diagnosed with HR+/HER2- A/MBC.

Kaplan-Meier survival analysis is used to descriptively characterize time to event outcomes. In this study, following time to event outcomes will be analyzed-

- Time to Real-world overall survival (rwOS)

The time origin for analysis of rwOS is start of the first-line therapy, and the terminal event is death. For patients not known to be deceased at the time of analysis, rwOS will be censored at the earliest of the last date of last contact or the end of the study period.

- Time to Real-world progression-free survival (rwPFS)

The time origin for analysis of rwPFS is start of the first-line therapy. Patients without a clinician-assessed progression event or death will be censored at the earliest of the following events: date of initiation of the 2nd line for patients with >1 line of therapy, date of last contact, or end of study period.

- Real world time to treatment discontinuation (rwTTD)

The time origin for analysis of rwTTD is start of the first-line therapy. Patients without first-line treatment discontinuation and who did not die will be censored at the earliest of the following events: last known usage of first-line treatment, or end of study period.

- Real world time to next treatment (rwTTNT)

The time origin for analysis of rwTTNT is start of the first-line therapy. Patients without a subsequent line of therapy initiation and who did not die will be censored at the earliest of the following events: date of last contact, or end of the study period.

- Real world time to chemotherapy (rwTTC)

The time origin for analysis of rwTTC is start of the first-line therapy. Patients who did not receive subsequent chemotherapy and who did not die will be censored at the latest of the following events: date of last contact, or end of the study period.

- Real world time to dose adjustment (rwTTDA)

The time origin for analysis of rwTTDA is start of the first-line therapy. Patients without a first-line treatment dose adjustment will be censored at the earliest of the following events: first-line treatment discontinuation, date of death, date of last contact, or end of the study period.

One Kaplan-Meier analysis is generated for each time to event endpoint. Kaplan-Meier analysis will include number of patients with events and censored patients, median, 25th percentile and 75th percentile times to event (in months), 95% CI of the quartiles and ranges (minimum and maximum). Kaplan-Meier analysis will be repeated in the subgroup of patients who received a starting dose of 125mg.

One Cox regression analysis will be generated for each time to event endpoint, provided the sample size supports the analysis. Demographic and baseline clinical characteristics, some examples are detailed in section 7.1, will be included to the extent that sample size permits. Results from this analysis results will include parameter estimates, p-values, standard errors, hazard ratios and 95 % CIs of hazard ratios. The proportional hazards assumption will be assessed graphically with the inspection of Schoenfeld residuals and by including interaction terms between the variables and log(time).

7.2.1 Safety Analyses

Not Applicable.

7.2.2 Summary of Analyses of the Study Outcomes

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroup	Statistical Method	Factors/Covariates/Strata	Missing Data
Summary of Demographic Characteristics	All patients meeting inclusion and exclusion criteria	1a	None	Frequency and percentage of subjects	Not Applicable	Numbers reported
Summary of clinical characteristics and comorbidities	All patients meeting inclusion and exclusion criteria	1a	None	Frequency and percentage of subjects	Not Applicable	Numbers reported
Treatment pattern	All patients meeting inclusion and exclusion criteria	1b	None	Frequency and percentage of subjects	Not Applicable	Numbers reported
Treatment Regime	All patients meeting inclusion and exclusion criteria	1b	None	Frequency and percentage of subjects	Not Applicable	Numbers reported
Time to rwOS, months	All patients meeting inclusion and exclusion criteria	2	125mg starting dose	Kaplan-Meier and Cox proportional hazards model	Factors defined in section 7.1	Censored
Time to rwPFS, months	All patients meeting inclusion and exclusion criteria	2	- Metastasis status - 125mg starting dose	Kaplan-Meier and Cox proportional hazards model	Factors defined in section 7.1	Censored
Time to rwTTD, months	All patients meeting inclusion and exclusion criteria	2	125mg starting dose	Kaplan-Meier and Cox proportional hazards model	Factors defined in section 7.1	Censored

Time to rwTTNT, months	All patients meeting inclusion and exclusion criteria	2	125mg starting dose	Kaplan-Meier and Cox proportional hazards model	Factors defined in section 7.1	Censored
Time to rwTTC, months	All patients meeting inclusion and exclusion criteria	2	125mg starting dose	Kaplan-Meier and Cox proportional hazards model	Factors defined in section 7.1	Censored
Time to rwTTDA, months	All patients meeting inclusion and exclusion criteria	2	125mg starting dose	Kaplan-Meier and Cox proportional hazards model	Factors defined in section 7.1	Censored

8 LIST OF TABLES AND TABLE SHELLS

Data in the tables will be presented using the following formatting guidelines. Means will be presented to 1 decimal place greater than the precision of the collected variable. Standard deviations will be presented to 2 decimal places greater than the precision of the collected variable. Medians, 25th percentiles, 75th percentiles, minimums and maximums will be presented to the same precision as collected. Percentages will be presented to 1 decimal place. P-values will be displayed to 4 decimal places.

8.1 Objective 1: Demographic Characteristics, Clinical Characteristics and Treatment Patterns

8.1.1 Demographic Data

Demographic Characteristics

Table 15.1.1. Patient Attrition

Criterion	Description	N Included	N Excluded
XXXXXXXXXX	XXXXXXXXXX	xxx	xxx
XXXXXXXXXX	XXXXXXXXXX	xxx	xxx
XXXXXXXXXX	XXXXXXXXXX	xxx	xxx
XXXXXXXXXX	XXXXXXXXXX	xxx	xxx
XXXXXXXXXX	XXXXXXXXXX	xxx	xxx
XXXXXXXXXX	XXXXXXXXXX	xxx	xxx

Table 15.1.2. Baseline Demographic Characteristics at Initial HR+/HER2- A/MBC Diagnosis

Variable/Statistic	palbociclib + AI (n=xxx)
Year of initial diagnosis	
n	xx
Median (Q1, Q3)	xxxx (xxxx, xxxx)
Min, Max	xxxx, xxxx
Year of metastatic diagnosis	
n	xx
Median (Q1, Q3)	xxxx (xxxx, xxxx)
Min, Max	xxxx, xxxx
Year of AMBC diagnosis	
n	xx
Median (Q1, Q3)	xxxx (xxxx, xxxx)
Min, Max	xxxx, xxxx
Age (years) at initial diagnosis	
n	xx
Mean (SD)	x.x (x.xx)
Median (Q1, Q3)	x.x (x.x, x.x)
Min, Max	x.x, x.x
Age category (years) at initial diagnosis, n (%)	
<50	n (x.x%)
50-64	n (x.x%)
65-74	n (x.x%)
≥75	n (x.x%)
Age (years) at A/MBC diagnosis	
n	xx
Mean (SD)	x.x (x.xx)
Median (Q1, Q3)	x.x (x.x, x.x)
Min, Max	x.x, x.x

Table 15.1.2. Baseline Demographic Characteristics at Initial HR+/HER2- A/MBC Diagnosis

Variable/Statistic	palbociclib + AI (n=xxx)
Age category (years) at A/MBC diagnosis, n (%)	
<50	n (x.x%)
50-64	n (x.x%)
65-74	n (x.x%)
≥75	n (x.x%)
Age (years) at start of palbociclib treatment	
n	xx
Mean (SD)	x.x (x.xx)
Median (Q1, Q3)	x.x (x.x, x.x)
Min, Max	x.x, x.x
Age category (years) at start of palbociclib treatment, n (%)	
<50	n (x.x%)
50-64	n (x.x%)
65-74	n (x.x%)
≥75	n (x.x%)
Age category (years) at death, n (%)	
<50	n (x.x%)
50-64	n (x.x%)
65-74	n (x.x%)
≥75	n (x.x%)
Alive	n (x.x%)
Sex, n (%)	
Male	n (x.x%)
Female	n (x.x%)
Transsexual	n (x.x%)
Other	n (x.x%)
Not Provided	n (x.x%)
Race, n (%)	
American Indian/Alaska Native	n (x.x%)
Asian	n (x.x%)
Black/African American/Native Hawaiian/Pacific Islander	n (x.x%)
White	n (x.x%)
Not Provided	n (x.x%)
Other	n (x.x%)
Ethnicity, n (%)	
Non-Hispanic/Non-Latino	n (x.x%)
Hispanic/Latino	n (x.x%)
Unknown	n (x.x%)
Insurance Category, n (%)	
Medicare/Medicaid	n (x.x%)
Commercial	n (x.x%)
Commercial and Medicare/Medicaid	n (x.x%)
None	n (x.x%)
Not Provided	n (x.x%)
Menopausal Status, n (%)	
Premenopausal	n (x.x%)
Postmenopausal	n (x.x%)

Table 15.1.2. Baseline Demographic Characteristics at Initial HR+/HER2- A/MBC Diagnosis

Variable/Statistic	palbociclib + AI (n=xxx)
Perimenopausal	n (x.x%)
Unknown	n (x.x%)
Not applicable	n (x.x%)
Region of Residence at A/MBC diagnosis, n (%)	
Northeast	n (x.x%)
Midwest	n (x.x%)
South	n (x.x%)
West	n (x.x%)

Clinical Characteristics and Comorbidities

Table 15.1.3. Clinical Characteristics and Comorbidities

Variable/Statistic	palbociclib + AI (n=xxx)
Stage at Initial Breast Cancer Diagnosis, n (%)	
Stage 0	n (x.x%)
Stage I	n (x.x%)
Stage IA	n (x.x%)
Stage IB	n (x.x%)
Stage II	n (x.x%)
Stage IIA	n (x.x%)
Stage IIB	n (x.x%)
Stage III	n (x.x%)
Stage IIIA	n (x.x%)
Stage IIIB	n (x.x%)
Stage IIIC	n (x.x%)
Stage IV	n (x.x%)
Unable to stage	n (x.x%)
Not found	n (x.x%)
Not Applicable	n (x.x%)
Histology, n (%)	
Adenoid cystic	n (x.x%)
Cribriform	n (x.x%)
Ductal	n (x.x%)
Inflammatory	n (x.x%)
Intraductal	n (x.x%)
Lobular	n (x.x%)
Medullary with lymphoid stroma	n (x.x%)
Medullary	n (x.x%)
NOS	n (x.x%)
Mucinous	n (x.x%)
Paget's disease and infiltrating	n (x.x%)
Paget's disease and intraductal	n (x.x%)
Papillary	n (x.x%)
Secretory	n (x.x%)
Squamous cell	n (x.x%)
Tubular	n (x.x%)
Performance Status at A/MBC diagnosis (ECOG Score), n (%)	
Sub-total	n (x.x%)
0	n (x.x%)
1	n (x.x%)
2	n (x.x%)
3	n (x.x%)
4	n (x.x%)
Undocumented	n (x.x%)
Total comorbidities, n (%)	
0	n (x.x%)
1	n (x.x%)
2	n (x.x%)
≥3	n (x.x%)
Charlson Comorbidity Index (CCI), n (%)	
0	n (x.x%)
1	n (x.x%)
2	n (x.x%)

Table 15.1.3. Clinical Characteristics and Comorbidities

Variable/Statistic	palbociclib + AI (n=xxx)
3	n (x.x%)
≥4	n (x.x%)
Time to Metastasis, n (%)	
≤12 months	n (x.x%)
13-24 months	n (x.x%)
25-36 months	n (x.x%)
>36 months	n (x.x%)
De novo metastatic	n (x.x%)
Disease free Interval, n (%)	
≤12 months	n (x.x%)
13-24 months	n (x.x%)
25-36 months	n (x.x%)
>36 months	n (x.x%)
De novo metastatic	n (x.x%)
Disease Free Interval (months)	
n	xx
Mean (SD)	x.x (x.xx)
Median (Q1, Q3)	x.x (x.x, x.x)
Min, Max	x.x, x.x
Metastatic Group, n (%)	
De novo	n (x.x%)
Recurrent	n (x.x%)

Table 15.1.4 Comorbidities Occurring in at Least 5% of Patients

Variable, n (%)	palbociclib + AI (n=xxx)
XXX	n (x.x%)
XXX	n (x.x%)
XXX	n (x.x%)
XXX	n (x.x%)

Comorbidities presented in descending order of frequency

Table 15.1.5. Summary of Sites of distant metastasis and disease burden at A/MBC diagnosis

Variable, n (%)	palbociclib + AI (n=xxx)
Number of distant metastatic sites	
1	n (x.x%)
2	n (x.x%)
≥3	n (x.x%)
Sites of distant metastasis: bone only	
Yes	n (x.x%)
No	n (x.x%)
Sites of distant metastasis: visceral	
Yes	n (x.x%)
No	n (x.x%)
Disease Burden: Metastatic Sites in Liver	
Multiple lesions	n (x.x%)
No metastasis at site	n (x.x%)
Single lesion	n (x.x%)
Unknown number of lesions	n (x.x%)
Disease Burden: Metastatic Sites in Lung	
Bilateral lungs	n (x.x%)
No metastasis at site	n (x.x%)
Single lung	n (x.x%)
Unknown single bilateral status	n (x.x%)
Disease Burden: Metastatic Sites in Bone	
Multiple sites	n (x.x%)
No metastasis at site	n (x.x%)
Single site	n (x.x%)
Unknown number of sites	n (x.x%)

Table 15.16. Sites of distant metastasis at A/MBC diagnosis

Variable, n (%)	palbociclib + AI (n=xxx)
Bone (Bone only or in addition to other sites)	n (x.x%)
Bone only	n (x.x%)
Chest wall	n (x.x%)
Contralateral breast	n (x.x%)
Distant Lymph node(s)	n (x.x%)
Visceral Sites	n (x.x%)
Liver	n (x.x%)
Lung	n (x.x%)
Peritoneum	n (x.x%)
Pleural nodules	n (x.x%)
Malignant pleural effusion	n (x.x%)
Skin	n (x.x%)
Brain*	n (x.x%)
Ovary	n (x.x%)
Other: Specify	n (x.x%)
Adrenal	n (x.x%)
Bone marrow	n (x.x%)
Colon	n (x.x%)
Fallopian tubes	n (x.x%)
Omentum	n (x.x%)
Parotid gland	n (x.x%)
Soft tissue	n (x.x%)
Stomach	n (x.x%)

*Includes both brain and spinal metastasis

Table 15.1.7. Systemic Therapy, Endocrine Therapy and Sensitivity in the Adjuvant Setting

Variable, n (%)	palbociclib + AI (n=xxx)
Adjuvant Systemic Therapy	
Yes	n (x.x%)
No	n (x.x%)
Endocrine Therapy: Yes	n (x.x%)
Endocrine Sensitivity: Yes	n (x.x%)
Endocrine Sensitivity: No	n (x.x%)
Endocrine Therapy: No	n (x.x%)

Table 15.1.8. Endocrine Resistance

Variable, n (%)	palbociclib + AI (n=xxx)
Primary Endocrine Resistance	
Yes	n (x.x%)
No	n (x.x%)
Secondary Endocrine Resistance	
Yes	n (x.x%)
No	n (x.x%)

Table 15.1.9. Follow-up Times in Months

Variable	palbociclib + AI (n=xxx)
Minimum, Maximum	xx.x, xx.x
25th percentile	xx.x
Median	xx.x
75th percentile	xx.x

Biomarkers

Table 15.1.10. HER2, ER and PR Status

Variable, n (%)	palbociclib + AI (n=xxx)
HER2 Status	
Negative	n (x.x%)
Discordant*	n (x.x%)
ER Status	
Positive	n (x.x%)
Negative	n (x.x%)
Unequivocal	n (x.x%)
Unknown	n (x.x%)
PR Status	
Positive	n (x.x%)
Negative	n (x.x%)
Unequivocal	n (x.x%)
Unknown	n (x.x%)

*Discordant HER2 status represents patients who have ISH and IHC tests with differing results that can not be otherwise adjudicated programmatically (ie ISH = Negative and IHC = Positive)

Table 15.1.11. HR2 and HER2 Specimen and Report Dates

Variable/Statistic	palbociclib + AI (n=xxx)
Year of HR Specimen	
n	xx
Median (Q1, Q3)	xxxx (xxxx, xxxx)
Min, Max	xxxx, xxxx
Year of HR Report	
n	xx
Median (Q1, Q3)	xxxx (xxxx, xxxx)
Min, Max	xxxx, xxxx
Year of HER2 Specimen	
n	xx
Median (Q1, Q3)	xxxx (xxxx, xxxx)
Min, Max	xxxx, xxxx
Year of HER2 Report	
n	xx
Median (Q1, Q3)	xxxx (xxxx, xxxx)
Min, Max	xxxx, xxxx

Table 15.1.12. BRCA Mutation Results

Variable/Statistic	palbociclib + AI (n=xxx)
BRCA1, n (%)	
Not tested	n (x.x%)
Tested	n (x.x%)
Mutation Not Detected	n (x.x%)
Mutated	n (x.x%)
BRCA2, n (%)	
Not tested	n (x.x%)
Tested	n (x.x%)
Mutation Not Detected	n (x.x%)
Mutated	n (x.x%)
BRCA1 Rearrangement, n (%)	
Not tested	n (x.x%)
Tested	n (x.x%)
Not Detected	n (x.x%)
Negative	n (x.x%)
Year of BRCA Report	
n	xx
Median (Q1, Q3)	xxxx (xxxx, xxxx)
Min, Max	xxxx, xxxx

Previous Treatment Modalities

Table 15.1.13. Treatment Received Prior to A/MBC diagnosis

Variable, n (%)	palbociclib + AI (n=xxx)
Breast Surgery	
Yes	n (x.x%)
1	n (x.x%)
2	n (x.x%)
≥3	n (x.x%)
No	n (x.x%)
Breast Surgery Before Metastasis	
Yes	n (x.x%)
1	n (x.x%)
2	n (x.x%)
≥3	n (x.x%)
No	n (x.x%)
Breast Surgery After Metastasis	
Yes	n (x.x%)
1	n (x.x%)
2	n (x.x%)
≥3	n (x.x%)
No	n (x.x%)
Breast Radiation Therapy	
Yes	n (x.x%)
1	n (x.x%)
2	n (x.x%)
≥3	n (x.x%)
No	n (x.x%)
Breast Radiation Therapy Before Metastasis	
Yes	n (x.x%)
1	n (x.x%)
2	n (x.x%)
≥3	n (x.x%)
No	n (x.x%)
Breast Radiation Therapy After Metastasis	
Yes	n (x.x%)
1	n (x.x%)
≥2	n (x.x%)
No	n (x.x%)
Chemotherapy	
Yes	n (x.x%)
No	n (x.x%)
Hormone therapy	
Yes	n (x.x%)
No	n (x.x%)

Table 15.1.14. Breast Surgery Types Before and After Metastasis

Variable, n (%)	Before Metastasis (n=xxx)	After Metastasis (n=xxx)	Overall (n=xxx)
Lumpectomy / excisional biopsy	n (x.x%)	n (x.x%)	n (x.x%)
Mastectomy, NOS	n (x.x%)	n (x.x%)	n (x.x%)
Modified radical mastectomy	n (x.x%)	n (x.x%)	n (x.x%)
Partial mastectomy	n (x.x%)	n (x.x%)	n (x.x%)
Radical mastectomy	n (x.x%)	n (x.x%)	n (x.x%)
Segmental mastectomy	n (x.x%)	n (x.x%)	n (x.x%)
Subcutaneous mastectomy	n (x.x%)	n (x.x%)	n (x.x%)
Surgery, NOS	n (x.x%)	n (x.x%)	n (x.x%)
Total mastectomy	n (x.x%)	n (x.x%)	n (x.x%)

Numbers based on the surgery counts. Patients may have more than one surgery.

Table 15.1.15. Radiation Body Sites Before and After Metastasis

Variable, n (%)	Before Metastasis (n=xxx)	After Metastasis (n=xxx)	Unknown Radiation Date (n=xxx)	Overall (n=xxx)
Chest wall	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Chest wall, regional lymph nodes	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Partial breast	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Regional lymph nodes	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Unknown	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Whole breast	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Whole breast, regional lymph nodes	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Chest wall	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Chest wall, regional lymph nodes	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)

Numbers based on the radiation counts. Patients may have more than one radiation therapy.

Prior Progression and Recurrence

Table 15.1.16. Progression and Recurrence Prior to Start of 1L Therapy for A/MBC Diagnosis

Variable, n (%)	palbociclib + AI (n=xxx)
Progression Before Start of 1L Therapy for A/MBC	
Yes	n (x.x%)
1	n (x.x%)
2	n (x.x%)
≥3	n (x.x%)
No	n (x.x%)
Progression Before Metastasis	
Yes	n (x.x%)
1	n (x.x%)
2	n (x.x%)
≥3	n (x.x%)
No	n (x.x%)
Recurrence Before Start of 1L Therapy for A/MBC	
Yes	n (x.x%)
1	n (x.x%)
2	n (x.x%)
≥3	n (x.x%)
No	n (x.x%)
Recurrence Before Metastasis	
Yes	n (x.x%)
1	n (x.x%)
2	n (x.x%)
≥3	n (x.x%)
No	n (x.x%)

Table 15.1.17. Progression Details Prior to Start of 1L Therapy for A/MBC diagnosis

Variable, n (%)	palbociclib + AI (n=xxx)
Progression Test Source	
Imaging	n (x.x%)
Imaging confirmed by biopsy	n (x.x%)
Unknown	n (x.x%)
Clinical Confirmation of Progression	
Care Everywhere	n (x.x%)
Discharge Summary	n (x.x%)
External Lab Report	n (x.x%)
Imaging Report	n (x.x%)
Media/scanned doc	n (x.x%)
Medical Oncology Note/Consult	n (x.x%)
Nursing Note	n (x.x%)
Other	n (x.x%)
Progress Note	n (x.x%)
Radiation Oncology Note / Consult	n (x.x%)
Surgical Note	n (x.x%)
Progression Linked to Therapy	
Yes	n (x.x%)
No	n (x.x%)

Numbers based on the progression counts. Patients may have more than one progression prior to A/MBC diagnosis.

Table 15.1.18. Recurrence Details Prior to Start of 1L Therapy for A/MBC diagnosis

Variable, n (%)	palbociclib + AI (n=xxx)
Recurrence Site	
Distant	n (x.x%)
Local	n (x.x%)
Regional	n (x.x%)
Recurrence Test Source	
Biopsy	n (x.x%)
Imaging	n (x.x%)
Imaging confirmed by biopsy	n (x.x%)
Unknown	n (x.x%)
Clinical Confirmation of Progression	
Care Everywhere	n (x.x%)
Discharge Summary	n (x.x%)
External Lab Report	n (x.x%)
Imaging Report	n (x.x%)
Media/scanned doc	n (x.x%)
Medical Oncology Note/Consult	n (x.x%)
Nursing Note	n (x.x%)
Other	n (x.x%)
Progress Note	n (x.x%)
Radiation Oncology Note / Consult	n (x.x%)
Surgical Note	n (x.x%)
Recurrence Linked to Therapy	
Yes	n (x.x%)
No	n (x.x%)

Numbers based on the recurrence counts. Patients may have more than one recurrence prior to A/MBC diagnosis.

8.2 Objective 2: Effectiveness Outcomes

8.2.1 Endpoint Data

Real world Overall Survival

Table 15.2.1.19. Kaplan-Meier Analysis of rwOS from Start of 1L Using Regimen-Based Lines of Therapy

OS	palbociclib + AI (n=xxx)
No. of Events/No. of Patients	xxx/xxx
No. of Censored	xx
Minimum, Maximum	xx.x, xx.x
Kaplan-Meier Estimates in months (95% CI)	
25th percentile	xx.x (xx.x, x,x)
Median	xx.x (xx.x, x,x)
75th percentile	xx.x (xx.x, x,x)

Figure 15.2.1.2. Kaplan-Meier Analysis of rwOS

Table 15.2.1.3. Cox Model for Assessing Factors Associated with rwOS from Start of 1L

Parameters	Estimate	Std Error	HR	95% CI for HR	P-Value
Age in years (≥75 vs <50)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Age in years (65-74 vs <50)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Age in years (50-64 vs <50)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Race (Black or African American vs White)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Race (Other vs White)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
ECOG/KPS (≥2 vs 0)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
ECOG/ KPS (1 vs 0)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Menopausal status (post vs pre or peri)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Metastatic group (de novo vs recurrent)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Stage at Diagnosis (IV vs 0 or I)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Stage at Diagnosis (III vs 0 or I)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Stage at Diagnosis (II vs 0 or I)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx

Table 15.2.1.3. Cox Model for Assessing Factors Associated with rwOS from Start of 1L

Parameters	Estimate	Std Error	HR	95% CI for HR	P-Value
Number of disease sites (≥3 vs 1)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Number of disease sites (2 vs 1)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Time from initial diagnosis to metastasis (≤36 vs >36 months)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Visceral disease (Yes vs No)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Prior endocrine therapy (Yes vs No)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Prior chemotherapy (Yes vs No)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Prior surgery (Yes vs No)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx
Prior radiation therapy (Yes vs No)	x.xxx	x.xxx	x.xxx	x.xxx-x.xxx	x.xxxx

Table 15.2.1.4. Kaplan-Meier Analysis of rwOS from Start of 1L Using Regimen-Based Lines of Therapy for Patients who Received 125mg Starting Dose
Figure 15.2.1.5. Kaplan-Meier Analysis of rwOS for Patients who Received 125mg Starting Dose

Table shells for the following analysis can be repeated as displayed above-

Real world Progression free Survival

Table 15.2.2.1. Kaplan-Meier Analysis of time to rwPFS from Start of 1L Using Regimen-Based Lines of Therapy

Figure 15.2.2.2. Kaplan-Meier Analysis of rwPFS

Table 15.2.2.3. Cox Model for Assessing Factors Associated with time to rwPFS from Start of 1L

Table 15.2.2.4. Progression Details After Start of 1L Therapy for A/MBC Diagnosis

Table 15.2.2.5. Kaplan-Meier Analysis of time to rwPFS from Start of 1L Using Regimen-Based Lines of Therapy by Metastasis Status

Figure 15.2.2.6. Kaplan-Meier Analysis of rwPFS by Metastasis Status

Table 15.2.2.7. Kaplan-Meier Analysis of time to rwPFS from Start of 1L Using Regimen-Based Lines of Therapy for Patients who Received 125mg Starting Dose

Figure 15.2.2.8. Kaplan-Meier Analysis of rwPFS for Patients who Received 125mg Starting Dose

Real world time to discontinuation

Table 15.2.3.1 Kaplan-Meier Analysis of time to rwTTD from Start of 1L Using Regimen-Based Lines of Therapy

Figure 15.2.3.2. Kaplan-Meier Analysis of rwTTD

Table 15.2.3.3. Cox Model for Assessing Factors Associated with time to rwTTD from Start of 1L

Table 15.2.3.4 Kaplan-Meier Analysis of time to rwTTD from Start of 1L Using Regimen-Based Lines of Therapy for Patients who Received 125mg Starting Dose

Figure 15.2.3.5 Kaplan-Meier Analysis of rwTTD for Patients who Received 125mg Starting Dose

Real world time to next treatment

Table 15.2.4.1. Kaplan-Meier Analysis of time to rwTTNT from Start of 1L Using Regimen-Based Lines of Therapy

Figure 15.2.4.2. Kaplan-Meier Analysis of time to rwTTNT

Table 15.2.4.3. Cox Model for Assessing Factors Associated with time to rwTTNT from Start of 1L

Table 15.2.4.4. Kaplan-Meier Analysis of time to rwTTNT from Start of 1L Using Regimen-Based Lines of Therapy for Patients who Received 125mg Starting Dose

Figure 15.2.4.5. Kaplan-Meier Analysis of time to rwTTNT for Patients who Received 125mg Starting Dose

Real world time to Chemotherapy

Table 15.2.5.1. Kaplan-Meier Analysis of time to rwTTC from Start of 1L Using Regimen-Based Lines of Therapy

Figure 15.2.5.2. Kaplan-Meier Analysis of time to rwTTC

Table 15.2.5.3. Cox Model for Assessing Factors Associated with time to rwTTC from Start of 1L

Table 15.2.5.4. Kaplan-Meier Analysis of time to rwTTC from Start of 1L Using Regimen-Based Lines of Therapy for Patients who Received 125mg Starting Dose

Figure 15.2.5.5. Kaplan-Meier Analysis of time to rwTTC for Patients who Received 125mg Starting Dose

Real world time to Dose Adjustment

Table 15.2.6.1. Kaplan-Meier Analysis of time to rwTTDA from Start of 1L Using Regimen-Based Lines of Therapy

Figure 15.2.6.2. Kaplan-Meier Analysis of time to rwTTDA

Table 15.2.6.3. Cox Model for Assessing Factors Associated with time to rwTTDA from Start of 1L

Table 15.2.6.4. Kaplan-Meier Analysis of time to rwTTDA from Start of 1L Using Regimen-Based Lines of Therapy for Patients who Received 125mg Starting Dose

Figure 15.2.6.5. Kaplan-Meier Analysis of time to rwTTDA for Patients who Received 125mg Starting Dose

Note-Each efficacy outcome will be analyzed as per the timepoints defined in section 5.

8.2.2 Safety Data

Not applicable

8.2.3 Medication/ Treatment Data

Treatment Patterns

Table 15.4.1. Total Number of Lines Per Patient from the Diagnosis of A/MBC

Variable, n (%)	palbociclib + AI (n=xxx)
1	n (x.x%)
2	n (x.x%)
3	n (x.x%)
4	n (x.x%)
≥5	n (x.x%)

Table 205.4.2. Treatments by Line of Therapy from the Diagnosis of A/MBC

Line	Regimen (Agents)	palbociclib + AI (n=xxxx)
1 (N=xxx)	xxxxxx	n (x.x%)
	xxxxxx	n (x.x%)
	xxxxxx	n (x.x%)
	…	
2 (N=xxx)	xxxxxx	n (x.x%)
	xxxxxx	n (x.x%)
	xxxxxx	n (x.x%)
	…	
3 (N=xxx)	xxxxxx	n (x.x%)
	xxxxxx	n (x.x%)
	xxxxxx	n (x.x%)
	…	
	xxxxxx	n (x.x%)
4 (N=xxx)	xxxxxx	n (x.x%)
	xxxxxx	n (x.x%)
	xxxxxx	n (x.x%)
	…	
5 (N=xxx)	xxxxxx	n (x.x%)
	xxxxxx	n (x.x%)
	xxxxxx	n (x.x%)
	…	

Figure 215.4.3. Proportion of Patients with Regimen by Line of Therapy from the Diagnosis of A/MBC

Dosing Description

Table 15.4.4. Dosing at Start and End of Treatment, n (%)

	End dose				
Starting dose	**75mg**	**100mg**	**125mg**	**Unknown**	**Total**
75 mg	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
100 mg	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
125 mg	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Unknown	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)
Total	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)	n (x.x%)

Table 15.4.5. Dosing description

Variable/Statistic	**palbociclib + AI (n=xxx)**
Dose adjustment	n (x.x)
No adjustment	n (x.x%)
Increase	n (x.x%)
Decrease	n (x.x%)
Unknown	n (x.x%)
Type of dose adjustment	
Hold	n (x.x%)
Schedule change	n (x.x%)
Dose delay	n (x.x%)
Hold	n (x.x%)
Cost	n (x.x%)
Patient refusal	n (x.x%)
Toxicity	n (x.x%)
Time (days) to Dose Adjustment	
n	xx
Mean (SD)	x.x (x.xx)
Median (Q1, Q3)	x.x (x.x, x.x)
Min, Max	x.x, x.x
Discontinuation	
No	n (x.x%)
Yes	n (x.x%)
Discontinuation reason	
Progression	n (x.x%)
Intolerance/Toxicity	n (x.x%)
Other/Unknown	n (x.x%)
Patient choice	n (x.x%)
Treatment for other diseases	n (x.x%)
Left health system	n (x.x%)
End of planned therapy	n (x.x%)
Changes in insurance	n (x.x%)
Death	n (x.x%)
Hospice referral	n (x.x%)

Table 15.4.5. Dosing description

Variable/Statistic	palbociclib + AI (n=xxx)
Physician choice	n (x.x%)
Treatment ongoing	n (x.x%)

8.2.4 Other Endpoints

Not applicable

9 APPENDIX

9.1 APPENDIX 1: Diagnosis and Procedure Codes used in the study

Variable	Code
Breast cancer	ICD9 174.x or 175.x or ICD10 C50.x

9.2 APPENDIX 2: Description of data elements used in the study

The following data elements will be extracted from feeds and/or curated by Certified Tumor Registrars (CTRs) for this study:

Data Elements	***Description***
Demographic characteristics	
Date of birth	*Year, month, day (Availability of the exact date will depend on the Expert de-ID approach)*
Date of initial BC diagnosis	*Date of initial breast cancer (BC) diagnosis*
Date of A/MBC diagnosis	*Date of advanced/metastatic breast cancer (A/MBC) diagnosis*
Patient sex	*Male, Female, Transsexual, Other, Not Provided*
Primary race	*American Indian/Alaska Native; Asian; Black/African American/Native Hawaiian/Pacific Islander; White; Not Provided; Other (Exact list will depend on the expert de-ID approach)*
Secondary race	*(if provided) (Exact list will depend on the expert de-ID approach)*
Ethnicity	*Non-Hispanic/Non-Latino; Hispanic/Latino; Unknown (Exact list will depend on the expert de-ID approach)*
Region of residence	*Northeast, Midwest, South, West* *Captured at A/MBC diagnosis (Exact list will depend on the expert de-ID approach)*
Insurance type	*Medicare/Medicaid; Commercial; Commercial and Medicare/Medicaid; None; Not Provided* *Captured at 1) date of A/MBC diagnosis; and 2) at initiation of palbo*
Menopause status	*Premenopausal; Postmenopausal; Perimenopausal; Unknown; Not applicable. Captured on date closest to but before: 1) A/MBC diagnosis; and 2) initiation of palbo*

	Menopausal status: captured if explicitly stated in clinician notes. Otherwise captured based on following definition of menopause from NCCN Guideline v.3.2019: *Prior bilateral oophorectomy (date of surgery)* *Age >=60 years old* *Age <60 years old and amenorrheic for 12 months+ in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression.* *Additionally, type, name, and start/end date of ovarian suppression agent is captured*
Date of death	*If patient vital status = deceased, date of death from the medical record (capturing from EMR, registries, third party integrations) (Availability of the exact date will depend on the Expert de-ID approach)*
Last contact date	*If patient is alive (not deceased), date of the last contact by a healthcare provider from the medical record (Availability of the exact date will depend on the Expert de-ID approach)*
Clinical characteristics	
Breast cancer histology	*List captured at initial breast cancer diagnosis including: Adenoid cystic; Cribriform; Ductal; Inflammatory; Intraductal; Lobular; Medullary with lymphoid stroma; Medullary, NOS; Mucinous; Paget's disease and infiltrating; Paget's disease and intraductal; Papillary; Secretory; Squamous cell; Tubular, and more*
ECOG/KPS performance score	*Score captured on date closest to (with a ± 60 day cutoff around) 1) A/MBC diagnosis; and 2) initiation of palbo*
Stage at initial BC diagnosis	*0, I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IIIC, IV, Unable to stage, Not found, Not applicable*
Presence of distant metastasis	*Yes; No* *Note: this variable would be "yes" if patient is diagnosed with de novo metastatic breast cancer or if patient developed metastasis after initial breast cancer diagnosis*
Date of first distant metastasis	*Same as initial BC diagnosis if de novo metastatic BC, otherwise captured as date that the patient developed distant metastatic disease*
Site(s) of distant metastasis at MBC diagnosis	*Bone; Chest Wall; Contralateral Breast; Distant Lymph node(s); Liver; Lung; Peritoneum; Pleural nodules; Malignant pleural effusion; Skin; Brain* (brain and spinal metastases)*; Ovary; Undocumented; Other, Specify;* *Visceral sites* (Liver, Lung, Peritoneum and Pleural nodules)*;*

	Bone only
Comorbidities	*List of comorbidities at time of A/MBC diagnosis (sourced from problem list encompassing entire patient journey and confirmed from clinician notes), including: anemia, heart arrhythmia, hypertension, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, hemiplegia, chronic obstructive pulmonary disease, ulcer disease, diabetes with chronic complications, diabetes without chronic complications, renal disease, connective tissue disease such as rheumatoid arthritis or lupus, Alzheimer's or other dementia, cirrhosis or other serious liver disease, non-breast cancer malignancy (excluding sites of breast cancer metastasis and malignant neoplasm of skin), metastatic solid tumor (other than breast cancer), HIV/AIDS, and other comorbidities of interest* *Note: comorbidities in bold are in CCI; CCI listed in derived variables section*
Biomarkers	
ER, PR, HER2 status	*Positive; Negative; Equivocal; Unknown*
ER, PR, HER2 test type	*ISH, IHC, NGS, PCR, Other, Unknown*
ER, PR, HER2 sample collection date	*Year, month, day*
ER, PR, HER2 report date	*Year, month, day*
BRCA status	*BRCA1 Mutation; BRCA2 Mutation; BRCA NOS Mutation*
BRCA sample collection date	*Year, month, day*
BRCA report date	*Year, month, day*
Treatment modalities prior to A/MBC diagnosis	
Breast surgery	*Yes; No*
Surgery type	*Partial mastectomy; Lumpectomy / excisional biopsy; Segmental mastectomy; Subcutaneous mastectomy; Total mastectomy; Modified radical mastectomy; Radical mastectomy; Extended radical mastectomy; Mastectomy, NOS; Surgery, NOS* *Note: if multiple, all will be listed (longitudinal data)*

Surgery date	*Year, month, day*
Breast radiation therapy	*Yes; No*
Radiation therapy site	*Whole breast; Partial breast; Chest wall; Regional lymph nodes; Unknown* *Note: limited to primary breast cancer site. If multiple, all will be listed (longitudinal data)*
Radiation start/end dates	*Year, month, day*
Chemotherapy	*Yes; No*
Recurrence	
Patient had recurrence	*Yes; No*
Recurrence date	*Year, month, day (Captures first time locally, first time regionally, and first time distant; if multiple sites, hierarchy prioritizes most advanced site)*
Recurrence site	*Local; Regional; Distant; Unknown*
Recurrence test source	*Biopsy; Imaging; Imaging confirmed by biopsy; Unknown*
Clinician confirmation of recurrence	*Sources including: Medical oncology consult/note; Radiation oncology note; Discharge summary; Other*
Recurrence linked to therapy	*Yes; No*
Progression	
Patient had progression	*Yes; No*
Progression date	*Year, month, day*
Progression test source	*Biopsy; Imaging; Imaging confirmed by biopsy; Unknown*
Clinician confirmation of progression	*Sources including: Medical oncology consult/note; Radiation oncology note; Discharge summary; Other*
Clinician confirmation date	*Year, month, day*

Progression linked to therapy	*Yes; No*
Complete systemic therapy history	
Therapy name	*Therapy name*
Administration route	*Categories including: Oral; Infusion; Injection; Other; Unknown*
Therapy start date	*Year, month, day*
Therapy end date	*Year, month, day*
Start reason	*Recurrence; Progression; Other reason not related to worsening disease*
Start reason source date	*Year, month, day (can be linked to clinician confirmation date of recurrence/progression if start reason is recurrence/progression)*
Stop reason	*Categories including: Progression; Toxicity; End of planned therapy; Insurance changes; Treatment ongoing; Other*
Stop reason source date	*Year, month, day (can be linked to clinician confirmation date of recurrence/progression if stop reason is recurrence/progression)*
Treatment part of clinical trial	*Yes; No*
Palbociclib-specific variables (captured in addition to above variables)	
Combination AI partner	*Letrozole, Anastrozole, Exemestane*
Concomitant LHRH Agonists	*Goserelin (Zoladex), Histrelin (Vantas), Leuprolide (Eligard, Lupron), Triptorelin (Trelstar)*
Dose 1 (start dose)	*125mg, 100mg, 75mg*
Dose 1 start date	*Year, month, day*
Dose n (where n>=2)	*125mg, 100mg, 75mg*
Dose n start date	*Year, month, day*
Dose n adjustment type or reason	*Categories include schedule change; dose delay; hold; cost; patient refusal; toxicity*

Variables that will be derived from curated data will include the following:

Data Elements	***Description***

Age at A/MBC diagnosis	*Age in years; age categories: <50, 50-64, 65 –74, ≥75 years (Exact list will depend on the expert de-ID approach)*
Age at start of palbociclib treatment	*Age in years; age categories: <50, 50-64, 65 –74, ≥75 years*
Date of death	*If patient vital status = deceased, date of death from the medical record (capturing from EMR, registries, third party integrations) (Availability of the exact date will depend on the Expert de-ID approach)*
Palbo dose change ever	*Yes; No*
Disease Free Interval (DFI)	*Months from the end of adjuvant therapy to the date of disease recurrence* *≤12 months, 13-24 months, 25-36 months* *>36 months* *Unknown*
Endocrine sensitivity	*≥12 months without recurrence/progression after completion of endocrine therapy in the adjuvant setting*
Primary endocrine resistance	*Relapse during first 2 years of adjuvant endocrine therapy or progressive disease within first 6 months of first-line endocrine therapy for metastatic breast cancer*
Secondary endocrine resistance	*Relapse while on adjuvant endocrine therapy but after first 2 years of treatment, relapse within 12 months of completing adjuvant endocrine therapy, or progressive disease 6 or more months after starting endocrine therapy for metastatic breast cancer*
Charlson Comorbidity Index (CCI)	*Calculated based on the presence of 17 Charlson comorbidities at A/MBC*
Line of therapy	*Line number (1; 2; 3; etc.) in the A/MBC setting assigned based on Syapse line of therapy algorithm*
Regimen medication(s)	*Systemic therapies included in line regimen defined by Syapse line of therapy algorithm*
Line start date	*Year, month, day*
Line end date	*Year, month, day*
Time to first dose change	*Days from palbo dose 1 start date to palbo dose 2 start date, if applicable*
Number of dose changes	*Number of dose reduction(s) and number of dose increases over the calendar time (quarter since February 2015) and over treatment cycle since palbo dose 1 start date*

Bone only distant metastasis at MBC diagnosis	*From sites of distant metastasis: bone only*
Visceral distant metastasis at MBC diagnosis	*From sites of distant metastasis: visceral sites* *Visceral sites defined as: Liver; Lung; Peritoneum; Pleural nodules; Malignant pleural effusion*
Disease burden at MBC diagnosis	*Lesions in liver, bone, or lung metastatic sites: Single, Multiple, Unknown*
Effectiveness Outcomes	
Real-world Overall Survival (rwOS)	*Length of time from the start of palbociclib + AI treatment to the earliest of the following: date of death, date of last contact, or the end of study period*
Real-world progression free survival (rwPFS)	*Length of time from the start of palbociclib + AI treatment to the earliest of the following: clinician-assessed progression event, date of death, date of last contact, or end of study period.* *Progression identified from tissue/pathology or imaging/radiology **and** confirmed by clinician (in 2 separate data points), from MA guidance:* *1. Medical Oncology Consult/Note (can also include medical oncologist history and physical (H&P)* *2. Radiation Oncology note/consult/(can also include radiation oncology H&P)* *3. Progress Note (can also include /H&P/Consult - use this option for physician of other discipline in the absence of numbers1and 2)* *4. Discharge Summary* *5. Nursing Note* *6. Care Everywhere/Scanned Documents/External lab reports (for information diagnosed outside of facility for which patient is being abstracted)* *7. Other*
Real world time to treatment discontinuation (rwTTD)	*Length of time from the start of palbociclib + AI treatment to the earliest of the following: date the patient discontinues first-line treatment, date of death, last known usage of first-line treatment, or end of study period*
Real world time to next treatment (rwTTNT)	*Length of time from the start of palbociclib + AI treatment to the earliest of the following: subsequent line of therapy initiation, date of death, date of last contact, or end of the study period*

Real world time to dose adjustment (rwTTDA)	*Length of time from the start of palbociclib + AI treatment to the earliest of the following: date of first-line treatment dose adjustment, date of death, last known usage of first-line treatment, or end of study period.*
Real world time to chemotherapy (rwTTC)	*Length of time from the start of palbociclib + AI treatment to the earliest of the following: the day before the start of subsequent chemotherapy for patients with evidence of chemotherapy, or date of death for any reason. Or, where censored, the latest of date of last contact, or end of the study period.*