Non-Interventional Study Protocol
A5481144

Patient Characteristics, Treatment Patterns, and Clinical Outcomes in Patients Diagnosed with HR+/HER2- Advanced/Metastatic Breast Cancer Receiving CDK4/6i + Aromatase Inhibitor (AI) Combination Therapy as Initial Endocrine-based Treatment

Statistical Analysis Plan
(SAP)

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable (first version).

2. INTRODUCTION

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

The treatment landscape for HR+/HER2- advanced and metastatic breast cancer (A/MBC) has changed as multiple CDK4/6i drugs in combination with aromatase inhibitor (AI) are approved for use in the first line and subsequent lines of therapy. The present study is designed to describe treatment patterns and clinical outcomes in patients diagnosed with HR+/HER2- A/MBC who received CDK 4/6i combination therapy with AI as initial endocrine-based treatment in the U.S. community oncology setting.

2.1. Study Design

This is an observational, retrospective study involving medical chart review. Eligible patients will be identified and accrued from the Concerto HealthAI Definitive Oncology Dataset. All study data are secondary data and will have been collected retrospectively from existing clinical data originally collected as part of routine care.

2.1.1. Study Population

The study will include adult patients 18 years or older, diagnosed with HR+/HER2- A/MBC who initiated CDK4/6i combination therapy with AI as the initial endocrine-based therapy on or after 2/3/2015 and before 4/1/2019.

2.1.2. Data Source

Concerto HealthAI maintains a network of community oncology practices representing a geographically and demographically diverse patient population. Data from these practices have been collected centrally in the Definitive Oncology Dataset, which is the source of data to be collected in this study.

Key features of the Definitive Oncology Dataset include the following.

- *Availability of both structured data (tables, rows and columns) and unstructured data (text and image documents, eg, physician progress notes). The unstructured information is generally not available in other Electronic Medical Record (EMR) data sources, although this is where much of the richest clinical information is found. Together with the structured data, Concerto HealthAI has access to an essentially complete version of the medical oncology health record for each patient. As a result, analysis does not need to rely on proxy measures of key clinical endpoints, as may be the case where only structured EMR data are available.*

2.1.3. Treatment/Cohort Labels

Patients will be grouped into the following CCI

- All Eligible Patients – patients satisfying protocol study inclusion/exclusion criteria and receiving CDK4/6i combination therapy with AI as initial endocrine-based therapy. CCI
- Palbociclib + AI Patients – patients receiving Palbociclib with AI as initial endocrine-based therapy.

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2.2. Study Objectives

Primary Objectives:

1. *All Eligible Patients:*
   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 stage of initial diagnosis, histology, Eastern Cooperative Oncology Group (ECOG) performance status (where available, Karnofsky performance status will be converted to corresponding ECOG score) and comorbid disease burden, HER2 and Estrogen receptor (ER)/ Progesterone receptor (PR) status, number and sites of distant metastasis at A/MBC diagnosis (if applicable); modalities of treatment received prior to A/MBC diagnosis (chemotherapy, hormone therapy, surgery, radiation therapy) 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 employed with administration of palbociclib, ribociclib, and abemaciclib. Description of the dosing will include the starting dose, end dose, dose adjustment (dose increase and dose reduction), reasons for dose adjustment (dose modification, schedule changes, dose delay, hold, or discontinuation), discontinuation, reason, and time to dose adjustment (discontinuation).*

2. *Among patients receiving Palbociclib + AI as initial endocrine-based therapy, examine clinical effectiveness outcomes including:*
   a. *Real-world progression-free survival (rwPFS) will be assessed for the initial endocrine-based therapy.*
   b. *Overall survival (OS) will be assessed from start of the initial endocrine-based therapy.*
   c. *Real-world tumor response (rwTR) will be assessed as best overall response for each regimen received within the initial endocrine-based therapy.*

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[redacted]

3. HYPOTHESES AND DECISION RULES

3.1. Statistical Hypotheses

Not applicable.

3.2. Statistical Decision Rules

Not applicable.

3.3. SAMPLE SIZE

The sample size of this study will be based on the actual number of eligible patients available for the study through CRN screening. The study will include all patients (estimated 1100 – 1300 patients) in the data set for the descriptive elements who meet the inclusion/exclusion criteria.

4. ANALYSIS SETS/POPULATIONS

4.1. Full Analysis Set

Includes all patients who satisfy all inclusion and exclusion criteria.

4.1.1. 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 a CDK4/6i in combination with an AI as initial endocrine-based therapy after A/MBC diagnosis on or after 2/3/2015 and before 4/1/2019.*
    - *Note that the date of the start of the inclusion period reflects the month that the first CDK4/6i (ie, Palbociclib) received U.S. 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).*

4.1.2. Exclusion Criteria

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

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

4.2. Subgroups

Summaries of study outcomes may be repeated focusing alternatively on but not limited to the following subgroups of interest—sample size permitting—which will be defined on the basis of:

- Age (years): ≤50, 51-64, 65-74, ≥75;
- Gender, if number of males is low then we can restrict results to females;
- Race: White, Black, Other;
- Disease stage at initial diagnosis: I or II, III, IV;
- ECOG performance status: 0, 1 or 2, ≥3;
- Site of metastasis: Visceral, Non-visceral, Bone only;
- Number of metastatic sites: 1, 2, ≥3;

- Menopausal status: premenopausal, perimenopausal, Postmenopausal, undocumented;
- Hormone therapy prior to A/MBC diagnosis: yes, no;
- Chemotherapy prior to A/MBC diagnosis: yes, no;
- Surgery prior to A/MBC diagnosis: yes, no;
- Radiation therapy prior to A/MBC diagnosis: yes, no;
- Disease free interval: ≤12 months, >12 months;
- Starting dose: by starting dose levels for Palbociclib, CCI respectively.

5. ENDPOINTS AND COVARIATES

- **Index date:** Date of A/MBC diagnosis.
- **Observation period:** February 3, 2015 through the data cutoff date (end of data curation). Since data curation will start in November 2019, this allows patients to have a potential follow-up of at least 6 months.
- **Follow-up:** Patients will be followed from the index date to the data cutoff date, or death, whichever comes first.

5.1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Variable	Operational definition
Demographic characteristics	
Age	Age at A/MBC diagnosis, years
Age category	≤50, 51-64, 65 –74, ≥75 years
Sex	Female or Male
Race	White, Black, Asian, Other, Unknown
Region of residence	Based on state where the patient resides: Northeast, Midwest, South, West
Insurance status	Private only, public only, public and private, or neither reported at index date and reported at initiation of the earliest endocrine-based therapy after the index date.
Clinical characteristics	
Menopausal status	(Pre, Peri, Post, UD) nearest in time to the date of, but before, index date.
Type of MBC	De novo MBC (newly diagnosed): Stage 4 at initial BC diagnosis Recurrent MBC: Stages 0-3 at initial BC diagnosis
Modalities of treatment received at any point prior to A/MBC diagnosis	Surgery (yes/no), Radiation (yes/no), Chemotherapy (yes/no), Hormone therapy (yes/no)

ECOG performance score	ECOG performance at index date (± 60 days), 0, 1,2,3,4,5, or missing. Where available, Karnofsky performance status will be converted to the corresponding ECOG score.
Disease stage at initial BC diagnosis	Stage I, II, III, IV, unknown/ undocumented
Disease stage at index date (date of A/MBC diagnosis)	IIIB, IIIC, or IV
Time from initial BC diagnosis to first MBC diagnosis	Months from the date of initial BC diagnosis to the date of metastatic diagnosis.
Disease free interval	The number of months between completion of adjuvant therapy and diagnosis of A/MBC.
Sites of distant metastasis at index date	Bone; Chest Wall; Contralateral Breast; Distant Lymph node(s); Liver; Lung; Peritoneum; Pleural nodules; Malignant pleural effusion; Skin; Brain; Undocumented; Other Specified. All sites will be reported as (yes/no).
Visceral metastasis at index date	Metastasis at one or more of the following sites: liver, pancreas, intestines, lung, heart, malignant pleural effusion, peritoneum, pleura. Other metastasis sites, including bone or non-visceral metastasis, may be present.
Non-visceral matastasis at index date	Metastasis at one or more of the following sites: bone, brain, skin, chest wall, contralateral breast, or distant lymph nodes.
Bone-only metastasis at index date	Bone metastasis, with no metastasis at any other identified site
Disease histology nearest in time to index date	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; Undifferentiated; Undocumented, Other, specify.

Endocrine sensitivity	Sensitive/Resistant/Refractory *Endocrine sensitive vs. resistant vs. refractory based on adjuvant endocrine therapy experience. Endocrine sensitive: ≥ 24 months without recurrence / progression after completion of endocrine therapy in the adjuvant setting; Endocrine resistant: recurrence / progression after completion of endocrine therapy, and within 24 months of completion of endocrine therapy; Endocrine refractory: recurrence / progression while on endocrine therapy in the adjuvant setting, defined as occurring while on or within < 30 days after discontinuation of endocrine therapy. The 30 day window allows that endocrine therapy may be discontinued because of a perceived progression before that progression is actually documented.*
Type of endocrine resistance	Primary/Secondary *Primary endocrine resistance defined as a relapse while on the first 2 years of adjuvant endocrine therapy or disease progression within the first 6 months of first-line endocrine therapy for A/MBC, while on endocrine therapy.* *Secondary (acquired) endocrine resistance defined as a relapse while on adjuvant endocrine therapy but after the first 2 years or a relapse within 12 months of completing adjuvant endocrine therapy, or disease progression ≥ 6 months after initiating endocrine therapy for A/MBC, while on endocrine therapy.*
Comorbidities present at index date	Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, hemiplegia, chronic obstructive pulmonary disease, ulcer disease, diabetes, renal disease, connective tissue disease such as rheumatoid arthritis or lupus, Alzheimer's or other dementia, cirrhosis or other serious liver disease, leukemia, lymphoma, metastatic solid tumor (other than breast cancer), and HIV/AIDS, hypertension and hyperlipidemia. Indicated as present or not indicated as present at index date.

Modified Charlson comorbidity index (CCI)	Weighted index of comorbid disease conditions (not including breast cancer) as specified by the Charlson Comorbidity Index.

5.2. TREATMENT PATTERN ENDPOINT(S)

Variable	Operational definition
Treatment Regimen Duration	Months from the start date to the end date of a treatment regimen. For ongoing regimen, the end date is the data cutoff date.
Treatment Sequence Duration	Months from the start date of the first treatment regimen to the end date of the last treatment regimen within the same line of therapy. For ongoing regimen, the end date is the data cutoff date. This will be calculated for up to 3 lines of therapy.
The following dosing information will be presented for palbociclib, CCI [redacted]	
Start dose	Start dose level of palbociclib, CCI [redacted]
End dose	End dose level of palbociclib, CCI [redacted]
Duration of Treatment	Months from the start date to the end date of the treatment. For ongoing treatment, the end date is the data cutoff date.
Reason for Discontinuing Treatment	Cost; Disease Progression; Patient Refusal/Request; Toxicity, specify; Death, Other, specify, Undocumented
Time to Dose Discontinuation	Months from the start date to the discontinuation date of the treatment.
Type of Dose Adjustments	Dose Modification; Schedule Changes; Dose Delay; Hold; Discontinuation
Time to First Dose Adjustment	Months from the start date to the first adjustment date of the treatment.

5.3. Efficacy/Effectiveness Endpoint(s)

Variable	Operational definition
Real-world progression-free survival	Time in months from the initial endocrine-based therapy to the first progression or censoring date will be calculated. *For the purpose of this study, lines of therapy will be defined as the following Progression-based lines, in which a disease progression must occur for a new regimen to be interpreted as a new line of therapy.* Event: Any death or disease progression. *Disease progression is taken to have occurred when a pathology report or radiological scan indicates disease progression and/or there is a physician progress note consistent with that determination.* If patients did not die or have disease progression, they were censored at their last visit date during the study period for patients with only one line of therapy.
Overall survival	Time in months from the initial endocrine-based therapy to death due to any cause or censoring date will be calculated. Event: Any death recorded in the data extract. Patients who did not die will be censored at the time of data cutoff (assuming this is the last date the SSDI is searched).
Real-world tumor response	Real-world tumor response (rwTR) will be assessed as best overall response for each regimen received within the initial endocrine-based therapy. *Responses will be classified as Complete response (CR); Partial response (PR); Stable disease (SD); Progressive disease (PD); Not evaluable (NE); or Undocumented. The date of the first positive response (CR or PR) and of the best overall response for each regimen will be collected.*
Response rate	The number of patients with complete response or partial response divided by the number of patients with at lease one tumor assessment while on the initial endocrine-based therapy.

Time to first positive response	Months from the start date of the initial endocrine based therapy to the date of the first positive response (CR or PR).
Duration of response	Month from the date of the first positive response (CR or PR) to the date of first PD assessment or death. Patients without a PD assessment or death are censored at the the data cutoff date.
Duration of initial endocrine-based treatment	Months from the start date of the initial endocrine based therapy to the end date of the initial endocrine-based therapy.
Duration of all treatment	Months from the start date of the initial endocrine-based therapy to the end date of the last line of treatment. Patients who are still receiving the initial endocrine-based therapy at the data cutoff date will be censored.
Duration of follow-up	Months from the index date to the date of death, or the data cutoff date, whichever came first. Patients who did not die will be censored at the data cutoff date

6. HANDLING OF MISSING VALUES

No imputation for missing values will be performed.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1. Statistical Methods

Mean, standard deviation, median, 1st quartile, 3rd quartile, inter-quartile range, minimum, and maximum will be provided when performing descriptive analysis of continuous data. Numbers and percentages will be provided when performing descriptive analysis of categorical data.

An unadjusted Kaplan Meier curve will be drawn to illustrate each time-to-event outcome. Medians and 95% confidence intervals obtained from the Kaplan-Meier curves will be reported.

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

7.2. Statistical Analyses

Description of demographic, clinical, and treatment characteristics

Descriptive analyses will be conducted to evaluate the demographic, clinical, and treatment characteristics each of the study cohorts. Results will be reported in aggregate. Categorical variables (eg, ECOG performance status) will be reported as frequency and percentage. Continuous variables such as age will be reported as mean, standard deviation, median, 1st quartile, 3rd quartile, inter-quartile range, minimum, and maximum. In the case of missing observations, the number and percentage of missing values will be reported.

Description of effectiveness outcomes

For each of the study cohorts, real-world tumor response and response rate will be reported as frequency and percentage. Real-world progression-free survival, overall survival, time to first positive response, duration of response, duration of initial endocrine-based treatment, duration of all treatment, and Duration of follow-up will be assessed with the Kaplan-Meier method with 95% CIs, and summary tables of the number of events and censored patients. No covariates will be included. All missing values are excluded.

7.2.1. Safety Analyses

None.

7.2.2. Summary of Analyses of Efficacy/Effectiveness Outcomes

Outcome	Analysis Set(s)	Supports Protocol Objective Number	Missing Data
Real-world progression-free survival	All Eligible Patients Palbociclib + AI Patients CCI [redacted]	2, 3	Excluded
Overall survival	All Eligible Patients Palbociclib + AI Patients CCI [redacted]	2, 3	Excluded
Real-world tumor response	All Eligible Patients Palbociclib + AI Patients CCI [redacted]	2, 3	Excluded
Response rate	All Eligible Patients Palbociclib + AI Patients CCI [redacted]	2, 3	Excluded
Time to first positive response	All Eligible Patients Palbociclib + AI Patients CCI [redacted]	2, 3	Excluded
Duration of response	All Eligible Patients Palbociclib + AI Patients CCI [redacted]	2, 3	Excluded

Duration of initial endocrine based treatment	All Eligible Patients Palbociclib + AI Patients CCI [redacted]	1b	Excluded
Duration of all treatment	All Eligible Patients Palbociclib + AI Patients CCI [redacted]	1b	Excluded
Duration of follow-up	All Eligible Patients Palbociclib + AI Patients CCI [redacted]	1b	Excluded

8. REFERENCES

9. APPENDICES

9.1. APPENDIX 1: Table and Figure shells

Table 1a. Summary of Baseline Demographics – All Eligible Patients

	All Eligible Patients (N=)
Age at A/MBC Diagnosis (years) Mean/SD N/Missing Values Min/Max First Quartile/Third Quartile Median/IQR	
Age Distribution (years), n (%) ≤50 51-64 65 –74 ≥75 Missing	
Sex, n (%) Female Male Missing	
Race, n (%) White Black Asian Other Unknown Missing	
Insurance Status, n (%) Private only Public only Public and Private Neither Public nor Private Missing	
Region of residence, n (%) Northeast Midwest South West Missing	

Table 1b. Summary of Baseline Demographics – Palbociclib + AI Patients

Repeat Table 1a for patients receiving Palbociclib with AI as initial endocrine-based therapy.

CCI [redacted]

Table 2a. Summary of Clinical Characteristics – All Eligible Patients

	All Eligible Patients (N=)
Number of Female Patients, n Menopausal Status, n (%)[a] Premenopausal Perimenopausal Postmenopausal Undocumented Missing	
Disease Stage at Initial Diagnosis, n (%) I II III IV Unknown/Undocumented Missing	
Disease Stage at Index Date, n (%) IIIB IIIC IV Missing	
Type of MBC De novo (Stage 4 at initial diagnosis) Recurrent (Stages 0-3 at initial diagnosis) Missing	
Time from Initial Diagnosis to First A/MBC Diagnosis Mean/SD N/Missing Values Min/Max First Quartile/Third Quartile Median/IQR	

Disease Histology, n (%) 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 Undifferentiated Undocumented Other, specify	
ECOG Performance Score[b], n (%) 0 - Normal activity 1 - Symptoms demonstrated, but the patient remains ambulatory, and able to perform self-care 2 - Ambulatory >50% of the time and requires occasional assistance 3 - Ambulatory <50% of the time and requires nursing care 4 - Bedridden 5 - Death Missing	
Comorbidities, n (%) Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular accident Hemiplegia Chronic obstructive pulmonary disease Ulcer disease Diabetes Renal disease Connective tissue disease Alzheimer's or other dementia Cirrhosis or other serious liver disease Leukemia Lymphoma	

Metastatic solid tumor (other than breast cancer) HIV/AIDS Hypertension Hyperlipidemia	
Modified Charlson Comorbidity Index[c] Mean/SD N/Missing Values Min/Max First Quartile/Third Quartile Median/IQR	
Sites of distant metastasis, n (%) Bone Chest wall Contralateral breast Distant lymph node(s) Liver Lung Peritoneum Pleural nodules Malignant pleural effusion Skin Brain Undocumented Other, specify	
Number of Metastatic Sites Mean/SD N/Missing Values Min/Max First Quartile/Third Quartile Median/IQR	
Visceral Metastasis[d] Yes No Missing	
Non-visceral Metastasis[e] Yes No Missing	
Bone-only Metastasis[f] Yes No Missing	
Modalities of Treatment, n (%) Surgery Radiation	

Chemotherapy Hormone therapy Missing	
Disease Free Interval (months) Mean/SD N/Missing Values Min/Max First Quartile/Third Quartile Median/IQR	
Endocrine Sensitivity, n (%) Sensitive Resistant Refractory Missing	
Endocrine Resistance, n (%) Primary Secondary Missing	

[a] Percentage is based on the number of female patients.
[b] Karnofsky performance status is converted to corresponding ECOG score
[c] Weighting of comorbid conditions (not including breast cancer) will follow the weighting as specified in the Charlson Comorbidity Index.
[d] Visceral: metastasis at one or more of the following sites: liver, pancreas, intestines, lung, heart, malignant pleural effusion, peritoneum, pleura. Other metastasis sites, including bone or non-visceral metastasis, may be present.
[e] Non-visceral: metastasis at one or more of the following sites: bone, brain, skin, chest wall, contralateral breast, or distant lymph nodes.
[f] Bone only: Bone metastasis, with no metastasis at any other identified site.

Table 2b. Summary of Clinical Characteristics – Palbociclib + AI Patients

Repeat Table 2a for patients receiving Palbociclib with AI as initial endocrine-based therapy.

CCI [redacted]

Table 3a. Summary of Treatment Regimen Duration – All Eligible Patients

		Treatment Regimen Duration (months)				
		n	%	Mean	SD	Median
Line 1	Regimenx	xxx	xxx	xxx	xxx	xxx
	Regimeny	xxx	xxx	xxx	xxx	xxx
	Regimenz	xxx	xxx	xxx	xxx	xxx
	…	xxx	xxx	xxx	xxx	xxx
Line 2	Regimenx	xxx	xxx	xxx	xxx	xxx
	Regimeny	xxx	xxx	xxx	xxx	xxx
	Regimenz	xxx	xxx	xxx	xxx	xxx
	…	xxx	xxx	xxx	xxx	xxx
Line 3	Regimenx	xxx	xxx	xxx	xxx	xxx
	Regimeny	xxx	xxx	xxx	xxx	xxx
	Regimenz	xxx	xxx	xxx	xxx	xxx
	…	xxx	xxx	xxx	xxx	xxx

Lines of therapy are progression-based and are restricted to the first 3 lines.

Table 3b. Summary of Treatment Regimen Duration – Palbociclib + AI Patients

Repeat Table 3a for patients receiving Palbociclib with AI as initial endocrine-based therapy.

CCI [redacted]

Table 4a. Summary of Treatment Sequencing Duration – All Eligible Patients

	Treatment Sequence		Duration (month)			
		n	%	Mean	SD	Median
One line	Line 1 Regimenx	xxx	xxx	xxx	xxx	xxx
	Line 1 Regimeny	xxx	xxx	xxx	xxx	xxx
	Line 1 Regimenz	xxx	xxx	xxx	xxx	xxx
	…	xxx	xxx	xxx	xxx	xxx
Two lines	Line 1 Regimen ==> Line 2 Regimen	xxx	xxx	xxx	xxx	xxx
	Line 1 Regimen ==> Line 2 Regimen	xxx	xxx	xxx	xxx	xxx
	Line 1 Regimen ==> Line 2 Regimen	xxx	xxx	xxx	xxx	xxx
	…	xxx	xxx	xxx	xxx	xxx

Three lines	Line 1 Regimen ==> Line 2 Regimen ==> Line 3 Regimen	xxx	xxx	xxx	xxx	xxx
	Line 1 Regimen ==> Line 2 Regimen ==> Line 3 Regimen	xxx	xxx	xxx	xxx	xxx
	Line 1 Regimen ==> Line 2 Regimen ==> Line 3 Regimen	xxx	xxx	xxx	xxx	xxx
	…	xxx	xxx	xxx	xxx	xxx

Lines of therapy are progression-based and are restricted to the first 3 lines.

Table 4b. Summary of Treatment Sequencing Duration – Palbociclib + AI Patients

Repeat Table 4a for patients receiving Palbociclib with AI as initial endocrine-based therapy.

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Repeat Table 4a for patients receiving Abemaciclib with AI as initial endocrine-based therapy.

Table 5a. Palbociclib Dosing Information

	Palbociclib (N=)
Starting Dose, n (%) Dose level 1 Dose level 2 Dose level 3	
End Dose, n (%) Dose level 1 Dose level 2 Dose level 3	
Palbociclib Treatment Status, n (%) Treatment Ongoing Treatment Discontinued	
Duration of Palbociclib Treatment (months) Mean/SD N/Missing Values Min/Max First Quartile/Third Quartile Median/IQR	
Duration of Palbociclib Treatment (months) <6	

6 – 12 13 – 24 25 – 36 >36	
Reason for Discontinuing Palbociclib Therapy, n (%) Cost Disease Progression Patient Refusal/Request Toxicity, specify Other, specify Undocumented	
Time to Dose Discontinuation Mean/SD N/Missing Values Min/Max First Quartile/Third Quartile Median/IQR	
Dose Adjustments, n (%) Dose Reduced 125mg – 100mg 125mg – 75mg 100mg – 75mg Dose Increased 75mg – 100mg 75mg – 125mg 100mg – 125mg	
Number of Patients Starting at 125 mg, n (%) Dose Reduced, n (%)[a]	
Type of Dose Adjustments Dose Modification Schedule Changes Dose Delay Hold Discontinuation	
Time to First Dose Adjustment Mean/SD N/Missing Values Min/Max First Quartile/Third Quartile Median/IQR	

[a] Percentage is based on number pf patients who start at 125 mg of Palbociclib.

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[redacted]

[redacted]

Table 6a. Summary of Real-world Progression-free Survival – All Eligible Patients

	All Eligible Patients (N=)
Number of Real-world Progression Events, n (%)	
Number Censored, n (%)	
Kaplan-Meier Estimates of Time to Event (months)	
Median (95% CI)	

Table 6b. Summary of Real-world Progression-free Survival - Palbociclib + AI Patients

Repeat Table 6a for patients receiving Palbociclib with AI as initial endocrine-based therapy.

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Table 7a. Summary of Overall Survival – All Eligible Patients

	All Eligible Patients (N=)
Number of All-cause Mortality, n (%)	
Number Censored, n (%)	
Kaplan-Meier Estimates of Time to Event (months)	
Median (95% CI)	

Table 7b. Summary of Overall Survival - Palbociclib + AI Patients

Repeat Table 7a for patients receiving Palbociclib with AI as initial endocrine-based therapy.

CCI [redacted]

Table 8a. Summary of Real-world Tumor Response – All Eligible Patients

	All Eligible Patients (N=) n (%)
Regimenx Complete Response Partial Response Stable Disease Progressive Disease Not Evaluable Undocumented	
Regimeny Complete Response Partial Response Stable Disease	

Progressive Disease Not Evaluable Undocumented	
Regimenz Complete Response Partial Response Stable Disease Progressive Disease Not Evaluable Undocumented	
…	

Real-world tumor response (rwTR) will be assessed as best overall response for each regimen received within the initial endocrine-based therapy.

Table 8b. Summary of Real-world Tumor Response – *Palbociclib + AI Patients*

Repeat Table 8a for patients receiving Palbociclib with AI as initial endocrine-based therapy.

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Table 9a. Summary of Response Rate – All Eligible Patients

	All Eligible Patients (N=) n (%)
Regimenx	
Regimeny	
Regimenz	
…	

Response rate is calculated as the number of patients with complete response or partial response divided by the number of patients with at lease one tumor assessment while on the initial endocrine-based therapy.

Table 9b. Summary of Response Rate – Palbociclib + AI Patients

Repeat Table 9a for patients receiving Palbociclib with AI as initial endocrine-based therapy.

CCI [redacted]

Table 10a. Time to First Positive Response - All Eligible Patients

	All Eligible Patients (N=)
Number of Positive Response, n (%)	
Number Censored, n (%)	
Kaplan-Meier Estimates of Time to Event (months)	
Median (95% CI)	

Table 10b. Time to First Positive Response - Palbociclib + AI Patients

Repeat Table 10a for patients receiving Palbociclib with AI as initial endocrine-based therapy.

CCI [redacted]

Table 11a. Duration of Response - All Eligible Patients

	All Eligible Patients (N=)
Number of PD or Death, n (%)	
Number Censored, n (%)	
Kaplan-Meier Estimates of Time to Event (months)	
Median (95% CI)	

Table 11b. Duration of Response - Palbociclib + AI Patients

Repeat Table 11a for patients receiving Palbociclib with AI as initial endocrine-based therapy.

CCI [redacted]

Figures

Kaplan-Meier curves for Palbociclib + AI initial endocrine therapy. Figures will contain the KM-estimated median survival and 95% confidence intervals in the legend.

Figure 1a: Real-world Progression-free Survival – All Eligible Patients
Figure 1b: Real-world Progression-free Survival – Palbociclib + AI Patients
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Overall Survival – All Eligible Patients
Figure 2b: Overall Survival – Palbociclib + AI Patients
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Figure 3a: Duration of Initial Endocrine-based Treatment – All Eligible Patients
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Figure 4a: Duration of All Treatment – All Eligible Patients
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Figure 5a: Duration of Follow-up – All Eligible Patients
Figure 5b: Duration of Follow-up – Palbociclib + AI Patients
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Figure 6a: Time to First Positive Response – All Eligible Patients
Figure 6b: Time to First Positive Response – Palbociclib + AI Patients
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Figure 7a: Duration of Response – All Eligible Patients
Figure 7b: Duration of Response – Palbociclib + AI Patients
CCI

Additional figures will be generated for designated subgroup analyses.