Non-Interventional Study Protocol
A5481178

Treatment Patterns And Clinical Outcomes Among Patients Receiving CDK4/6 inhibitors Combinations For HR+/HER2- Advanced/Metastatic Breast Cancer In A Canadian Real World Setting

Statistical Analysis Plan
(SAP)

Version: *2.0*

Author: PPD

Date: *2023-02-16*

TABLE OF CONTENTS

1 AMENDMENTS FROM PREVIOUS VERSION(S)

Amendment number	Date	SAP section(s) changed	Summary of amendment(s)	Reason
Version 2.0	2023-02-16	Title page	Change of protocol version identifier from "version 1.0" to "version 2.0" and the date from "2021-11-22" to "2023-01-24" and the author from PPD [redacted]	SAP information has been updated. Change of staff at PPD [redacted]
Version 2.0	2023-02-16	2.2 STUDY OBJECTIVES *and* 5.1 EFFICACAY AND ENDPOINT(S) *and* 7.2 STATISTICAL ANALYSES	Change of "Secondary objective" with the deletion of "To evaluate efficacy of current treatment for Canadian breast cancer patients using surrogates for time to next treatment in the real-world setting including: • The length of treatment for the first line (TTNT1), the length of treatment for the second line (TTNT2), the time from cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor to starting chemotherapy (TTC) and overall survival (OS) • The length of treatment for short term versus long term responders" which is now included with the exact similar wording to the CCI [redacted] section, except for the following wording "…the time from cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor to starting chemotherapy (TTC)…" which was replaced by "…the time from the date of ABC/MBC diagnosis to starting chemotherapy (TTC)…"in addition,	The secondary objective was adapted as the initial planned sample size (e.g., 180 patients) will be dramatically lower than expected (less than 30% of initial sample size); consequently, CCI [redacted] As per clinical expert insight, the definition of TTC was clarified to the time from the date of ABC/MBC diagnosis to starting chemotherapy

Amendment number	Date	SAP section(s) changed	Summary of amendment(s)	Reason
			"…last known activity" was replaced by "date of last follow-up or death" These updates have been made throughout the document.	
Version 2.0	2023-02-16	3.1 STATISTICAL HYPOTHESES *and* 7.2 STATISTICAL ANALYSES *and* 8. LIST OF TABLES AND TABLE SHELLS	Sentence "The planned data analyses are descriptive in nature and no formal hypotheses will be tested." Was updated to "The planned data analyses are descriptive in nature and are subject to modification based on sample size and final data specifications. No formal hypotheses will be tested." This update has been made throughout the document.	This change is to provide further clarity on the conduction of data analyses, in accordance with the amended protocol.
Version 2.0	2023-02-16	3.2 STATISTICAL DECISION RULES	The following sentence was deleted "Although we will be using a $p < 0.05$ to declare significance"	This change was made since there is no hypothesis testing
Version 2.0	2023-02-16	4.4 SUBGROUPS	Following sentence has been included "Subgroup analyses will be descriptive in nature and will depend on adequate sample size."	This change is to provide further clarity on the conduction of data analyses, in accordance with the amended protocol.
Version 2.0	2023-02-16	4.4 SUBGROUPS *and* 7.2 STATISTICAL ANALYSES	Definition of pre- and post-CDK4/6 subgroups have been updated to: • Pre-CDK subgroup is defined as ABC/MBC patients starting systemic therapy before the introduction of CDK 4/6 inhibitor (January 2016 to May 2016). • Post-CDK subgroup is defined as ABC/MBC patients starting systemic therapy after the introduction of CDK 4/6	Sentence has been updated to provide better clarity around the definition of pre- and post-CDK4/6

Amendment number	Date	SAP section(s) changed	Summary of amendment(s)	Reason
			inhibitor (January 2019 to May 2019). This update has been made throughout the document.	
Version 2.0	2023-02-16	7.1 STATISTICAL METHODS	The following sentences were deleted: "Differences between subsets of patients will be compared using appropriate tests based on number of groups and normality of distribution (e.g. Student's paired t-test, Wilcoxon signed rank, ANOVA). Normality will be assessed using the Shapiro Wilk test for continuous variables. " and "Differences between subsets of patients will be analyzed using the $\chi 2$ test, Fisher's exact test or Mcnemar's test as appropriate."	These testing are not applicable.
Version 2.0	2023-02-16	7.2 STATISTICAL ANALYSES	Definition of short-term responder has been updated to "those who are on first line therapy for up to 3 to 6 months" and the definition of long-term responder has been updated to "those who are on first line therapy for over 6 months." This update has been made throughout the document.	This change was requested by PPD as this is a more appropriate way of defining short- and long-term responders
Version 2.0	2023-02-16	8. LIST OF TABLES AND TABLE SHELLS	ESAS has been removed from all demographic and baseline characteristics tables.	As decided by PPD removing ESAS due to lack of reporting in the medical notes
Version 2.0	2023-02-16	8. LIST OF TABLES AND TABLE SHELLS	Footnote for table 12 and figures 18, 19 and 20 have been updated to "[a]Defined as treatments started before March 11, 2020 [b] Defined as treatments started on or after March 11, 2020"	Sentence has been updated to provide better clarity around the definition of before and during COVID-19

2 INTRODUCTION

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

Breast cancer is the main cause of cancer death in women worldwide, with hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) tumours being the most commonly diagnosed. Endocrine therapy is a mainstay of breast cancer treatment. In the PALOMA clinical trials, adding Palbociclib resulted in greater median progression free survival (PFS) than endocrine therapy alone. Since its approval in Canada in 2016, Palbociclib has been used in patients with HR+/HER2- advanced/metastatic breast cancer (ABC/MBC), but little is known about its real-world use and clinical outcomes in a Canadian setting.

2.1 STUDY DESIGN

This study will be a retrospective chart review of structured and unstructured data from EHRs stored at Sinai Health. Pentavere's DARWEN™ technology will be trained to extract data variables from the structured and unstructured EHR data (Table 1). CCI [redacted] *. Once the data variables are extracted from the EHRs, descriptive analyses will be conducted.*

Data extracted will include Study population

The study period will extend from 01 January 2016 to 01 October 2021 (Figure 1). All female patients who are ≥18 years of age and are diagnosed with HR+/HER2- ABC/MBC and received a CDK4/6 inhibitor at Sinai Health during the study period will be included in the study. It is estimated that there will be approximately 300 diagnoses of MBC within the study period at Sinai Health, of which approximately 180 will be HR+/HER2-. Follow-up data from EHRs will be included up to the extent that they are available within the study period. Pre-index data (stage at initial breast cancer diagnosis, treatment being received at ABC/MBC diagnosis) may be extracted from EHRs up to 12 months before the index date.

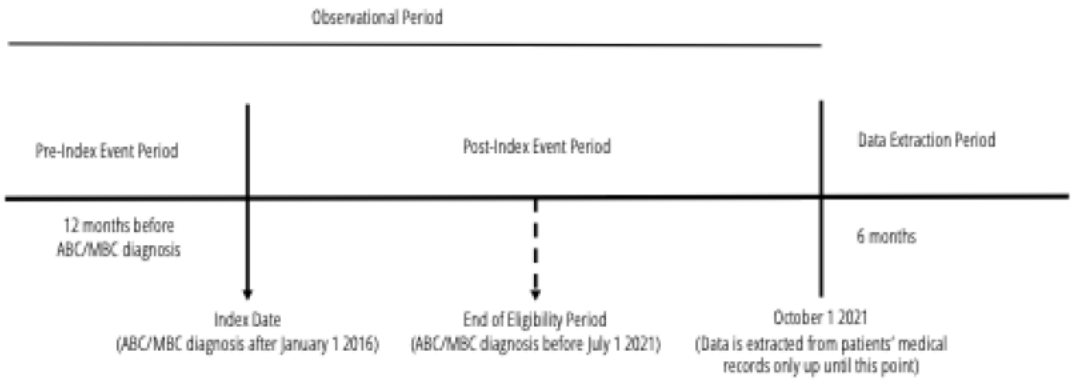


Figure 1. Study Design Flow Chart

Data source

Patients will be selected with dates of diagnosis of HR+/HER2- ABC/MBC between 01 January 2016 and 01 July 2021. Study data will be extracted from Sinai Health EHRs up to 12 months before ABC/MBC diagnosis until the end of the study period (01 October 2021, Figure 1)

Treatment/cohort labels

1. Patients treated with Palbociclib combination treatment
2. Patients treated with CDK4/6 inhibitor.

2.2 STUDY OBJECTIVES

The following objectives are taken from the protocol:

Primary objective

- *To characterize real world treatment patterns among patients with HR+/HER2- ABC/MBC receiving palbociclib combination treatment (non-steroidal AI (NSAI) [letrozole or anastrozole], or fulvestrant)*

Secondary objectives

- *To determine pre- and post-CDK4/6i treatment patterns and sequencing in ABC/MBC patients.*

CCI [redacted]

- [redacted]
- [redacted]

[redacted]

3 HYPOTHESES AND DECISION RULES

3.1 STATISTICAL HYPOTHESES

The planned data analyses are descriptive in nature and are subject to modification based on sample size and final data specifications. No formal hypotheses will be tested.

3.2 STATISTICAL DECISION RULES

These studies are not powered to answer a formal hypothesis.

4 ANALYSIS SETS/POPULATIONS

4.1 FULL ANALYSIS SET

Inclusion criteria

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

1. *≥ 18 year old female*
2. *HR+/HER2- breast cancer diagnosis with confirmed metastatic or advanced disease*
3. *Diagnosed with ABC/MBC between 01 January 2016 and 01 July 2021*
4. *Treatment with CDK4/6 inhibitor*

Exclusion criteria

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

1. *Patient does not have ABC/MBC*
2. *Patient has indicated HR- or HER2+ status*
3. *Patient received a CDK4/6i as part of a clinical trial*

4.2 SAFETY ANALYSIS SET

Not applicable.

4.3 OTHER ANALYSIS SET

The primary objective will include only patients who received at least one dose of Palbociclib during the study period.

The secondary and CCI objectives will include all patients in the full analysis set.

4.4 SUBGROUPS

Subgroup analyses for the primary and secondary objectives will be conducted in patients who are potentially pre-menopausal, where possible. Patients who are 50 years old or younger and are on a LHRH antagonist will be included in this subgroup. Subgroup analyses will be descriptive in nature and will depend on adequate sample size.

The secondary objective will include the following subgroups for specified analyses, where possible:

- Pre-CDK subgroup is defined as ABC/MBC patients starting systemic therapy before the introduction of CDK 4/6 inhibitor (January 2016 to May 2016).
- Post-CDK subgroup is defined as ABC/MBC patients starting systemic therapy after the introduction of CDK 4/6 inhibitor (January 2019 to May 2019).

CCI

5 ENDPOINTS AND COVARIATES

5.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

CCI

CCI

- CCI [redacted]

5.2 SAFETY ENDPOINTS

Not applicable.

5.3 SAFETY ENDPOINTS

Not applicable.

CCI [redacted]

5.5 ENDPOINTS

Variable	*Role*	*Data source(s)*	*Operational definition*
Patient demographics	*Baseline characteristic, potential confounder, sub-group identifier*	*Patient EHR*	• *Date of birth* • *Sex* • *Date of death*
Clinical characteristics	*Baseline characteristic, potential confounder, sub-group identifier*	*Patient EHR*	• *Date of ABC/MBC diagnosis* • *Age at ABC/MBC diagnosis (years)* • *ECOG performance score at index date (0, 1, 2, 3, 4)* • *ESAS* • *Date of last follow-up* • *Organ level metastatic sites (bone, brain, lungs, liver; number of sites)* • *Tumour stage at initial breast cancer diagnosis (I, II, III, IV, Unknown)* • *Tumour grade*

			• *Tumour histology* • *ER and PR receptor status (Positive, Negative, Unknown)* • *HER2 status (Positive, Negative, Unknown)* • *Concomitant LHRH agonists*
Comorbidities	*Baseline characteristic, potential confounder, sub-group identifier*	*Patient EHR*	• *Atrial fibrillation* • *Hypertension* • *Coronary Artery Disease/Myocardial infarction/Angina* • *Diabetes Mellitus* • *Stroke*
Treatments	*Exposure*	*Patient EHR*	• *Systemic Therapies (therapy start and stop date including combination therapies, and line of therapy)* • *Surgeries* • *Radiation Treatment*
Clinical outcomes	*Outcome*	*Patient EHR*	• *TTNT1* • *TTNT2* • *TTC* • *Overall Survival (landmark 3y)*

ECOG, Eastern Cooperative Oncology Group; EHR, Electronic Health Record; ER, Estrogen Receptor; ESAS, Edmonton Symptom Assessment System; HER2, Human Epidermal Receptor Growth Factor 2; LHRH, Luteinizing Hormone-Releasing Hormone; PR, Progesterone Receptor; TTC, time from date of ABC/MBC diagnosis to starting chemotherapy; TTNT1, length of treatment for the first line; TTNT2, length of treatment for the second line

6 HANDLING OF MISSING VALUES

For categorical variables, the number of missing responses will be shown as a separate category in the analysis. For continuous variables, the number of non-missing observations will be presented. Limited use of imputation methods will be used for missing dates. For instance, if the month and year are present for a date, then "15" would be input as the date to create a complete observation. Excluding dates, no other imputation methods will be used for missing or incomplete data.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

The following analyses are expected to be conducted in R.

Analyses for continuous Data

Continuous variables will be described by the number of patients with valid/non-missing observations using mean, standard deviation (SD), quantiles (Q1, median, Q3), minimum and maximum.

Analyses for Categorical Data

Categorical variables will be described by frequencies and related percentages.

Analyses for time to event end points.

Time to event variables will be analyzed using Kaplan-Meier curves (TTNT1, TTNT2, TTC, OS). Numbers at risk and cumulative incidence will be reported for each curve.

7.2 STATISTICAL ANALYSES

Treatment patterns and changes:

Treatment patterns among patients with HR+/HER2- ABC/MBC receiving Palbociclib will be analysed as the primary objective of this study. This analysis will be conducted in all patients who have received Palbociclib combination treatment. Subgroup analyses on patients who are likely to be pre-menopause might also be conducted if applicable. This analysis will be descriptive in nature and is subject to modification based on sample size and final data specifications. No statistical tests will be utilized. Continuous and categorical variables will be described using methods outlined in Section 7.1 of this document. Sankey diagrams and/or bar charts may also be used to illustrate sequencing and changes in treatment patterns if appropriate. The above-mentioned analyses will use the following or similar R packages: 'tables', 'ggplot', and 'networkD3'.

Type	Objective	Endpoint	Population	Statistical Method/Test	Covariates used	Method of adjustment for missing values	Role of the analysis related to study objectives
Table	1	Not applicable	- All patients who have received Palbociclib	Descriptive stats	Systemic therapies	Missing data will be summarized in table.	To describe treatment patterns during

			combination treatment. - Pre-menopausal patients[a]			Missing days from dates will be handled as per section 6 of this document.	study period.
Bar chart	1	Not applicable	- All patients who have received Palbociclib combination treatment. - Pre-menopausal patients[a]	Descriptive stats	Systemic therapies	Missing data will be excluded. Missing days from dates will be handled as per section 6 of this document.	To illustrate changes in treatment patterns by year.
Sankey diagram	1	Not applicable	- All patients who have received Palbociclib combination treatment. - Pre-menopausal patients[a]	Descriptive stats	Systemic therapies	Missing data will be excluded. Missing days from dates will be handled as per section 6 of this document.	To illustrate sequencing of treatments.

[a] Patients who are potentially pre-menopausal may be analyzed as a subgroup for this objective. Please refer to section 4.4 of this document for further details about how this group is defined.

Pre- and Post-CDK treatment patterns:

Describing pre- and post-CDK treatment patterns and sequencing in ABC/MBC patients is one of the secondary objectives of this study. To explore treatment patterns and sequencing before the introduction of CDK4/6 inhibitor ("pre-CDK" subgroup), ABC/MBC patients diagnosed and starting systemic therapy before the introduction of Palbociclib in Canada (i.e. January 2016 to May 2016) will be investigated. To explore treatment patterns and sequencing after introduction of CDK4/6 inhibitors, a similar length of time (i.e. January – May) will be investigated; however, this will be done in 2019 to allow for sufficient time for education and uptake of CDK4/6 inhibitor usage in

clinical practice ("post-CDK" subgroup). The above dates are the time periods we propose based on clinical relevance, but they are contingent upon clinician input and review of primary objective results and are subject to change.

Treatment patterns for systemic therapy for the pre-CDK subgroup and post-CDK subgroup will be described. Sequencing of therapies received after CDK treatment will be described. Continuous and categorical variables will be described using methods outlined in Section 7.1 of this document. Bar charts may also be used to illustrate changes in treatment patterns over time if appropriate. The above-mentioned analyses will use the following or similar R packages: 'tables' and 'ggplot'.

Type	**Supports Protocol Objective Number**	**Endpoint**	**Population**	**Statistical Method/Test**	**Covariates used**	**Method of adjustment for missing values**	**Role of the analysis related to study objectives**
Table	2	Not applicable	-Pre-CDK subgroup -Post-CDK subgroup	Descriptive stats Comparisons tests (e.g. t-test, ANOVA, Wilcoxon, Fischer)	Systemic therapies	Missing data will be summarized in table. Missing days from dates will be handled as per section 6 of this document.	To describe treatment patterns pre and post CDK.
Bar chart	2	Not applicable	-Pre-CDK subgroup -Post-CDK subgroup	Descriptive stats	Systemic therapies	Missing data will be excluded. Missing days from dates will be handled as per section 6 of this document.	To illustrate treatment patterns over time.

Time to event analysis:

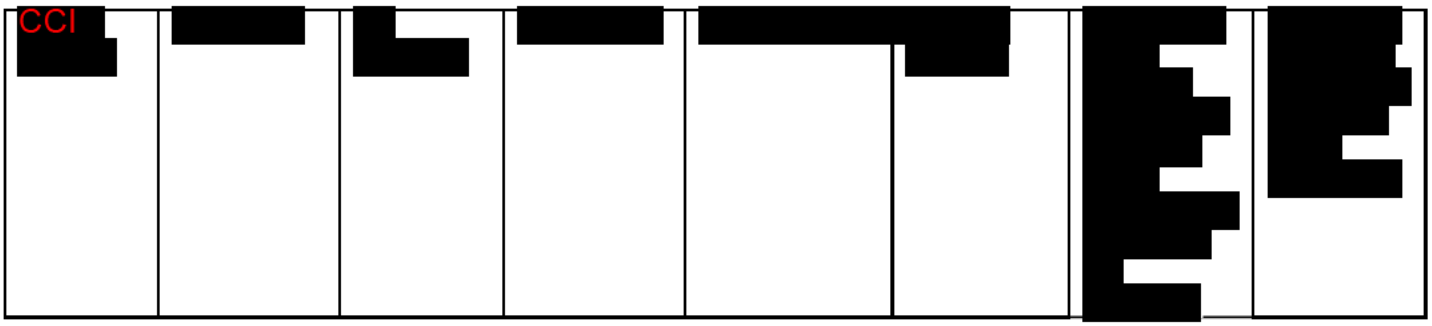
CCI [redacted] Numbers at risk and cumulative incidence will be reported for each curve. CCI [redacted] if deemed necessary, to explore differences between variables such as clinical characteristics, baseline co-morbidities, types of treatments, lines of therapy, or 'responders' (i.e., patients who remained on treatment for 3 months or longer) and 'non-responders' (i.e., patients who remained on treatment for less than 3 months). Subgroup analyses may be conducted on pre-menopausal patients, if appropriate. Short term responders will be defined as those who are on first line therapy for up to 3 to 6 months and long term responders as those who are on first line therapy for over 6 months; the exact most appropriate definition will be defined after consulting with clinicians. The above-mentioned analyses will use the following or similar R packages: 'survminer' and 'tables'.

Type	Supports Protocol Objective Number	Endpoint	Population	Statistical Method/Test	Covariates used	Method of adjustment for missing values	Role of the analysis related to study objectives
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Patients who are potentially pre-menopausal are included in this subgroup. Please refer to section 4.4 of this document for further details about how this group is defined.

CCI

Type	Supports Protocol Objective Number	Endpoint	Population	Statistical Method/Test	Covariates used	Method of adjustment for missing values	Role of the analysis related to study objectives
CCI							



7.2.1 Safety Analyses

As this is a retrospective analysis, it is expected all adverse events will already have been reported at the time it was reported and thus safety analyses are not applicable for this study.

7.2.2 Summary of all Analyses

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroup	Statistical Method	Strata	Missing Data
Baseline Characteristics	All patients	1	None	Descriptive Stats	None	Missing data will be summarized in table. Missing days from dates will be handled as per section 6 of this document.
Treatment patterns	- All patients who have received Palbociclib combination treatment.	1	Pre-menopausal patients[a]	Descriptive stats, Bar charts, Sankey Diagram	None	Missing data will be summarized in table and excluded from figures. Missing days from dates will be handled as per section 6 of this document.
Treatment patterns and sequencing pre and post CDK	- All patients	2	-Pre-CDK subgroup	Descriptive stats,	None	Missing data will be summarized in table. Missing

			-Post-CDK subgroup	Bar charts,		days from dates will be handled as per section 6 of this document.
Treatment duration (TTNT1/TTNT2)	- All patients	Exploratory	Premenopausal patients[a]	KM Curve	Systemic therapies	Missing data will be excluded. Missing days from dates will be handled as per section 6 of this document.
Time to chemotherapy (TTC)	- All patients	Exploratory	Premenopausal patients[a]	KM Curve	Systemic therapies	Missing data will be excluded. Missing days from dates will be handled as per section 6 of this document.
Overall Survival	- All patients	Exploratory	Premenopausal patients[a]	KM Curve	Systemic therapies	Missing data will be excluded. Missing days from dates will be handled as per section 6 of this document.
Impact of COVID-19	- All patients	Exploratory	- Patients diagnosed one year before and within first year of the pandemic	Descriptive Stats, KM Curve, Bar charts, Sankey Diagram	None	Missing data will be excluded. Missing days from dates will be handled as per section 6 of this document.

[a] Patients who are potentially pre-menopausal are included in this subgroup. Please refer to section 4.4 of this document for further details about how this group is defined.

8 LIST OF TABLES AND TABLE SHELLS

PLEASE NOTE: The below tables and proposed analyses reflect the complete list of desired variables and analyses to be included in the study. However, inclusion of variables and type of analyses conducted will be dependent on availability of data from source documents and are subject to modification based on sample size and final data specifications.

Table 1: Demographics and Baseline characteristics of all patients and premenopausal patients.

Variables	Overall (N=)[a]	Premenopausal Patients (N=)[b]
Age		
N		
Mean (SD)		
Median		
Q1,Q3		
Minimum-Maximum		
Sex		
Female		
Male		
Unknown		
ECOG		
0		
1		
2		
3		
4		
Unknown		
Organ level metastatic site		
Bone		
Brain		
Lungs		
Liver		
Number of metastatic sites		
0		
1		
2		
3		
4		
Comorbidities		
Atrial fibrillation		
Hypertension		

Coronary Artery Disease/Myocardial infarction/Angina Diabetes Mellitus Stroke		
Tumour stage at diagnosis I II III IV Unknown		
Tumour grade 1 2 3 Unknown		
Tumour histology Lobular Carcinoma Ductal carcinoma Mixed DCIS LCIS Other Unknown		
ER Receptor status Positive Negative Unknown		
PR Receptor status Positive Negative Unknown		

[a] Includes all study patients

[b] Includes all study patients who are potentially in pre-menopause. Please refer to section 4.4 of this document for further details about how this group is defined.

Table 2: Demographics and Baseline characteristics of all Palbociclib treated patients and Palbociclib treated premenopausal patients.

Variables	**Palbociclib treated patients (N=)[a]**	**Premenopausal Patients (N=)[b]**

Age N Mean (SD) Median Q1,Q3 Minimum-Maximum		
Sex Female Male Unknown		
ECOG 0 1 2 3 4 Unknown		
Organ level metastatic site Bone Brain Lungs Liver		
Number of metastatic sites 0 1 2 3 4		
Comorbidities Atrial fibrillation Hypertension Coronary Artery Disease/Myocardial infarction/Angina Diabetes Mellitus Stroke		
Tumour stage at diagnosis I II III IV Unknown		
Tumour grade 1		

2		
3		
Unknown		
Tumour histology		
Lobular Carcinoma		
Ductal carcinoma		
Mixed		
DCIS		
LCIS		
Other		
Unknown		
ER Receptor status		
Positive		
Negative		
Unknown		
PR Receptor status		
Positive		
Negative		
Unknown		

[a] Includes patients who received Palbociclib treatment
[b] Includes patients who received Palbociclib treatment and who are potentially in pre-menopause. Please refer to section 4.4 of this document for further details about how this group is defined.

Table 3: Demographics and Baseline characteristics stratified by type of responder

Variables	**Short term responders (n=)[a]**	**Long term responders (n=)[b]**
Age		
N		
Mean (SD)		
Median		
Q1,Q3		
Minimum-Maximum		
Sex		

Female Male Unknown		
ECOG 0 1 2 3 4 Unknown		
Organ level metastatic site Bone Brain Lungs Liver		
Number of metastatic sites 0 1 2 3 4		
Comorbidities Atrial fibrillation Hypertension Coronary Artery Disease/ Myocardial infarction /Angina Diabetes Mellitus Stroke		
Tumour stage at diagnosis I II III IV Unknown		
Tumour grade 1 2 3 Unknown		
Tumour histology Lobular Carcinoma Ductal carcinoma Mixed		

DCIS LCIS Other Unknown		
ER Receptor status Positive Negative Unknown		
PR Receptor status Positive Negative Unknown		

[a] Defined as those who are on first line therapy for up to 3-6 months
[b] Defined as those who are on first line therapy for more than 6 months

Table 4: Demographics and Baseline characteristics stratified by pre and post CDK subgroups

Variables	**Pre-CDK[a] (N=)**	**Post CDK[b] (N=)**
Age N Mean (SD) Median Q1,Q3 Minimum-Maximum		
Sex Female Male Unknown		
ECOG 0 1 2 3 4 Unknown		
Organ level metastatic site Bone Brain Lungs Liver		
Number of metastatic sites 0 1		

2		
3		
4		
Comorbidities		
Atrial fibrillation		
Hypertension		
Coronary Artery Disease/Myocardial infarction/Angina		
Diabetes Mellitus		
Stroke		
Tumour stage at diagnosis		
I		
II		
III		
IV		
Unknown		
Tumour grade		
1		
2		
3		
Unknown		
Tumour histology		
Lobular Carcinoma		
Ductal carcinoma		
Mixed		
DCIS		
LCIS		
Other		
Unknown		
ER Receptor status		
Positive		
Negative		
Unknown		
PR Receptor status		
Positive		
Negative		
Unknown		

[a] Defined as treatment started between January 2016-May 2016
[b] Defined as treatment started between January 2019- May 2019

Table 5: Demographics and Baseline characteristics stratified by time of diagnosis.

Variables	Before COVID-19[a] (N=)	During COVID-19[b] (N=)

Age N Mean (SD) Median Q1,Q3 Minimum-Maximum		
Sex Female Male Unknown		
ECOG 0 1 2 3 4 Unknown		
Organ level metastatic site Bone Brain Lungs Liver		
Number of metastatic sites 0 1 2 3 4		
Comorbidities Atrial fibrillation Hypertension Coronary Artery Disease/Myocardial infarction/Angina Diabetes Mellitus Stroke		
Tumour stage at diagnosis I II III IV Unknown		
Tumour grade 1		

2 3 Unknown		
Tumour histology Lobular Carcinoma Ductal carcinoma Mixed DCIS LCIS Other Unknown		
ER Receptor status Positive Negative Unknown		
PR Receptor status Positive Negative Unknown		

[a] Defined as patients who were diagnosed between March 10, 2019 – March 10, 2020.
[b] Defined as patients who were diagnosed between March 11, 2020-March 11, 2021.

Treatment patterns and changes:

Table 6: Line 1 Treatment Patterns in patients who received Palbociclib

Variables	**Overall (N=)[a]**	**Pre-menopausal patients (N=)[b]**
Chemotherapy N, Mean Tx duration (SD)		
Chemo drug 1, n (%)		
Chemo drug 2, n (%)		
…		
Targeted therapy N, Mean Tx duration (SD)		
Targeted drug 1, n (%)		
Targeted drug 2, n (%)		
…		
…(Any other Class of therapy observed)		

[a] Includes all patients who received Palbociclib

[b] Includes patients who received Palbociclib and who are potentially in pre-menopause. Please refer to section 4.4 of this document for further details about how this group is defined.

Treatment patterns and changes in patients who received Palbociclib:

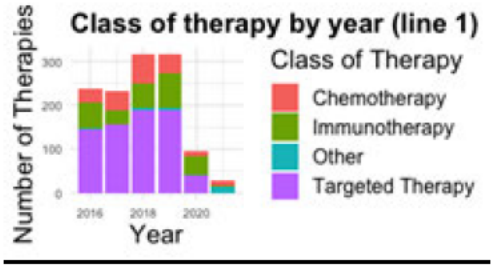


Figure 1: Classes of treatments over time in patients who received Palbociclib. Similar plots will be created for all lines of therapy. Stacked bar charts can be either absolute values (as shown) or percentages, as required.

Sankey Diagram

Figure 2: Sankey Diagram of treatment of patients who received Palbociclib

Treatment patterns and changes in patients who received Palbociclib who are potentially in pre-menopause.

Bar charts

Figure 3: Classes of treatments over time in patients who received Palbociclib who are potentially in pre-menopause. Please refer to Figure 1 for reference as to how bar charts will look. Similar plots will be created for all lines of therapy.

Sankey Diagram

Figure 4: Sankey Diagram of treatment of patients who received Palbociclib who are potentially in pre-menopause

Pre and Post-CDK treatment patterns:

Table 7: Pre and post-CDK treatment patterns and sequencing in patients

	Pre-CDK[a]			Post-CDK[b]		
	Line 1	**Line 2**	**Line 3**	**Line 1**	**Line 2**	**Line 3**
Chemotherapy N, Mean Tx duration (SD)						
Chemo type 1, n (%)						
Chemo type 2, n (%)						
…						
Targeted therapy N, Mean Tx duration (SD)						
Targeted type 1, n (%)						
Targeted type 2, n (%)						
…						
…						

[a] Defined as treatment started between January 2016-May 2016
[b] Defined as treatment started between January 2019- May 2019

Table 8: Sequencing of therapies after CDK 4/6 inhibitor

	Overall (N=)
Post-CDK received in L1	
Medicinal product name 1, n (%)	
Medicinal product name 2, n (%)	
…	
Post-CDK received in L2	
Medicinal product name 1, n (%)	
Medicinal product name 2, n (%)	
…	
Post-CDK received in L3	
Medicinal product name 1, n (%)	
Medicinal product name 2, n (%)	
…	

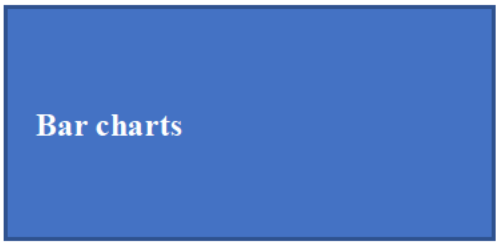


Figure 5: Classes of treatments over time in all patients. Please refer to Figure.1 for reference as to how bar charts will look. Similar plots will be created for all lines of therapy.

Time to event analyses in all patients:

Figure 6: TTNT1 in all patients by type of treatment

Figure 7: TTNT2 in all patients by type of treatment

Figure 8: TTC in all patients by type of treatment

Figure 9: Overall Survival in all patients by type of treatment

Table 9: Length of Line 1 treatment in short term vs long term responders

Variables	Short term responders (n=)[a]	Long term responders (n=)[b]
Chemotherapy N, Mean Tx duration (SD)		
Chemo type 1 N Mean (SD) Median Q1,Q3 Minimum-Maximum		
Chemo type 2 N Mean (SD) Median Q1,Q3 Minimum-Maximum		
…		
Targeted therapy N, Mean Tx duration (SD)		
Targeted type 1 N Mean (SD) Median Q1,Q3 Minimum-Maximum		
Targeted type 2 N Mean (SD) Median Q1,Q3 Minimum-Maximum		
…		

[a] Defined as those who are on first line therapy for up to 3 to 6 months
[b] Defined as those who are on first line therapy for more than 6 months

Time to event analyses in pre-menopausal patients:

Figure 10: TTNT1 in patients who are potentially in pre-menopause by type of treatment

Figure 11: TTNT2 in patients who are potentially in pre-menopause by type of treatment

Figure 12: TTC in patients who are potentially in pre-menopause by type of treatment

Figure 13: Overall Survival in patients who are potentially in pre-menopause by type of treatment

Table 10: Length of Line 1 treatment in short term vs long term responders in pre-menopausal patients[a]

Variables	Short term responders (n=)[b]	Long term responders (n=)[c]
Chemotherapy N, Mean Tx duration (SD)		
Chemo type 1 N Mean (SD) Median Q1,Q3 Minimum-Maximum		
Chemo type 2 N Mean (SD) Median Q1,Q3 Minimum-Maximum		
…		
Targeted therapy N, Mean Tx duration (SD)		
Targeted type 1 N Mean (SD) Median Q1,Q3 Minimum-Maximum		
Targeted type 2 N Mean (SD) Median Q1,Q3 Minimum-Maximum		
…		
…		

[a] Includes patients who are potentially in pre-menopause. Please refer to section 4.4 of this document for further details about how this group is defined.
[b] Defined as those who are on first line therapy for up to 3 to 6 months
[c] Defined as those who are on first line therapy more than 6 months

Impact of COVID-19:

Treatment patterns in patients who were diagnosed before and during COVID-19:

Table 11: Treatment patterns in patients diagnosed before and during COVID-19.

	Before COVID-19[a]	**During COVID-19[b]**
Total visits from treatment, n		
Total visits from surgeries, n		
Total visits from radiation, n		
Total number of ABC/MBC diagnoses, n		
Average duration between date of diagnosis and line 1 treatment initiation. N Mean (SD) Median Q1,Q3 Minimum-Maximum		
Class and type of therapy initiated for Line 1 treatment.		
Chemotherapy N, Mean Tx duration (SD)		
Chemo type 1, n (%)		
Chemo type 2, n (%)		
…		
Targeted therapy N, Mean Tx duration (SD)		
Targeted type 1, n (%)		
Targeted type 2, n (%)		
…		
…		

[a] Defined as patients who were diagnosed between March 10, 2019 – March 10, 2020.
[b] Defined as patients who were diagnosed between March 11, 2020-March 11, 2021.

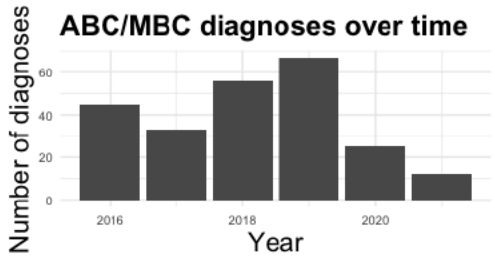


Figure 14: Number of MBC diagnoses over time (example graph).

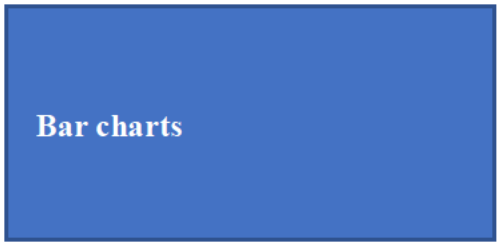


Figure 15: Classes of treatments in all patients who were diagnosed 1 year before and 1 year during COVID-19. Please refer to Figure.1 for reference as to how bar charts will look. Similar plots will be created for all lines of therapy.

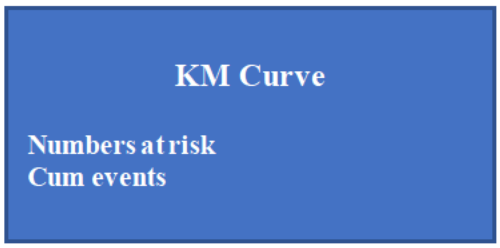


Figure 16: TTNT1 in patients who were diagnosed 1 year before and 1 year during COVID-19.

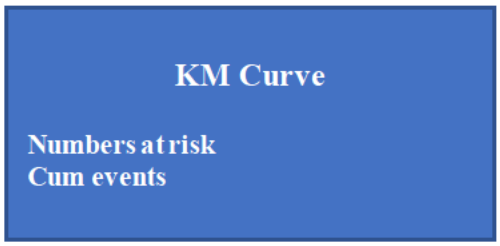


Figure 17: Overall survival in patients who were diagnosed 1 year before and 1 year during COVID-19.

Treatment patterns in patients who were treated before and during COVID-19:

Table 12: Treatment patterns before and during COVID-19

	Before COVID-19[a]			During COVID-19[b]		
	Line 1	**Line 2**	**Line 3**	**Line 1**	**Line 2**	**Line 3**
Chemotherapy N, Mean Tx duration (SD)						
Chemo type 1, n (%)						
Chemo type 2, n (%)						
…						
Targeted therapy N, Mean Tx duration (SD)						
Targeted type 1, n (%)						
Targeted type 2, n (%)						

[a] Defined as treatments started before March 11, 2020
[b] Defined as treatments started on or after March 11, 2020

Sankey Diagram (before COVID-19)[a]

Figure 18: Treatment patterns before COVID-19[a].
[a] Defined as treatments ending before March 11, 2020

Sankey Diagram (During COVID-19)[a]

Figure 19: Treatment patterns during COVID-19[a].
[a] Defined as treatments started on or after March 11, 2020

KM Curve

Numbers at risk
Cum events

Figure 20: TTNT1 in patients who started first line treatments before (before March 11, 2020) and during COVID-19 (on or after March 11, 2020).

9 REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2021.
2. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2019 [Internet]. Toronto, ON: Canadian Cancer Society; 2019 September [cited 2021 February 10]. Available from: cancer.ca/Canadian-Cancer-Statistics-2019-EN
3. Canadian Cancer Society. Survival Statistics for Breast Cancer [Internet]. Canadian Cancer Society. [cited 2021 February 10]. Available at: https://www.cancer.ca/en/cancer-information/cancer-type/breast/prognosis-and-survival/survival-statistics/?region=ab
4. Dai X, Xiang L, Li T, Bai Z. Cancer hallmarks, biomarkers and breast cancer molecular subtypes. Journal of Cancer. 2016;7(10):1281.
5. McCain J. First-in-class CDK4/6 inhibitor palbociclib could usher in a new wave of combination therapies for HR+, HER2− breast cancer. Pharmacy and Therapeutics. 2015;40(8):511.
6. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S, Gauthier E. Palbociclib and letrozole in advanced breast cancer. New England journal of medicine. 2016;375(20):1925-36.
7. Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, Harbeck N, Loibl S, Huang Bartlett C, Zhang K, Giorgetti C. Palbociclib in hormone-receptor–positive advanced breast cancer. New England Journal of Medicine. 2015;373(3):209-19.
8. Pfizer. IBRANCE Product Monograph [Internet]. 2021 July 15 [cited 2021 October 10]. Available at: https://www.pfizer.ca/pm/en/IBRANCE.pdf
9. Petch J, Batt J, Murray J, Mamdani M. Extracting Clinical Features From Dictated Ambulatory Consult Notes Using a Commercially Available Natural Language Processing Tool: Pilot, Retrospective, Cross-Sectional Validation Study. JMIR Med Inform. 2019;7(4):e12575.

10 APPENDICES

10.1 APPENDIX 1: DATA DERIVATION DETAILS

Age at diagnosis: Age in years rounded down to nearest whole year

- Date of diagnosis – Date of birth)

Menopause status: Potential menopause status at diagnosis

- Patients ≤50 years old and on a LHRH antagonist may potentially be in pre-menopause.

A1.1 Definition and use of visit windows in reporting

A1.2 Further definition of endpoints

10.2 APPENDIX 2: ADDITIONAL STATISTICAL METHODOLOGY DETAILS

A2.1 Further Details of the Statistical Methods

10.3 APPENDIX 3: DIAGNOSIS AND PROCEDURE CODES USED IN THE STUDY