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

Study information

Title	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
Protocol number	A5481178
Protocol version identifier	Version 3.0
Date	13 February 2023
Active substance	Palbociclib
Medicinal product	Palbociclib (IBRANCE®; PD-0332991)
Research question and objectives	To describe the current treatment patterns, changes over time, and clinical outcomes of adult female patients receiving palbociclib combination treatments for metastatic breast cancer in a Canadian real world setting, including demographic and clinical characteristics. Primary objective • To characterize real world treatment patterns among patients with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2-) - advanced/metastatic breast cancer (ABC/MBC) receiving palbociclib combination treatment

	Secondary objectives • To determine pre- and post- Cyclin-dependent kinase (CDK) 4/6i treatment patterns and sequencing in ABC/MBC patients CCI [redacted]
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC/MBC	Advanced/metastatic breast cancer
AE	Adverse events
AEM	Adverse event monitoring
AI	Aromatase Inhibitor
CDK	Cyclin-dependent kinase
CDK4/6	Cyclin-dependent kinase 4 and 6
CI	Confidence Interval
COVID-19	COronaVIrus Disease 2019
CSV	Comma separated values
ECOG	Eastern Cooperative Oncology Group
EHR	Electronic health record
EMR	Electronic Medical Record
ER	Estrogen Receptor
GPP	Guidelines for Good Pharmacoepidemiology Practices
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
IEC	Independent ethics committee
IRB	Institutional review board
IRIS	Ibrance Real world Insights Study

ISPE	International Society for Pharmacoepidemiology
LHRH	luteinizing hormone-releasing hormone
NIS	Non-interventional study
NLP	Natural language processing
NSAI	Non steroidal aromatase inhibitor
OS	Overall survival
PFS	Progression Free Survival
PR	Progesterone receptor
RCT	Randomized clinical trial
SABCS	San Antonio Breast Cancer Symposium
SD	Standard deviation
TTNT1	Length of treatment for the first line
TTNT2	Length of treatment for the second line
TTC	Time from date of ABC/MBC diagnosis to starting chemotherapy
SAP	Statistical analysis plan
VM	Virtual machine
YRR	Your reporting responsibility

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD MD PhD FRCPC	Medical Oncologist and Director of the PPD and Medical Director of the Cancer Program for PPD		PPD
PPD , PhD	Medical Advisor (Oncology)		PPD
PPD PharmD	Medical Advisor (Oncology)		PPD
PPD MPH	Clinical Progam Lead		PPD

4. ABSTRACT

Title: 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.

Version 3.0

Date of the abstract: 13 February 2023

Main Author and affiliation:
PPD

Rationale and background: 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.

Research question and objectives: The primary objective of this study is to explore patient demographics, clinical characteristics, treatment patterns and changes, and clinical outcomes of adult female patients with HR+/HER2- ABC/MBC in Canada, who received a CDK4/6i based therapy for their ABC/MBC.

Study design, study size, and population: This study will be a retrospective chart review of patient records from Sinai Health based cancer clinics. All records from female patients ≥18 years old with HR+/HER2- ABC/MBC diagnosed at this site between 01 January 2016 and 01 July 2021 will be used. It is estimated that there will be approximately 300 diagnoses of ABC/MBC within the study period at Sinai Health, approximately 180 of which will be HR+/HER2-. Only patients who have taken a CDK4/6 inhibitor in combination with an endocrine therapy will be included in this study. Using electronic health records (EHRs) stored within Sinai Health, natural language processing (NLP) algorithms (ie, Pentavere's DARWEN™ technology) will be trained to extract data variables from the EHR data.

Variables and data sources: NLP algorithms will be trained to extract data relevant to patient demographics, treatment patterns, treatment changes, and clinical outcomes. These variables will be extracted from structured and unstructured EHR data. The data variable rules and definitions will be developed in collaboration with Sinai Health clinicians. The use of NLP as a method of chart review is more efficient and cost-effective than manual review.

Data analysis: All analyses will be descriptive in nature and all subject to modification based on sample size and final data specifications. No inferential statistical analyses will be conducted. Categorical variables will be described using the number of observations and

number and percent (%) in each category. Numeric variables will be described using the number of observations, mean and standard deviation, and minimum, maximum, median and interquartile range. Treatment patterns and changes over time of patients on Palbociclib will be reported. Time to event will be described using an unadjusted Kaplan-Meier chart and the survival median.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Version 3.0	13 February 2023	Section: STUDY INFORMATION	**Change of protocol version identifier** from "*version 2.0*" to "*version 3.0*" and **the date** from "*12 November 2021*" to "*13 February 2023*" **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)…*" **Change of "The authors"** section, the author and contact information of PPD, PhD Director of Clinical Operations and Head Scientist, PPD PPD is replaced by PPD, MPH, Clinical Program Lead, PPD [redacted]	The changes in the study information section are driven by the study protocol amendment. 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); 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 Change of staff at Pentavere (vendor) occurred: PPD [redacted]

			This latter change also applies to the section **3. Responsible Parties**	
Version 3.0	13 February 2023	Section: LIST OF ABBREVIATIONS	Changed the definition of TTC from "Time from date CDK4/6 treatment to starting chemotherapy" to "time from date of ABC/MBC to starting chemotherapy"	This change was requested by PPD as this is a more appropriate way of deriving TTC
Version 3.0	13 February 2023	Section 4: ABSTRACT	Change from: **"Version 2.0, Date of the abstract:** 12 November 2021, PPD " To: "**Version 3.0, Date of the abstract:** 13 February 2023, PPD In the **Data analysis** section, first sentence changed from "*Data analysis:* All analyses will be descriptive in nature." to: "*Data analysis:* All analyses will be descriptive in nature and all subject to modification based on sample size and final data specifications"	These changes in the abstract section are driven by the study protocol amendment. This change is to provide further clarity on the conduction of data analyses.
Version 3.0	13 February 2023	Section 6: MILESTONES	Change of date for **Start of study collection** from "*31 January 2021*" to "*12 October 2022*" Change of date for **End of data collection** from "*30 June 2022*" to "*31 March 2023*" Change of date for **Data summary report** from "*28 February 2022*" to "*15 April 2023*" Change of date for **Interim report** from "*29 April 2022*" to "*31 May 2023*" Change of date for **Final study report** from "*31 August 2022*" to "*30 June 2023*"	Dates of original planned milestones had become obsolete due to significant delays, so the new milestones dates better reflect the new anticipated milestones.
Version 3.0	13 February 2023	Section *8:* RESEARCH QUESTION AND OBJECTIVES	Deletion of the following **secondary objectives** : "*To evaluate efficacy of current treatment for Canadian breast cancer patients using surrogates for time to next treatment in real-world setting including:* *o The length of treatment for the first line (TTNT1), the length of treatment for the second line (TTNT2), the time from date of ABC/MBC*	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); CCI [redacted]

			diagnosis to chemotherapy (TTC) and overall survival (OS) *o The length of treatment for short term versus long term responders"* CCI [redacted]	
Version 3.0	13 February 2023	Section 9.7: DATA ANALYSIS	Sentence "The planned data analyses are descriptive in nature." was updated to "The above planned data analyses are descriptive in nature and all subject to modification based on sample size and final data specifications"	This change is to provide further clarity on the conduction of data analyses.

6. MILESTONES

Milestone	Planned date
Start of data collection	12 October 2022
End of data collection	31 March 2023
Data Summary Report	15 April 2023
Interim report	31 May 2023
Final study report	30 June 2023

7. RATIONALE AND BACKGROUND

As the most common cancer diagnosis globally, breast cancer accounts for 1 in 4 cancer cases and 1 in 6 cancer deaths in females. In 2020, breast cancer resulted in 685,000 deaths making it the fifth leading cause of cancer deaths worldwide (1). In Canada, the age-standardized mortality rate for breast cancer has declined 48% since the 1980s, likely due to improved screening and available therapies (2). Despite this downward trend in mortality, 5 year survival rates are very different between those with stage 0-I (100%), stage II (93%), and stage III (72%) breast cancer and those with stage IV breast cancer (22%) (3).

Greater knowledge of breast cancer heterogeneity has resulted in the use of subtype classification to more accurately manage disease. Breast tumours are classified according to their expression of hormone receptors (HR) and human epidermal growth factor receptor 2 (HER2) (4). Most prevalent in breast cancer classification is HR status, by which tumours that grow in the presence of estrogen and progesterone are classified as HR positive (HR+). HR+

tumours generally respond better to endocrine therapy and people with these tumours have higher overall survival (OS) than those that are HR negative (HR-) (4). Together with HR status, HER2 status is an important feature of tumour classification, with HER2+ tumours having worse prognosis than HER2- tumours. HR+/HER2- tumours are the most commonly diagnosed subtype of breast cancer and respond well to endocrine therapy (4).

Endocrine therapies, such as letrozole and fulvestrant, are a mainstay of HR+ breast cancer treatment, sometimes in combination with other therapies. The PALOMA-1 trial evaluated palbociclib, a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, in combination with letrozole in patients with HR+/HER2-ABC/MBC. Palbociclib combination therapy with letrozole demonstrated median progression-free survival (PFS) of 20.2 months versus 10.2 months in patients receiving letrozole and placebo (5). These results were confirmed by the success of the phase III PALOMA-2 study, in which palbociclib and letrozole combination treatment demonstrated greater median PFS than letrozole and placebo (24.8 months and 14.5 months, respectively) (6). In cases of disease progression despite initial endocrine therapy, the PALOMA-3 trial demonstrated that palbociclib combination with fulvestrant resulted in median PFS of 9.2 months compared to 3.8 months in those receiving fulvestrant and placebo (4,7). Currently, palbociclib is indicated for use in combination with any aromatase inhibitor or fulvestrant for those with HR+/HER2- ABC/MBC (8).

Understanding the effectiveness of new treatments in a diverse clinical practice as a complement to randomized clinical trial (RCT) data is important as this provides evidence of the clinical benefit of these treatments in a more heterogeneous population with comorbid conditions and variations in care delivery seen in routine clinical practice. Real-world outcomes for patients with ABC/MBC who were treated with palbociclib in combination with an aromatase inhibitor (AI) or fulvestrant have been reported in several publications and at medical congresses. A comparative effectiveness analysis of palbociclib + letrozole versus letrozole alone was presented at the San Antonio Breast Cancer Sympoisum (SABCS) 2019 congress and subsequently published. Using the Flatiron Health Analytics Database, a total of 1,430 female patients with HR+/HER2-MBC in the first-line setting were included in the analysis demonstrating in an adjusted HR for PFS of 0.58 (95% confidence interval(CI), 0.49-0.69; $P < 0.0001$), and an adjusted HR for OS of 0.66 (95% CI, 0.53-0.82; $P = 0.0002$) (9). From a Canadian perspective, another study reported on the Ibrance® Real World Insights Study (IRIS) involving medical chart review of 247 patients with ABC/MBC treated with palbociclib in combination with either AI (n=212) or fulvestrant (n=33) (10). The 12-month progression-free rate was 90.3% for patients treated with palbociclib + AI and and the 6-month progression free survival rate was 91% for those treated with palbociclib + fulvestrant. The 12-month survival rates were 95.6% for palbociclib + AI and 100% for palbociclib + fulvestrant (10).

Palbociclib has been used in Canada since its initial approval by Health Canada in 2016, and there remains a need to better understand treatment patterns and outcomes in practice for Canadian patients with a longer follow-up. Real world data is necessary to understand these

trends and subsequent clinical outcomes to inform future treatment decisions in the HR+/HER- ABC/MBC population.

8. RESEARCH QUESTION AND OBJECTIVES

To describe current treatment patterns, changes over time, and clinical outcomes of adult female patients receiving palbociclib combination treatments for metastatic breast cancer in a Canadian real world setting, including demographic and clinical characteristics.

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

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9. RESEARCH METHODS

9.1. 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). The data variable rules and definitions will be pre-defined in collaboration with Sinai Health clinicians. Once the data variables are extracted from the EHRs, descriptive analyses will be conducted.

Data extracted will include characteristics of the patient population, comorbidities, treatment sequence, and treatment outcomes of those with HR+/HER2- ABC/MBC receiving palbociclib combination therapy.

9.2. Setting

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 ABC/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.

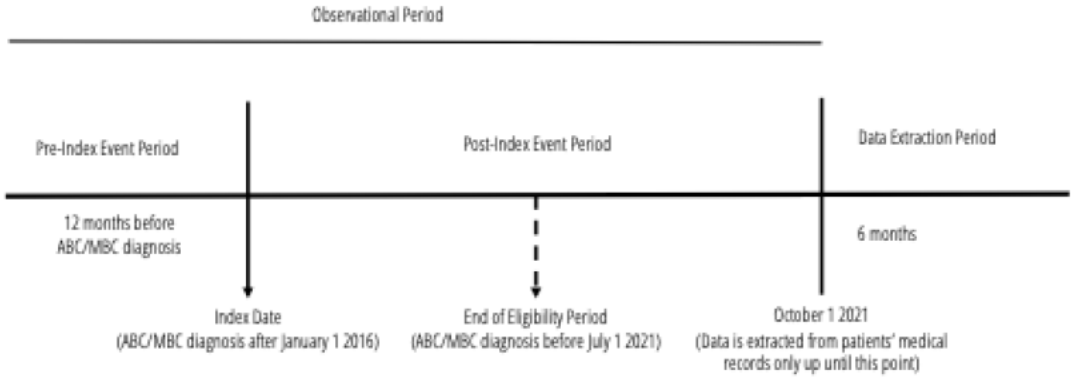

Figure 1. Study Design Flow Chart

9.2.1. 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

9.2.2. 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

9.3. Variables

Table 1. List of study variables to be extracted (where feasible)

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 to starting chemotherapy; TTNT1, length of treatment for the first line; TTNT2, length of treatment for the second line

9.4. Data sources

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).

9.5. Study size

All female patients who are ≥18 years of age and are diagnosed with HR+/HER2- ABC/MBC at Sinai Health during the study period will be included in the study. It is estimated that there will be approximately 300 diagnoses of ABC/MBC within the study period at Sinai Health, of which approximately 180 will be HR+/HER2-. All analyses are descriptive in nature and so sample size calculations are not applicable.

9.6. Data management

At Sinai Health's direction, DARWEN™ shall run in a secure environment that meets Siniai Health's IT and privacy requirements. DARWEN™ engine structures data optionally on a compute cluster, using models supported/reinforced, if needed, through additional training on Sinai Health data. DARWEN™ engine outputs patient-level data which can be structured as a Comma separated values (CSV) on the VM.

Data extracted from Sinai Health EHRs and curated by DARWEN™ will be retained by Sinai Health for research purposes in a row and column dataset in the file-type/format of their choosing. Sinai Health retains all ownership and rights to the data.

Pentavere will provide Pfizer with aggregate data following Sinai Health's approval. Aggregate data will be sent to Pfizer directly from Sinai Health by Pentavere when directed to do so by Sinai Health, and, if requested, a secured share drive can be created for data storage and transfer. Pentavere will comply with Sinai Health procedures regarding content, archiving, records management of process documents, and electronic transfer of these aggregate data.

9.6.1. Case report forms/Data collection tools/Electronic data record

As described above, data extracted from Sinai Health EHRs and curated by DARWEN™ compliant process will result in de-identified aggregated patient data.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the third party responsible (Sinai Health/Pentavere) agrees to keep records, including the identity of all participating patients, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting

minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 25 years after completion or discontinuation of the study, as required by Health Canada's regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment. Statistical analyses will be performed by PPD. The data will be analyzed using R (version and packages will be detailed in final SAP).

Descriptive analyses will be performed to summarize patients' baseline characteristics and outcomes of interest across the study cohort. Continuous variables will be described by the number of patients with valid/non-missing observations using mean, standard deviation (SD), minimum, maximum and quantiles (Q1, median, Q3). Categorical variables will be described by frequencies and related percentages. Number of missing observations will be reported for all variables. Time to event will be described using unadjusted Kaplan-Meier chart that will visually estimate the distribution of times to some events (i.e. progression), and will take into account those patients for which the event has not as yet occurred. Numbers at risk, cumulative incidence and survival medians will be reported for each curve. Endpoint definitions and how patients are censored for each endpoint will be further described in the SAP. Visualizations may be used to further describe treatment patterns, patient journeys, and other outcomes of interests if appropriate. The above planned data analyses are descriptive in nature and all subject to modification based on sample size and final data specifications. No inferential statistical analyses will be conducted.

Missing data will be excluded on a case by case basis and will not be imputed. This will mean that each table will not necessarily be based on the same number of patients.

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9.8. Quality control

Study data variables specified in this protocol will be extracted, where available, from the site's EHR into row and column datasets by Pentavere in an AI-enhanced manner using their DARWEN™ technology. DARWEN™ is an AI engine that compiles the identified source data (e.g. medical records from disparate systems) into a harmonized format and enables rapid data extraction via either AI-assisted manual approaches by trained abstractors or AI algorithmic approaches.

Definitions and rules for the extraction of each study data variable will be developed by Pentavere in partnership with the site clinicians in collaboration with Pfizer. To ensure shared understanding of these extraction rules (termed the Gold Standard Rules) each site and Pentavere will each manually extract data for a small subgroup of patients. Concordance will be calculated and discrepancies between extracted data will be explored and Gold Standard Rules will be refined and finalized. Pentavere will then extract data for a larger subgroup of patients, leveraging DARWEN™'s AI-assisted manual approaches. This dataset will be used as the ground truth to tune and measure the performance of DARWEN™, which are built on the same Gold Standard Rules. DARWEN™ structures data using models trained on various external datasets supported/reinforced (if needed) through additional training on the site's data for the study's specific Gold Standard Rules. The Sinai Health clinical team will sign off on and approve the dataset, triggering it to be locked, before any subsequent analyses will be undertaken.

Data extracted by DARWEN™ is the sole property of Sinai Health. During the course of the study, Pentavere will adhere to all Sinai Health confidentiality/privacy procedures.

Pentavere's DARWEN™ technology has been previously used to conduct research in tuberculosis, lung cancer, heart failure, diabetes, and mental health. When comparing the accuracy of DARWEN™ technology and manual chart abstraction, the technology demonstrated very high (96%) overall accuracy (11, 12).

9.9. Limitations of the research methods

As with any retrospective study, there is potential for selection bias, misclassification bias and reviewer bias. Patients who received palbociclib prior to approval or off-label are not represented in this study. To minimize selection bias, inclusion and exclusion criteria were finalized before data collection and inclusion criteria were kept to a minimum. We expect minimal misclassification bias as the data will be curated using trained and validated language processing algortihms. Given this is a descriptive study and the data was collected not to test one specific hypothesis, we anticipate very minimal reviewer bias.

The generalizability of this study will depend on the representativeness of PPD n. It is possible the results may not be generalizable to larger populations since this study only includes one site. To increase generalizability of results to a larger population, our study has limited exclusion criteria.

Due to the observational design of the study, treatments received by patients may be subject to a channeling bias and thus must be interpreted with caution.

It is expected the quality of the data should be generally high, but we anticipate a small degree of missing data for any variables curated using DARWEN™. Limitation from missing or incomplete data may lead to insufficient data for stratified analyses. No imputation of missing data is planned. The proportion of subjects with missing data for key variables collected in the study will be described.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

For the duration of the study the personal data will be stored in encrypted electronic form and password protected with access audited to ensure that only authorized study staff have access. Long-term retention of study data will be maintained at the study site in a secure manner as per study agreement. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether

a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

As this study is a retrospective non-interventional study, it is expected that reporting of all safety events have already been appropriately performed and documented at the time data was recorded through its primary data collection mechanism (capturing of patients notes within the electronic medical record, EMR, system).

REQUIREMENTS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans,

X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the AEM form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. PPD

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) Training for Vendors".*

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the

trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Two progress reports and a final observational study report will be shared with Pfizer and the Sinai Health teams.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if third party responsible (Sinai Health/Pentavere) is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. 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. DeMichele A, Cristofanilli M, Brufsky A, Liu X, Mardekian J, McRoy L, Layman RM, Emir B, Torres MA, Rugo HS, Finn RS. Comparative effectiveness of first-line palbociclib plus letrozole versus letrozole alone for HR+/HER2- metastatic breast cancer in US real-world clinical practice. Breast Cancer Res. 2021 Mar 24;23(1):37.
10. Mycock K, Zhan L, Taylor-Stokes G, Milligan G, Mitra D. Real-World Palbociclib Use in HR+/HER2- Advanced Breast Cancer in Canada: The IRIS Study. Curr Oncol. 2021 Jan 24;28(1):678-688.
11. 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.
12. Gauthier, M-P; Law, J; Le, L; Li, JJN; Zahir, S; Sung, M; Pettengell, C; Darwish, L; Aviv, S; Chu, R; Sacher, A; Liu, G; Bradbury, P; Shepherd, FA; Leighl, NB. Validation of scalable, automated data extraction in an advanced lung cancer patient population [Advance online publication]. 2021. [Available at: https://library.iaslc.org/conference-program?product_id=24&author=Marie-pier%20Gauthier&category=&date=2021-09-09&session_type=&session=OA08&presentation=04&keyword=&cme=undefined&]

14. LIST OF TABLES

Table 1. List of study variables to be extracted (where feasible)

15. LIST OF FIGURES

Figure 1. Study Design Flow Chart

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

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