NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	*Demographics, patient characteristics, treatment patterns and clinical outcomes of patients treated with Palbociclib in a real life setting in Israel*
Protocol number	*A5481160*
Protocol version identifier	*4*
Date	*30 August 2022*
Active substance	*L01XE33 (Palbociclib)*
Medicinal product	*Ibrance (Palbociclib)*
Research question and objectives	*To describe patient demographics, clinical characteristics, clinical outcomes and treatment patterns of adult breast cancer patients who have initiated palbociclib combination treatment as per the national basket of health services in January 2018 until August 2020 for all lines of therapy.* *New follow up to 30 June 2022*
Author	*Dr.* PPD *Pfizer Pharmaceuticals Israel Ltd.* *P.O.Box 12133, 9 Shenkar St.* *Herzliya Pituach, Israel 4672509* PPD PPD *Professor* PPD PPD *Dr.* PPD PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC/MBC	advanced/metastatic breast cancer
AE	adverse events
AEM	adverse events monitoring
AI	aromatase inhibitor
ANOVA	analysis of variance
ATC	anatomical therapeutic chemical
BMI	body mass index
CDK	cyclin-dependent kinase
CDK4/6-I	cyclin-dependent kinase 4 and 6 inhibitors
CI	confidence internal
CIOMS	council for international organizations of medical sciences
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CPT	current procedural terminology
CRF	case report form
CVD	cardiovascular disease
DCT	data collection tool
ECOG	Eastern Cooperative Oncology Group
ER+	Estrogen receptor positive
FDA	food and drug administration
gBRCAm	germline breast cancer gene mutation
GIS	geographic information systems
HER2	human epidermal growth factor receptor 2
HER2-	human epidermal growth factor receptor 2 negative
HMO	health maintenance organization
HR	hormone receptor
HR+	hormone receptor positive
ICD-9	international classification of diseases ,ninth revision
IEC	independent ethics committee
IQR	interquartile range
IRB	international review board
ISPOR	international society for pharmacoeconomics and outcomes research
K-M	kaplan-meier (curve)
MHS	Maccabi Healthcare Services
N	number
NIS	non-interventional study
CCI	CCI

PDF	portable document format
PR+	progesterone receptor positive
RWE	real-world evidence
SD	standard deviation
SES	socioeconomic status
TTNT	time to next treatment
USA	united sates of america
YRR	your reporting responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Dr PPD PhD	Senior Medical Advisor, NI Study Lead of the protocol	Pfizer Pharmaceuticals Israel Ltd.	9 Shenkar St. Hertzelia, Israel
PPD Bpharm, MSc	Epidemiologist, sub-investigator of the protocol	PPD	PPD Israel
Dr PPD MD	Head Oncologist	PPD	PPD Israel
Prof PPD PHD MHA	PPD Principal Investigator of the protocol	PPD	PPD Israel

4. AMENDMENTS AND UPDATES

[redacted]

5. MILESTONES

Milestone	Planned date
Start of data collection	*08 November 2020*
End of data collection	*30 June 2022*
Final study report	*31 December 2022*

6. RATIONALE AND BACKGROUND

Breast cancer is a major cause of mortality in females worldwide. Hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) breast cancer is the most commonly diagnosed subtype accounting for around 75% of all diagnosed breast cancers[1]. Palbociclib is a first in class cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor that has been approved for use in HR+/HER2- advanced/ metastatic breast cancer (ABC/ MBC) patients in a number of indications on the basis of efficacy demonstrated in 3 pivotal clinical trials; PALOMA-1 and PALOMA 2 (initial endocrine-based therapy) and PALOMA-3 (after progression following endocrine therapy) [2,3]. As a result of the recent approvals there is a need to understand the real world usage and clinical outcomes of patients receiving CDK4/6 inhibitors, including palbociclib, in order to inform future treatment decisions.

There is high level of screening and awareness for breast cancer in Israel. Palbociclib was included in the national health basket and therefore reimbursed since January 2018 in all lines of treatment, according to the labeling.
Although there is Real-World Evidence (RWE) on palbociclib published from the USA, Argentina, Germany and Italy [4,5,6] there is no awareness of RWE with palbociclib coming from Israel.

7. RESEARCH QUESTION AND OBJECTIVES

Primary Objective: To describe patient demographics, clinical characteristics, clinical outcomes and treatment patterns of adult breast cancer patients who have initiated palbociclib combination treatment as per the national basket of health services in January 2018 until August 2020 for all lines of therapy. Extended follow up for treatment patterns to 30th June 2022.

CCI

8. RESEARCH METHODS

8.1. Study design

This is a population based retrospective database study that will include patients with metastatic, HR+/ HER2- breast cancer and who initiated first or subsequent lines of treatment with palbociclib. Data will be available from Maccabi Healthcare Services (MHS) database in Israel for patients who received approval for treatment with palbociclib since 01 January 2018 until 31 August 2020.

Treatment amendment and extension:Treatment lines will be rerun for the same patient cohort for an additional year and a half of follow-up to 30 June 2022.

The database review followed by a medical record review will capture data from approximately 500-700 patients on demographics, clinical characteristics, disease history, treatment history, palbociclib dosing, clinical outcomes and post-palbociclib combination therapy treatment data. The study will be descriptive in nature therefore no control or comparator groups will be included.

8.2. Setting

Patients (age ≥18 years) will be identified from MHS purchase data between 01 July 2017 until 31 August 2020.
Index date will be defined as date of initiation of palbociclib treatment.

Patient records must meet the following criteria to be eligible for the medical record reviews. Patients must be at least 18 years of age at index date and they must have been diagnosed with HR+/HER2- ABC/ MBC. Patients must have received palbociclib combination in line with Israel approved indications. A minimum of 6 months follow up of palbociclib combination therapy prior to date of medical record review will be necessary for inclusion. This will permit the capture of meaningful clinical outcomes data. Patients will be followed through the end of the observation period, date of death or left the health maintenance organization (HMO).

A full list of the inclusion criteria can be found in Section 9.2.1.

8.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:
1. A diagnosis of metastatic breast cancer, based on the National/MHS cancer registry.
2. Newly diagnosed metastatic breast cancer patients and newly treated with palbociclib within 6 months of diagnosis, in any line of treatment in the metastatic setting.
3. Available data on palbociclib treatment for at least 6 months.
4. Continuous healthcare plan enrolment in MHS for at least one year before index date.
5. At least 18 years of age at index date.

8.2.2. Exclusion criteria

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

1. Patients that initiated HER2 inhibitors.

8.3. Variables

The following variables will be collected from the MHS electronic database and non-structured data extracted from PDF files of patient data:

Variable	Source	Role in study	Period of measurement	Reporting phase	Operational definition
Demographic and Clinical and health related characteristics at baseline					
PatID	MHS structured data	Data linkage		Not reported	Unique patient identifier used to link clinical records. This information will not be disclosed to the study sponsor.
Gender	MHS structured data	Baseline characteristic	Prior medical history	Reported	Male/Female
Age	MHS structured data	Baseline characteristic	Baseline	Reported	Patient's age (in years) at index date.
Age groups	MHS structured data	Baseline characteristic	Baseline	Reported	Groups such as <50 versus ≥50
Body mass index (BMI)	MHS structured data	Baseline characteristic	Baseline	Reported	Median (Interquartile Range - IQR)
BMI groups	MHS structured data	Baseline characteristic	Baseline	Reported	Underweight (BMI<18.5), normal (BMI 18.5-24.9), overweight (BMI 25-25.9), obese (BMI ≥30), missing
Smoking history	MHS structured data	Baseline characteristic	Baseline	Reported	Ever smoker, never smoker, unknown.

Menopausal status	MHS structured data	Baseline characteristic	Baseline	Reported	Pre-, peri- or post-menopausal
Region of residence	MHS structured data	Baseline characteristic	Baseline	Reported	North, South, Central region
Socioeconomic status	MHS structured data	Baseline characteristic	Baseline	Reported	Based on a points system, categorized as low (1-4), medium (5-6), high (7-10)
Co-morbidities	MHS validated registries	Baseline characteristic	Baseline	Reported	For cardiovascular disease, cerebrovascular disease, stroke, congestive heart failure, diabetes mellitus, chronic kidney disease, hypertension, Chronic obstructive pulmonary disease (COPD).
Variable	**Source**	**Role in study**	**Period of measurement**	**Reporting phase**	**Operational definition**
Chronic diseases	MHS structured data	Baseline characteristic	Baseline	Reported	Depression as defined by ICD-9 codes.
Deyo-Charlson Comorbidity index	MHS structured data and MHS validated registries	Baseline characteristic	Baseline	Reported	
Co-medications	MHS structured data	Baseline characteristic	Baseline	Reported	At least 2 purchases within 3 months prior to index date.
Genetic counselling for gBRCAm (germline Breast Cancer gene mutation)	MHS structured data	Baseline characteristic	Baseline	Reported	yes/no

Genetic testing for gBRCAm performed	MHS structured data	Baseline characteristic	Baseline	Reported	yes/no
Death	MHS structured data	Endpoint	After index date		Death is captured from National Insurance Data
Disease Characteristics					
Date of initial breast cancer diagnosis	National cancer registry	Baseline characteristic	Baseline	Reported	Records may be incomplete
Histology	Extracted from PDF patient data files	Baseline characteristic	Baseline	Reported	
Location of metastases	Extracted from PDF patient data files	Baseline characteristic	Baseline	Reported	Bone, brain, lymph nodes, ovary, visceral
Visceral/non visceral status	Extracted from PDF patient data files	Baseline characteristic	Baseline	Reported	Non-visceral, visceral (lungs, liver), bone only
Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis	Extracted from PDF patient data files	Baseline characteristic	Baseline	Reported	Grouped as 0-1, 2, 3-4, unknown/missing
Molecular status data: performed HER2/ HR tests	Extracted from PDF patient data files	Baseline characteristic	Baseline	Reported	yes/no
Hormone sensitivity	Extracted from PDF patient data files	Baseline characteristic	Baseline	Reported	primary or secondary resistance
Variable	**Source**	**Role in study**	**Period of measurement**	**Reporting phase**	**Operational definition**
Progression of disease from imaging	Extracted from PDF patient data files	Baseline characteristic	Baseline	Reported	
Treatment Characteristics					

Index treatment regimen	MHS structured data	Treatment characteristic	Study observation period	Reported	Palbociclib combination treatment - combination with aromatase inhibitor or fulvestrant.
Lines of therapy	MHS structured data and PDF patient data files.	Treatment characteristic	Study observation period	Reported	Identified according to the sequence of dispensed medications.
Median duration of each line of therapy	MHS structured data	Treatment characteristic	Study observation period	Reported	Duration in weeks or months between the start and stop of each line of therapy will be reported as mean (SD) and median (IQR)
Number of cycles of index treatment	MHS structured data	Treatment characteristic	Study observation period	Reported	Mean (SD) and Median (IQR)
Index palbociclib treatment dose	MHS structured data	Treatment characteristic	Study observation period	Reported	Mean (SD) and Median (IQR)
Index palbociclib treatment dose schedule change	MHS structured data	Treatment characteristic	Study observation period	Reported	Proportion of patients with dose changes
Date of treatment initiation	MHS structured data	Treatment characteristic	Study observation period	Not Reported	First date will be used if a regimen consists of more than one drug given on different dates.
Index treatment end date	MHS structured data	Treatment characteristic	Study observation period	Not Reported	Date of final treatment for each drug or regimen. It is possible that the patient's treatment stop date is not documented if the patient dies, is lost to follow up or is still on therapy. The final treatment date death date or end of

					study date will be uses, whichever is earliest.
Variable	**Source**	**Role in study**	**Period of measurement**	**Reporting phase**	**Operational definition**
Post-palbociclib treatment duration	MHS structured data	Clinical Outcomes	Study observation period	Not Reported	The regimen received by patients following discontinuation from the palbociclib treatment. The duration (in weeks) between the start and stop of the post-palbociclib treatment. Findings will be summarized as the mean (± SD) and median (range) of values.
Proportion of patients who progress/ do not progress	MHS structured data and PDF patient data files.	Clinical Outcomes	Study observation period	Reported	Using imaging files, the proportion of patients who progress and do not progress from the index treatment until 6, 12 and 24 months will be summarized as the count and percentage of the following: Patients with ongoing index treatment Patients who died following index treatment Patients who advanced to a subsequent treatment Patients who did not advance to a

					subsequent treatment for unknown reasons
Time to chemotherapy after palbociclib treatment	MHS structured data	Clinical Outcomes	Study observation period	Reported	Time to chemotherapy (Kaplan Meier method median (95% CI)) from end of index treatment and start of chemotherapy. Summary of number of events and censored patients at 6, 12, 18, 24 months.
Time to next treatment (TTNT)	MHS structured data	Treatment characteristic	Study observation period	Reported	TTNT will be defined as the interval (in weeks or months) between the start of the index treatment date and the date of the next-line treatment. Patients who did not advance to the next treatment will be censored on the study end date or death, whichever occurs first. Kaplan-Meier (K-M) method with 95% CI and summary tables of

					events and censored patients at 6, 12, 18, 24 months.
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8.3.1. Demographic characteristics at baseline (from structured electronic database):

- Patient demographics: age, age group and gender.
- Region of residence (North, Central, South).
- Socioeconomic status (SES): based on a score ranked with 1 (lowest) to 10 derived for commercial purposes by Points Location Intelligence using geographic information systems (GIS) and data such as expenditures related to retail chains, credit cards and housing. This score is highly correlated with SES measured by the Central Bureau of Statistics[1]. SES will be categorized into low (1-4), medium (5-6) and high (7-10).

8.3.2. Clinical and health related characteristics at baseline:

- Body mass index (BMI) will be categorized using standard cut-points [2].
- Baseline chronic diseases will be identified using previously validated MHS automated chronic disease registries for the following co-morbidities: diabetes [3], cardiovascular disease (CVD) [4], chronic kidney disease (CKD) [5] , hypertension [6], COPD, other patient relevant condition (if applicable) e.g. depression.
- Deyo-Charlson Comorbidity index (using validated MHS patient registries where available).
- Co-medications – Minimum of 2 purchases within the 3 months period prior to index date.
- Menopausal status.

- Cancer history will be obtained from National Cancer Registry [7] data available through 2015 and MHS cancer registry data which draws from pathology reports and diagnoses linked to cancer medication approvals through 2017.
- Smoking status (ever/never/unknown) will be obtained from the MHS database and/or physician reports.
- Genetic counselling for germline BRCA mutation carried out yes/no.
- Testing for germline BRCA mutation carried out yes/no.

8.3.3. Treatment patterns:

- Number (N) (%) patients receiving first, second- and third-line treatments by drug name and therapeutic group, median duration of each line of therapy, and number of cycles for each line of therapy. Treatment lines are defined according to the sequence of dispensed medications, with information captured both from pharmacy database (for medications approved by the HMO), and from hospital medical records (including information on medications provided by private insurance and clinical studies) using the following algorithm. Any drug purchased within 1 month of a new line is considered part of that line. Cessation of a drug from a combination regimen is considered the same line as the patient is not receiving additional treatment. Cessation is likely due to tolerance issues or adverse effects although we do not know the reason as our data is from purchase data.
  Addition of a new drug to a current regimen is considered a new treatment line.
- Index treatment regimen - palbociclib combination partner: Aromatse Inhibitors (AI) or fulvestrant; Subsequent therapy per lines of therapy.
- Dosing and dose changes, interruptions, delays, and discontinuations associated with palbociclib therapy.
- Treatment lines will be rerun for extended follow up to 30 June 2022.

8.3.4. Cancer related variables:

These variables will extracted from patient PDF files/ letters sent to MHS from the physician.

- Date of initial breast cancer diagnosis.
- Histology.
- Location of metastases: bones, brain, visceral, lymph nodes, other.

- ECOG performance status at diagnosis.
- Molecular status data: performed HER2/ HR tests (yes/no).
- Hormone sensitivity: primary or secondary resistance.
- Progression of disease from imaging.

8.3.5. Clinical outcomes for palbociclib (analysed separately by therapy line):

- N (%) progression at 6, 12 and 24 months.
- Duration of treatment on palbociclib (Median time on treatment).
- Time on treatment for subsequent line of therapy.
- Time to chemotherapy after palbociclib treatment.
- CCI [redacted]

8.4. Data sources

Data will be extracted from the Maccabi Health Services (MHS) database. MHS is a nationwide health plan (payer-provider) representing a quarter of the population in Israel. The MHS database contains longitudinal data on a stable population of 2.2 million people since 1993 (with <1%/year moving out). Data are automatically collected and include comprehensive laboratory data from a single central lab, full pharmacy prescription and purchase data, and extensive demographic data on each patient. MHS uses the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding systems as well as self-developed coding systems to provide more granular diagnostic information beyond the ICD codes. Medications are coded according to the Israeli coding system with translations to Anatomical Therapeutic Chemical (ATC) coding system wherever available. Procedures are coded using Current Procedural Terminology (CPT) codes.

8.5. Study size

Sample size calculations are not applicable as this is a descriptive study. The expected number of patients eligible for the study is about 500-700 patients.

8.6. Data management

Part of the data will be collected from the main database, such as demographics, comorbidities, systemic therapy (not including chemotherapy like cisplatin or carboplatin), date of death. Data that is not available in the main database such as tumor characteristics (stage of disease, histology), chemotherapy (cisplatin, carboplatin), response (from imaging results), biomarker status, metastases site, Eastern Cooperative Oncology Group (ECOG) results, and discontinuation will be extracted through additional chart review from medical letters in PDF format by trained data extractors. Extracted data will be recorded in an electronic case report form created for this study using Microsoft Access Database. All data is anonymous and does not leave the MHS system.

SPSS version 24 and R data processing and statistical software will be used.

8.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. MHS shall ensure that the CRFs are securely stored at Maccabi Research & Innovation Institute in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

MHS has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed MHS or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

8.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, MHS agrees to keep all study-related records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and physician records), copies of all CRFs, 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 MHS according to local regulations or as specified in the research agreement, whichever is longer. MHS must ensure that the records continue to be stored securely for so long as they are retained.

If MHS becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless MHS and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

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

8.7. Data analysis

Data will consist of structured data from the MHS electronic database and non-structured data extracted from PDF files of patient data. Data validation will be performed and consist of quality control checks for appropriate values, logical sequences and quantity of missing values. Missing data will be identified and reported in the results tables as percentages for all variables. If there is a large amount of missing or illogical data, a decision to include, exclude or impute that variable will be subsequently made based on the study sponsor's decision.

Descriptive analyses will be conducted to evaluate the demographic, clinical and treatment characteristics overall, as well as for 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) and median (Inter quartile range). In the case of missing observations, the number and percentage of missing values will be reported. Chi-square testing will be used to assess associations between categorical variables when patient counts for single cells within the results tables are greater or equal to 5. When distribution cannot be assumed to be Chi-square, then Fisher's exact test will be used. Depending on normality, analysis of variance (ANOVA)/t-tests or Kruskall-Wallis tests will be used for continuous variables. An alpha level of 0.05 will be the primary criterion for statistical significance of this study.

Time from treatment initiation until progression (as determined in the patient record) and drug discontinuation will be determined for the calculation of median time on treatment.

Duration of treatment on palbociclib, Time on treatment for subsequent line of therapy and Time to chemotherapy after palbociclib treatment and CCI [redacted] Plots will be generated. Patients are censored at end of study or left MHS.

Sub- analyses will be carried out for palbociclib.

All analyses will be conducted using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp, and a P value < 0.05 is considered statistically significant.

8.8. Quality control

Quality control checks on MHS data are built into the "Clicks" physician visit management system and further quality control is carried out by the BI department.

8.9. Strength and limitations of the research methods

In general the study will be prone to selection bias and misclassification errors due to its observational design. Another potential limitation of the study could be the level of missing data. The possibility of selection bias is minimized because the study aims to include all metastatic breast cancer patients treated at MHS during a specified time period. In order to minimize the bias due to secondary data extraction from existing medical records, appropriate quality checks will be done by the analytical team. These checks include, but are not limited to, examination of missing and out of range values, comparison of data estimates to established norms, use of appropriate statistical methods to counteract the bias, wherever possible. Data cleaning procedures will be implemented

and updated at each data export and a review of clinical charts will be planned. A uniform handling of data that is conflicting, ambiguous, missing, or unknown will be performed. No statistical imputation of missing data is planned.

The study population and practice patterns captured in this study are from one health care provider and may not be representative of the country's breast cancer patient population and treatment practices. Therefore, the generalizability of the results may be limited. Small number of patients in certain stratification groups may result in wide CIs for estimates generated during the analyses. ECOG performance status, which is likely predictive of anti-cancer treatment and CCI [redacted] Due to the descriptive nature of the study no inferences regarding casualty can be drawn from the results.

8.10. Other aspects

Not applicable

9. PROTECTION OF HUMAN SUBJECTS

9.1. 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.

Patient personal data will be stored at Maccabi Research & Innovation Institute in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. MHS 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, MHS 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, any 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. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the research agreement and applicable privacy laws.

9.2. 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 and exemption will be received from the ethics committee.

9.3. 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. The study will be conducted per approval of the Maccabi Research Committee and the local Institutional Review Boards.
All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

9.4. 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:

- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
  http://www.ispor.org/workpaper/practices_index.asp
- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS)
- Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
- Israeli Ministry of Health regulation 14 – Medical trials in Human subjects

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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 data collection tool 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. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

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.

Human Review of Structured Data

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A report will be provided on completion of the entire study in a Word format. This report will incorporate methodology, sample, tables of results and summaries. All documents used throughout the study will be contained within the report as appendices. Results of this study may be submitted to conferences and journals for publication. As per Pfizer's requirements, the project will only be considered complete upon delivery of the full study report and close of all study publications.

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 MHS 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.

12. REFERENCES

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ANNEX 1. LIST OF STAND ALONE DOCUMENTS

1. Baseline demographic and clinical characteristics of patients diagnosed with metastatic breast cancer 2018-2019 split by Palbociclib as first-, second- or third line (n=XX).

		First Line	Second Line	Third Line	Total n=XXX

Demographic Variables					
Age	median (IQR)				
	<65				
	>=65				
Gender	male				
	female				
Region of residence	Central				
	North				
	South				
Socioeconomic status*	low				
	medium				
	high				
Clinical Variables					
Deyo-Charlson Comorbidity Index (without malignancy or HIV)	mean (SD)				
	0				
	1				
	2				
	3				
	≥4				
Co-morbidities	Diabetes mellitus				
	Cardiovascular disease				
	Stroke				
	Congestive heart failure				
	Hypertension				
	Chronic kidney disease				

	Chronic obstructive pulmonary disease				
	Other (e.g. depression)				
Co-medications					
Smoking	Ever smoker				
	Never smoker				
	Unknown				
BMI					
Menopausal status	Pre/Peri menopausal				
	Postmenopausal				
Genetic counselling for gBRCAm	Yes				
	No				
Testing for gBRCAm	Yes				
	No				

2. Cancer related characteristics of patients with breast cancer at baseline

		First Line	**Second Line**	**Third Line**	**Total (n)**
Histology					
Location of metastases	Brain				
	Bone				

	Visceral				
	Lymph nodes				
	Other				
ECOG	0-1				
	2				
	3-4				
	Unknown/missing				
Hormone sensitivity	Primary				
	Secondary				
Molecular status data: performed HER2 / HR tests	HR+ [Estrogen Receptor positive (ER+), Progesterone Receptor positive (PR+) or both]				
	HER2+				

3. Time on Palbociclib treatment

Line of treatment (first-, second- or third line)	**N**	**Number (%) discontinued**	**Median time on treatment (95% CI), months**	**% on treatment at 3 months**	**% on treatment at 6 months**	**% on treatment at 12 months**	**% on treatment at 24 months**	**Log rank P value**

4. Palbociclib treatment patterns

ANNEX 2. ADDITIONAL INFORMATION

Line of treatment (first-, second- or third line)	Combination partner: AI or Fulvestrant	Number (%) of dose reductions from 125mg to 100mg	Number (%) of dose reductions from 100mg to 75mg	Number (%) of dose reductions from 125mg to 75mg	Number (%) of dose Interruptions	Number (%) of discontinuations

Not applicable