NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Descriptive Analyses of Clinical Characteristics and Treatment Patterns of Breast Cancer Patients Initiating Palbociclib (Ibrance®) Treatment in Japan by Using MDV Database
Protocol number	A5481115
Protocol version identifier	4.0
Date	31 March 2021
Active substance	Palbociclib
Medicinal product	Ibrance
Research question and objectives	Palbociclib (Ibrance®) was launched in Japan in December 2017. This study will describe the characteristics of patients initiating treatment with palbociclib by using Medical Data Vision (MDV) database (claim data base) in terms of demographic and clinical characteristics, real-world utilization of palbociclib (e.g. line of therapy, concomitant use of other chemotherapy/endocrine therapy/supportive drugs), among the patients with breast cancer following its launch in Japan.
Author	PPD Ph.D. PPD Pfizer Japan 3-22-7, Yoyogi, Shibuya-ku, Tokyo 151-8589 Japan

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC	Advanced breast cancer
AE	Adverse event
AEM	Adverse event monitoring
AI	Aromatase inhibitor
ATC	Anatomical therapeutic chemical classification system
CDK	Cyclin-dependent kinase
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CSS	Clinical Study Support, Inc.
DNA	Deoxyribonucleic acid
DPC	Diagnosis Procedure Combination
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ER	Estrogen receptor
FDA	Food and Drug Administration
G-CSF	Granulocyte-Colony Stimulating Factor
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
ICD	International Statistical Classification of Diseases and Related Health Problems
ICD-10	ICD 10th revision
IEA	International Epidemiological Association
IEC	Independent ethics committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LH-RH	Luteinizing Hormone-Releasing Hormone
MDV	Medical Data Vision Co., Ltd.
NE	Not estimable
NIS	Non-interventional study
PFS	Progression-free survival
QC	Quality control
SAP	Statistical Analysis Plan
TTF	Time to treatment failure

3. RESPONSIBLE PARTIES

Name, degree(s)	Job Title	Affiliation	Address
PPD Ph.D. PPD	PPD	PPD Pfizer Japan	3-22-7, Yoyogi, Shibuya-ku, Tokyo 151-8589 Japan
PPD Ph.D. PPD	PPD Pfizer Japan	PPD	3-22-7, Yoyogi, Shibuya-ku, Tokyo 151-8589 Japan
PPD	PPD	PPD Pfizer Japan	3-22-7, Yoyogi, Shibuya-ku, Tokyo 151-8589 Japan
		PPD Pfizer Japan	3-22-7, Yoyogi, Shibuya-ku, Tokyo 151-8589 Japan
PPD Ph.D.		Clinical Study Support Inc.	2F, 1-11-20 Nishiki, Naka-ku, Nagoya 460-0003 Japan
Ph.D.		Clinical Study Support Inc.	2F, 1-11-20 Nishiki, Naka-ku, Nagoya 460-0003 Japan
, M.D., Ph.D.		Aichi Cancer Center Hospital	1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681 Japan

4. ABSTRACT

- Title:
  Descriptive Analyses of Clinical Characteristics and Treatment Patterns of Breast Cancer Patients Initiating Palbociclib (Ibrance®) Treatment in Japan by Using Medical Data Vision Co., Ltd.(MDV) Database (version 3.0, 01 December 2019)
  PPD Ph.D. PPD , Pfizer Japan 3-22-7, Yoyogi, Shibuya-ku, Tokyo 151-8589 Japan

- Rationale and background:
  Palbociclib is the first Cyclin-dependent kinase (CDK) 4/6 inhibitor approved in Japan in combination with endocrine therapy for treatment of hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2-) advanced breast cancer. Palbociclib was approved in September 2017 and launched in December 2017. In the Japanese package insert for palbociclib, the data for only 59 Japanese patients who were administrated palbociclib in PALOMA-2 and PALOMA-3 studies is described. Also neither treatment line nor concomitant treatment drug is defined in the Japanese package insert and there is no data for treatment sequence of palbociclib. Thus retrieving data from real world setting for palbociclib is necessary to clarify the treatment pattern of palbociclib in Japan for the appropriate use and this non-interventional study was planned. This study aims to describe patient demographic, treatment patterns and treatment duration among HR+/HER2- advanced breast cancer(ABC) patients who initiated palbociclib. In addition, this study will describe subsequent treatment patterns and treatment duration after palbociclib-based therapy. In addition, this study will describe how treatment paradigm changes with the launch of new treatment option, CDK4/6 inhibitor.

- Research question and objectives:
  The primary objective of this study is to describe patient demographics, treatment patterns and treatment duration of palbociclib, and subsequent treatment patterns and treatment duration after palbociclib-based therapy among advanced metastatic breast cancer patients in Japan initiating treatment with palbociclib following drug launch in Japan (15 December 2017).
  The secondary objective of the study is to describe patient demographics, treatment patterns of ABC patients and treatment duration of endocrine therapy, and subsequent treatment patterns and treatment duration after endocrine therapy among advanced metastatic breast cancer female patients to address treatment paradigm changes in Japan with the launch of new treatment option.

- Study design:
  This is a retrospective observational study focusing on patients diagnosed with breast cancer in Japan using de-identified claim data from MDV database. Patients who meet the inclusion criteria will be retrospectively selected from MDV database.

- Population:
  Japanese patients diagnosed with breast cancer and whose data were entered into MDV database from April 2008 will be included in this study.

- Variables:
  Age, Gender, Weight, Height, Palbociclib treatment date, Palbociclib daily dose, Palbociclib treatment duration, Endocrine therapy combined with palbociclib, Treatment pattern of each lines of therapy, Chemotherapy treatment pattern, Endocrine therapy treatment pattern, Endocrine therapy treatment duration, Time to treatment failure, G-CSF treatment date, Antibiotics treatment date, Blood test date, Duration of the adjuvant therapy, Duration from surgery to the starting of 1st line therapy

- Study size:
  This is a descriptive study and sample size and power calculations are not applicable. All eligible patients with breast cancer diagnosis and who received endocrine therapy drugs and who didn't receive anti-HER2 therapy drugs (defined as HR+/HER2- breast cancer) will be included in the analysis. According to a preliminary feasibility assessment, the number of HR+/HER2- breast cancer patients is 10,3124.

- Data analysis:
  The primary objective of this study is to describe patient demographics, treatment patterns and treatment duration of palbociclib, and subsequent treatment patterns and treatment duration after palbociclib-based therapy among the advanced metastatic breast cancer female patients in Japan initiating treatment with palbociclib following drug launch in Japan. The secondary objective of the study is to describe patient demographics, treatment patterns of ABC patients and treatment duration of endocrine therapy, and subsequent treatment patterns and treatment duration after endocrine therapy among advanced metastatic breast cancer female patients to address treatment paradigm changes in Japan with the launch of new treatment option. For the advanced metastatic breast cancer male patients, the analysis will be exploratory. 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.

- Milestones:
  Completion of feasibility assessment 10 December 2018 (Done)
  Start of data collection April 2008 (Already started by Medical Data Vision Co., Ltd.)
  End of data collection 31 October 2022
  Final study report November 2023

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason

1	27 March 2019	ANNEX 1. Appendix 1	Replace Appendix 1	Due to finalization of SAP
2	01 December 2019	Section 3, 4, 5, 8, 9 Appendix 1, included "other cancer type" in exclusion criteria of the algorithm	Change NI study lead, Add the objective, Add the variable	Due to consideration the protocol update based on the first data analysis result
3	31 March 2021	Section 8-9	Addition of objectives to reveal the demographic and clinical characteristics of ABC patients and to analyze endocrine based therapy for ABC patients	To describe treatment paradigm changes with the launch of new treatment option, CDK4/6 inhibitor.
		Section 8-9	Revise the description to clarify the objectives	To clarify the objectives by accurate description.
		Section 7	Addition of background of new objectives Revision of the description	To explain the reason of objectives added at amendment. To clarify the background by accurate description.
		Section 9.2.1, Appendix 1	Addition to Inclusion criteria. #3 Diagnosis of secondary malignant neoplasm based on ICD-10 (C77.x, C78.x, C79.x)	To exclude adjuvant endocrine therapy clearly from endocrine therapy for metastatic setting owing to the addition of the objectives
		Section 9.3. Variables	Addition of Variables	To describe the duration of endocrine therapy based on the addition of objectives
		Section 9.4 Data sources	Addition of the description.	To describe data sources more accurately.
		Section 4, 6 and Table 1	Change milestones and data period	To follow-up the study for longer-term.
		Section 2	Addition of abbreviations.	Due to the addition of objectives for the amendment.
		Appendix 2	Addition of compounds	To add newly approved compounds
		Section 3	Change NI study co-lead	

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	10 December 2018 (Done)
Start of data collection	April 2008 (Already started by Medical Data Vision Co., Ltd.)
End of data collection	31 October 2022

Final study report	November 2023

7. RATIONALE AND BACKGROUND

Breast cancer is the most common cancer in women in Japan, with nearly 74,000 new cases diagnosed in 2012 and the incidence rate has steadily increased. In 2014, there are over 10,000 deaths as breast cancer patients[1]. Breast cancer prevalence rate of Japanese women by age group began to increase from the 30s, peaked in the latter half of the 40s, after that it remained almost constant, and gradually decreased from the late sixties[2].

When the metastasis is seen at the first diagnosis (about 6% of breast cancer patients), the prognosis is remarkably poor and the 5-year survival rate drops to 26.3%[3]. In addition, even if metastasis is not seen at the time of initial diagnosis, it is estimated that about 20% to 30% of patients will have metastasis / recurrence after radical treatment for the primary tumor[4]. According to The Japanese Breast Cancer Society Clinical Practice Guidelines for Breast Cancer 2018[2], the objectives for metastatic/recurrent breast cancer are (1) The prolongation of survival and (2) The improvement/maintenance of the quality of life.

Approximately two-thirds of breast cancers are hormone receptor positive (HR+)[5]. Endocrine therapy is the mainstay of treatment for patients with HR+ disease. The first-line endocrine treatment for HR+/HER2- advanced breast cancer typically includes aromatase inhibitors (e.g. anastrozole, letrozole, or exemestane) and estrogen receptor antagonists (e.g. tamoxifen or fulvestrant)[2]. The choice of primary endocrine therapy for patients with HR+/HER2- advanced breast cancer is often based on several considerations including prior use of postoperative adjuvant endocrine therapy, potential side effects, progression free period of pretreatment drugs, and menopausal status of patients.

Palbociclib is an oral, cyclin-dependent kinase (CDK) 4/6 inhibitor, which prevents deoxyribonucleic acid (DNA) replication by prohibiting progression from G1 to S phase during cell division, thereby preventing tumor cell proliferation through cell cycle control. The clinical studies in which HR+/HER2- advanced or metastatic breast cancer were conducted in combination with endocrine therapy. The PALOMA-2 study (the global phase 3) showed that progression-free survival (PFS) was improved with palbociclib plus letrozole compared to placebo plus letrozole in the treatment of postmenopausal women with estrogen receptor (ER)+/HER2- advanced breast cancer in the first-line setting. Median PFS [95% Confidence interval (CI)] was 24.8 [22.1-not estimate (NE)] months for palbociclib plus letrozole, and 14.5 (12.9-17.1) months for placebo plus letrozole[6]. In the PALOMA-3 study (the global phase 3), the combination of palbociclib and fulvestrant was associated with significant improvements in PFS compared with fulvestrant plus placebo in patients with ER+/HER2- advanced breast cancer as the second or later than second treatment [the median PFS (95% CI) was 11.2 (9.5-12.9) months for palbociclib plus fulvestrant, and 4.6 (3.5-5.6) months for placebo plus letrozole]. Additionally both pre-menopausal and post-menopausal patients were included in the PALOMA-3 study and the efficacy of palbociclib treatment was observed regardless of the menopausal status[7, 8, 9]. Another study, A5481010 study (Japan phase 2) was conducted in Japan and the 1-year disease free survival rate (90% CI) that was

the primary endpoint for the study was 75.0% (61.3-84.4). The PFS, one of the secondary endpoints did not reach the median (95% CI was 16.7 months to NE)[10].

Palbociclib is the first CDK4/6 inhibitor approved in Japan in combination with endocrine therapy for treatment of HR+/HER2- advanced breast cancer. Palbociclib was approved in September 2017 and launched in December 2017. In the Japanese package insert for palbociclib, the data for only 59 Japanese patients who were administrated palbociclib in PALOMA-2 and PALOMA-3 studies is described. Also neither treatment line nor concomitant treatment drug is defined in the Japanese package insert and there is no data for treatment sequence of palbociclib. Therefore, real world data for palbociclib is needed to clarify the treatment pattern of palbociclib in Japan. This study aims to describe patient demographic, treatment patterns and treatment duration among HR+/HER2- advanced breast cancer (ABC) patients who initiated palbociclib. In addition, this study will describe subsequent treatment patterns and treatment duration after palbociclib-based therapy. In addition, this study will describe how treatment paradigm changes with the launch of new treatment option, CDK4/6 inhibitor. Recommendations and usage of treatments vary between countries according to the approval and availability of individual agents. Endocrine treatment has long been recommended over chemotherapy for systemic therapy. In the Japanese Breast Cancer Society Clinical Practice guidelines for Breast Cancer 2018, aromatase inhibitor(AI) monotherapy, combination of AI and CDK4/6 inhibitor, and fulvestrant monotherapy had been recommended with the same recommendation level for initial treatment of postmenopausal HR+HER2- ABC. In 2020, the recommendation level was reconsidered and combination of AI and CDK4/6 inhibitor is most strongly recommended in the guideline. But there is limited information on the real-world use and treatment outcome of these endocrine based therapies in Japan. As the additional objectives, this study aims to describe patient demographic, treatment patterns and treatment duration among HR+/HER2- ABC patients who initiated endocrine based therapy for advanced/metastatic setting.

8. RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study is to describe patient demographics, treatment patterns and treatment duration of palbociclib, and subsequent treatment patterns and treatment duration after palbociclib-based therapy among advanced metastatic breast cancer female patients in Japan initiating treatment with palbociclib following drug launch in Japan (15 December 2017). The secondary objective of the study is to describe patient demographics, treatment patterns of ABC patients and treatment duration of endocrine therapy, and subsequent treatment patterns and treatment duration after endocrine therapy among advanced metastatic breast cancer female patients to address treatment paradigm changes in Japan with the launch of new treatment option. For the advanced metastatic breast cancer male patients, the analysis will be conducted exploratory because male patients are extremely rare and they were not included in clinical studies. More specifically, Medical Data Vision (MDV) database will be utilized to achieve the following research objectives:

1. To characterize the demographic and clinical characteristics of ABC patients at the initiation of treatment with palbociclib

2. To describe the treatment patterns of palbociclib, including line of therapy and type of endocrine therapy combined with palbociclib, and initial dosage

3. To evaluate time to treatment failure (TTF) of palbociclib in combination with endocrine therapy by the line of therapy

4. To describe the treatment patterns of subsequent therapy after end of palbociclib treatment, including line of therapy and type of treatment

5. To evaluate TTF of subsequent therapy after end of palbociclib treatment

6. To describe changes in treatment pattern before and after the launch of palbociclib, the revision of clinical guideline in Japan.

7. To describe the use of antibiotics and/or G-CSF during treatment with palbociclib

8. To describe the frequency of blood tests during treatment with palbociclib

9. To characterize the demographic and clinical characteristics of ABC patients at the initiation of treatment for ABC

10. To describe the treatment patterns of each line of therapy for ABC patients

11. To evaluate TTF of endocrine therapy for ABC patients

12. To describe the treatment patterns of subsequent therapy after end of endocrine therapy for ABC patients, including line of therapy and type of treatment

13. To evaluate TTF of subsequent therapy after end of endocrine therapy for ABC patients

14. To describe the use of antibiotics and/or G-CSF during treatment with endocrine therapy for ABC

9. RESEARCH METHODS

9.1. Study design

This is a retrospective observational study focusing on patients diagnosed with breast cancer in Japan using de-identified claim data from MDV database. Patients who meet the inclusion criteria will be retrospectively selected from MDV database. The algorithm to define the first line treatment for advanced breast cancer is described in appendix 1.

9.2. Setting

Japanese patients diagnosed with breast cancer and whose data were entered into MDV database from April 2008 will be included in this study. MDV data will be extracted for each patient from the first data to following data period (Table 1).

Table 1 Data period

Analysis year	Data period
First Year	April 2008 to December 2018
Second Year	April 2008 to August 2019
Third Year	April 2008 to December 2020
Fourth Year	April 2008 to October 2021
Fifth Year	April 2008 to October 2022

Patients meeting all of the following criteria will be selected for analysis.

9.2.1. Inclusion criteria

Patients whose data were entered into MDV database from April 2008 will be included and must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Diagnosis of breast cancer based on International statistical classification of diseases and related health problems 10th revision (ICD-10) (C50.xx);
2. Received at least one prescription of endocrine therapy drugs during the index period (See Appendix 2).
3. Diagnosis of secondary malignant neoplasm based on ICD-10 (C77.x, C78.x, C79.x)

9.2.2. Exclusion criteria

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

1. Received at least one prescription of anti-HER2 therapy (Trastuzumab, Trastuzumab emtansine, Pertuzumab, and Lapatinib tosilate hydrate: see Appendix 2) during the index period.

9.3. Variables

The variables are described in the following table. The detailed definitions are included in the SAP.

Table 2 Variables

Variable	Role	Data source(s)	Operational definition
Age	Baseline characteristic	• At date of prescription for first line treatment for advanced breast cancer • At palbociclib treatment initiation	Structured data field

Gender	Baseline characteristic	• At date of prescription for first line treatment for advanced breast cancer • At palbociclib treatment initiation	Structured data field
Weight	Baseline characteristic	• At palbociclib treatment initiation	Only in patient Structured data field
Height	Baseline characteristic	• At date of prescription for first line treatment for advanced breast cancer	Only in patient Structured data field
Palbociclib treatment date	exposure	• Date of each prescription order for palbociclib	Structured data field
Palbociclib daily dose	exposure	• At each prescription order	Structured data field
Palbociclib treatment duration	exposure	• Duration from first prescription to last prescription for palbociclib	Structured data field
Endocrine therapy combined with palbociclib	exposure	• Endocrine therapy prescribed with palbociclib	See Appendix 2
Treatment pattern of each lines of therapy	exposure	• At each prescription order	See Appendix 2
Chemotherapy treatment pattern	exposure	• Start and end date of each order/prescription, drug name for chemotherapy drugs	See Appendix 2
Endocrine therapy treatment pattern	exposure	• Start and end date of each order/prescription, drug name for endocrine therapy drugs	See Appendix 2
Endocrine therapy treatment duration	exposure	• Duration from first prescription to last prescription for endocrine therapy drugs	See Appendix 2
Time to treatment failure	exposure	• Time to treatment failure is defined as the time from the start date of treatment to end date of treatment. Time to treatment failure will be censored at patient disenrollment or end of study period	Structured data field
G-CSF treatment date	exposure	• Date of each order/prescription	Based on ATC code "L03A1"
Antibiotics treatment date	exposure	• Date of each order/prescription	Based on ATC code "J01" and "J02"
Duration of the adjuvant therapy	exposure	• Date of each order/prescription	See the SAP
Duration from surgery to the starting of 1st line therapy	exposure	• Date of each order/prescription	See the SAP
Blood test date	exposure	• Date of each order	See the SAP

9.4. Data sources

MDV Database in based on health claims data and administrative data or Diagnosis Procedure Combination (DPC) data from over 360 Japanese acute hospitals.

The database is released and maintained by Medical Data Vision Inc., Ltd. The data contained in the database includes anonymized patient identifier, age, gender, diagnosis based on ICD code, medical procedures, prescriptions, inpatient/outpatient status, and

laboratory data. The database does not include information about treatment outcomes or details of diagnosis. The data are updated monthly. Data collected from April 2008 will be used in this study.

9.5. Study size

This is a descriptive study and sample size and power calculations are not applicable. All eligible patients with breast cancer diagnosis and who received endocrine therapy drugs and who didn't receive anti-HER2 therapy drugs (defined as HR+/HER2- breast cancer) will be included in the analysis. According to a preliminary feasibility assessment, the number of HR+/HER2- breast cancer patients is 10,3124.

9.6. Data management

This is a retrospective and non-interventional study using the Medical Data Vision Inc (MDV) database whose data collection is controlled by MDV. In this study, Pfizer will request data extraction based on inclusion/exclusion criteria to MDV, and CSS and Pfizer will use the dataset which is quality control (QC)'d by MDV for analysis.

Patient data are provided by MDV. Initial assessments will be made using descriptive statistics and data visualization: histograms, bar charts, and box plots of variables. Reasonable thresholds will be set to identify extreme outliers (e.g. 1.5 * interquartile range). Assumptions of normal distributions of the analysis variables will be evaluated. All data management and statistical analyses will be conducted using Statistical Analysis Software (SAS v. 9.4) and R version 3.4.0 or later (The R Foundation for Statistical Computing). Further details regarding data management will be stated in a SAP.

9.7. Data analysis

The primary objective of this study is to describe patient demographics, treatment patterns and treatment duration of palbociclib, and subsequent treatment patterns and treatment duration after palbociclib-based therapy among the advanced metastatic breast cancer female patients in Japan initiating treatment with palbociclib following drug launch in Japan. For the advanced metastatic breast cancer male patients, the analysis will be exploratory.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a 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.

9.7.1. Statistical methods

Descriptive statistics will be reported for continuous variables using mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum. Categorical variables will be reported using frequencies and proportions. Missing values will also be reported for each variable. For proportions, 95% confidence intervals will be provided using Wilson score method when appropriate.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the 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.

9.7.1.1. Objectives

9.7.1.1.1. Treatment pattern and target population of palbociclib

Demographic and clinical characteristics (as listed in section 9.3 in Table 2) will be descriptively summarized for all patients initiating palbociclib and will be explored by line of therapy (provided data are sufficient).

Treatment pattern of palbociclib will be assessed based on the percentage of patients initiating palbociclib line, as first-line, second-line, and so on. Specifically, the number of patients initiating palbociclib line (e.g. first-line, second-line) divided by the total number of patients initiating any cancer treatment line (as first-line, second-line, and so on, respectively) will be calculated. Moreover, the distribution of each endocrine treatment combination with palbociclib line, as percentages, will be assessed.

9.7.1.1.2. Time to treatment failure of palbociclib in combination with endocrine therapy

Time to treatment failure of palbociclib in combination with endocrine therapy is defined as time from the date of first palbociclib prescription to the to the date of last palbociclib prescription or to the date of the next line of therapy (described in the SAP), defined as the end of palbociclib treatment. Duration will be calculated in days and descriptively summarized. Also, Kaplan-Meier analysis will be performed to analyze time to treatment failure, and Kaplan-Meier curves will be presented. For this purpose, time to treatment failure will be censored at the earliest of any of the following: latest patient record, or the end of the study period. Regarding censoring, details will be specified in the SAP. Analysis will be stratified by the treatment line position (e.g. first-line, second-line).

9.7.1.1.3. Treatment pattern of subsequent therapy after palbociclib, including line of therapy and type of treatment

For the first treatment line with palbociclib, the proportion of each anti-cancer drug in the subsequent therapy after palbociclib will be calculated, as the number of patients having the corresponding anti-cancer drug in the subsequent therapy divided by the total number of patients with a subsequent therapy after palbociclib line. Moreover, the proportion of each treatment line regimen (including anti-cancer drug category combinations) will be calculated in a similar manner. Additionally, the same analysis will be performed after stratification by the position of palbociclib line (e.g. first-line, second-line), when possible. Details will be described in the SAP.

9.7.1.1.4. Time to treatment failure of subsequent therapy after palbociclib

Time to treatment failure of subsequent therapy after palbociclib is defined as time from the date of first next line of therapy after end of palbociclib treatment to the date of lost to follow-up or to the date of the second next line of therapy. Duration will be calculated in days and descriptively summarized. Also, Kaplan-Meier analysis will be performed to analyze time to treatment failure, and Kaplan-Meier curves will be presented. For this purpose, time to treatment failure will be censored at the earliest of any of the following: latest patient record, or the end of the study period. Regarding censoring, details will be specified in the SAP.

9.7.1.1.5. Changes in treatment pattern (e.g. before vs. after the launch, annual review after launch of palbociclib)

Within each specific time intervals (Time interval definition will be addressed in the SAP), for each therapy, the proportion of patients initiating the corresponding therapy (as first-line, second-line, and so on), defined as the number of patients initiating the corresponding therapy (as first-line, second-line, and so on) divided by the total number of patients initiating any cancer treatment line (as first-line, second-line, and so on, respectively). Results will be graphically displayed using bar plots.

9.7.1.1.6. Use of antibiotics and/or G-CSF after administration of palbociclib

The proportion of patients prescribed antibiotics and the proportion of patients prescribed G-CSF during treatment with palbociclib will be calculated as the number of patients prescribed the corresponding treatment divided by the total number of patients prescribed palbociclib.

9.7.1.1.7. Frequency of Blood Test

The frequency of blood test after administration of palbociclib will be calculated as the number of patients prescribed the corresponding treatment divided by the total number of patients prescribed palbociclib.

9.7.1.1.8. Treatment pattern and target population of each line of therapy for ABC

Demographics and clinical characteristics (as listed in section 9.3 in Table 2) will be descriptively summarized for patients initiating endocrine therapy and will be explored by line of therapy within each time interval, in which each therapy started (the time intervals will be defined in the SAP). Line of therapy will be defined based on the drugs described in appendix 2.

Treatment pattern of endocrine therapy will be assessed based on the percentage of patients initiating endocrine therapy, as first-line, second-line, and so on. Specifically, the number of patients initiating endocrine therapy (e.g. first-line, second-line) divided by the total number of patients initiating any cancer treatment line (as first-line, second-line, and so on, respectively) will be calculated.

9.7.1.1.9. Time to treatment failure of endocrine therapy

Time to treatment failure of endocrine therapy is defined as the time from the date of first prescription of endocrine therapy to the date of last endocrine prescription or to date of the next line of therapy, defined as the end of the therapy. Descriptive summary for the time to treatment failure will be calculated using Kaplan-Meier method and Kaplan-Meier curves will be also presented. Time to treatment failure will be censored at the latest date of the patient record in the database or the end of the study period, whichever occurred first, if the end of treatment is not confirmed in the database. The analysis will be stratified by the line of endocrine therapy (e.g. first-line, second-line) and the time intervals, in which each therapy started (the time intervals will be defined in the SAP).

9.7.1.1.10. Treatment pattern of subsequent therapy after endocrine therapy, including line of therapy and type of treatment

Treatment pattern of anti-cancer drugs following the first line endocrine therapy will be summarized using the number and proportion of patients having each anti-cancer drug in patients who received a subsequent therapy after the first line endocrine treatment. The pattern of treatment regimen (including combination of anti-cancer drugs; details will be described in the SAP) will be summarized in the same manner. Moreover, the treatment pattern of anti-cancer drugs and regimens following the second and later line of endocrine therapy will be summarized for each line respectively if the sample size is feasible.

9.7.1.1.11. Time to treatment failure of subsequent therapy after endocrine therapy

Time to treatment failure of the subsequent therapy after endocrine therapy of any line is defined as the time from the date of first prescription of the subsequent therapy to the date of end of treatment defined as the initiation the next line of therapy. Descriptive summary of the time to treatment failure will be calculated for each line of the previous endocrine therapy using Kaplan-Meier method and Kaplan-Meier curves will be also presented. Time to treatment failure will be censored at the latest date of the patient record in the database or the end of the study period, whichever occurred first, if the end of treatment is not confirmed in the database.

9.7.1.1.12. Use of antibiotics and/or G-CSF after initiation of treatments for ABC

The proportion of patients prescribed antibiotics and the proportion of patients prescribed G-CSF during treatment for ABC will be calculated as the number of patients prescribed the corresponding treatment divided by the total number of patients treated for ABC. The analysis will be explored by line of therapy and type of treatment.

9.8. Quality control

This study is a retrospective observational study using quality controlled data in a pre-existing database, and primary data collection will not be conducted. As for the data provided, quality of the data is guaranteed by MDV. All of these processes are consistently managed in-house.

Data analysis will be outsourced to Clinical Study Support, Inc. (CSS).

CSS has a professional team to verify accuracy of the data. For quality assurance of analysis, CSS will conduct code review of all modules of program for generating analysis datasets, and perform a descriptive statistics review of all variables. Program development for generating datasets will be conducted by two trained analysts in an independent manner (double programming), and the consistency between the datasets will be assessed. Analysis outputs, including tables and figures, will be generated by one trained analyst and their qualities reviewed by another trained analyst, independently.

9.9. Limitations of the research methods

The complete medical history of patients may not be obtained because of the limited data period in MDV database, which means that the patients cannot be followed up once they change hospitals, and data of patients prior to the registration to the database are not fully available. Therefore, the past medical history or a treatment history may be missing for some patients. Also, it should be noted that the reason of loss to follow-up is not available in MDV database. For these reasons, attention should be paid regarding information bias, when interpreting insights obtained about palbociclib utilization in real-world settings.

9.10. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, 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 institutional review boards (IRBs)/independent ethics committees (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), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making, International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, The ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies, Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data, FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study does not involve data collection on individual patients by their treating healthcare professionals and the MDV data used in this study does not intend to identify product safety information. The MDV data for this study will be completed online via a secure website The MDV data does not provide a free text field where study participants could specify information that may constitute product safety information. Further, routine communication with study participants via email or phone with CSS is not expected during the conduct of the study. However, it is possible that a study participant may volunteer product safety information to CSS while in conversation about the MDV data for any other reason (e.g., seeking information about the purpose of the study); this information must be reported as described below.

The following safety events must be reported on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form: serious and non-serious adverse events (AEs) when associated with the use of the Pfizer product, and scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure **(all reportable, regardless of whether associated with an AE)**, when associated with the use of a Pfizer product.

In the event that a study participant volunteers product safety information, CSS must complete the NIS AEM Report Form and submit to Pfizer within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form is the study participant's contact information; complete contact information should be obtained so that, once the NIS AEM Report Form is sent to Pfizer, the NIS AEM Report Form can be

assessed and processed according to Pfizer's standard operating procedures, including requests for follow-up to the study participant.
CSS who will serve to code review of all modules of program for generating analysis datasets and perform a descriptive statistics review of all variables must complete the following Pfizer training requirements:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

These trainings must be completed by CSS 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. The study vendor will also provide copies of all signed training certificates 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

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 MDV 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 The latest cancer ganjoho.jp (National Cancer Center, the Center for Cancer Control and Information Services); http://ganjoho.jp/reg_stat/statistics/stat/summary.html.

2 The Japanese Breast Cancer Society. Clinical Practice Guidelines for Breast Cancer 2018; http://jbcs.gr.jp/guidline/2018/

3 National cancer institute. Surveillance, Epidemiology, and End Results Program. SEER Stat Fact Sheets: Female Breast Cancer.; http://seer.cancer.gov/statfacts/html/breast.html.

4 Metastatic Breast Cancer Network. Educating Empowering Advocating, Education, Incidence and Incidence Rates; http://mbcn.org/education/category/incidence-and-incidence-rates.

5 Harvey JM, et al. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol. 1999;17:1474-81.

6 Finn RS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016;375:1925-36.

7 Turner NC, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015;373:209-19.

8 Cristofanilli M, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016;17:425-39.

9 Loibl S, et al. Palbociclib Combined with Fulvestrant in Premenopausal Women with Advanced Breast Cancer and Prior Progression on Endocrine Therapy: PALOMA-3 Results. Oncologist. 2017;22: 1028-38.

10 Tamura K, Mukai H, Naito Y, et al. Phase I study of palbociclib, a cyclin-dependent kinase 4/6 inhibitor, in Japanese patients. Cancer Sci 107 (2016) 755–63.

14. LIST OF TABLES

15. LIST OF FIGURES

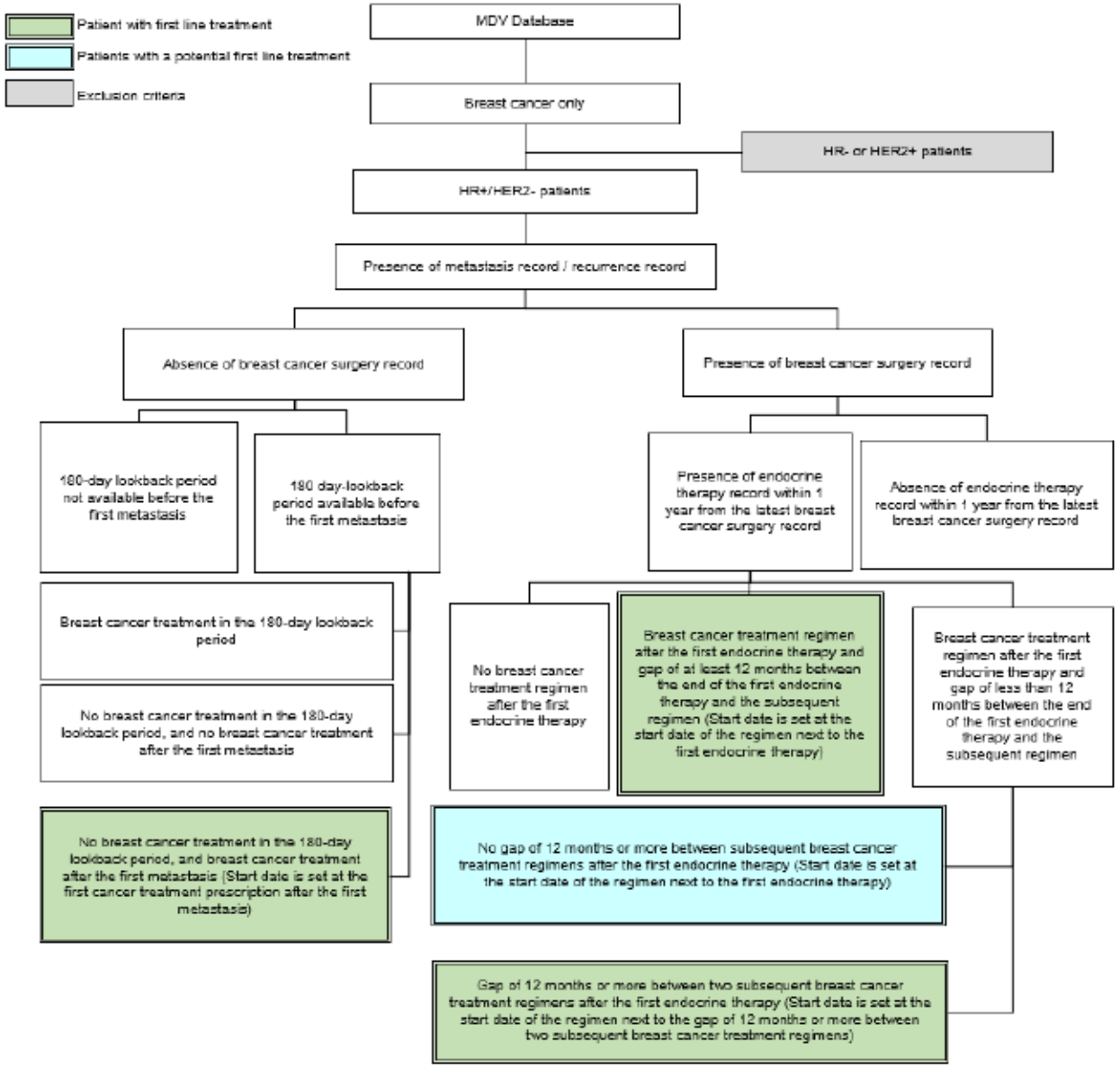
Not applicable

ANNEX 1. ADDITIONAL INFORMATION

Appendix 1: Algorithm to define the first line treatment for advanced breast cancer

Appendix 2: List of Treatment Drugs for Breast Cancer

Appendix 1: Algorithm to define the first line treatment for advanced breast cancer



Appendix 2: List of Treatment Drugs for Breast Cancer

(1) Endocrine therapy drugs

Generic name	Abbreviation	Trade name	Route of administration	Therapeutic category
Anastrozole	ANA	Arimidex, others*	Oral	Aromatase inhibitor
Exemestane	EXE	Aromasin, others*	Oral	Aromatase inhibitor
Goserelin acetate [a)]	ZOL	Zoladex	Subcutaneous injection	LH-RH agonist
Tamoxifen citrate	TAM	Nolvadex, others*	Oral	Selective estrogen receptor modulator
Toremifene citrate	TOR	Fareston, others*	Oral	Selective estrogen receptor modulator
Fulvestrant	FUL	Faslodex	Intramuscular injection	Selective estrogen receptor downregulator
Medroxyprogesterone acetate	MPA	Hysron-h200, others*	Oral	Oral antineoplastic progestin
Leuprorelin acetate [a)]	LPR	Lupron, others*	Subcutaneous injection	LH-RH agonist
Letrozole	LET	Femara	Oral	Aromatase inhibitor

LH-RH: Luteinizing Hormone-Releasing Hormone a) Goserelin acetate and Leuprorelin acetate are excluded from the treatment drugs for breast cancer for this study.

(2) Antibody therapeutic drugs

Generic name	Abbreviation	Trade name	Route of administration	Therapeutic category
Denosumab[a)]	Dmab	RANMARK	Subcutaneous injection	Human anti-RANKL monoclonal antibody
Trastuzumab		Herceptin	Intravenous injection	Humanized anti-HER2 monoclonal antibody
Trastuzumab emtansine	T-DM1	Kadcyla	Intravenous injection	Trastuzumab and DM1 antibody–drug conjugate
Bevacizumab	Bmab	Avastin	Intravenous injection	Humanized anti-VEGF monoclonal antibody
Pertuzumab		Perjeta	Intravenous injection	Humanized anti-HER2 monoclonal antibody
Trastuzumab Deruxtecan	T-DXd	Enhertu	Intravenous injection	Trastuzumab and DXd antibody–drug conjugate

a) Denosumab is excluded from the treatment drugs for breast cancer for this study.

(3) Small molecular compounds

Generic name	Abbreviation	Trade name	Route of administration	Therapeutic category
Everolimus		Afinitor	Oral	mTOR inhibitor
Palbociclib		Ibrance	Oral	CDK4/6 inhibitor
Lapatinib tosilate hydrate		Tykerb	Oral	HER1/HER2 tyrosine kinase inhibitor

Abemaciclib		Verzenio	Oral	CDK4/6 inhibitor
Olaparib		Lynparza	Oral	PARP1 inhibitor

(4) Cytotoxic chemotherapy drugs

Generic name	Abbreviation	Trade name	Route of administration	Therapeutic category
Irinotecan hydrochloride hydrate	CPT-11	Campto, others*	Intravenous injection	Topoisomerase I inhibitor
Epirubicin hydrochloride	EPI	Pharmorubicin, others*	Intravenous injection	Antitumor antibiotic
Eribulin mesylate	HAL	Halaven	Intravenous injection	Microtubule inhibitor
Capecitabine	CAP	Xeloda	Oral	Antimetabolite
Carboplatin	CBDCA	Paraplatin, others*	Intravenous injection	Platinum compound
Gemcitabine hydrochloride	GEM	Gemzar, others*	Intravenous	Antimetabolite
Cyclophosphamide hydrate	CPA	Endoxan	Oral/Intravenous injection	Alkylating agent
Cisplatin	CDDP	Briplatin, others*	Intravenous injection	Antineoplastic
Tegafur–uracil	UFT	UFT	Oral	Antimetabolite
Tegafur–gimeracil–oteracil potassium	S-1	TS-1, others*	Oral	Antimetabolite
Doxifluridine	5'DFUR	Furtulon	Oral	Antimetabolite
Doxorubicin hydrochloride	ADM	Adriacin, others*	Intravenous injection	Antitumor antibiotic
Docetaxel hydrate	DTX	Taxotere, others*	Intravenous injection	Taxoid
Paclitaxel	PTX	Taxol, others*	Intravenous injection	Taxoid
Nab- Paclitaxel (Albmin suspended)	nab-PTX	Abraxane	Intravenous injection	Taxoid
Vinorelbine tartrate	VNB	Navelbine, others*	Intravenous injection	Vinca alkaloid
fluorouracil	5-FU	5-FU	Intravenous injection	antimetabolite
Mitomycin C	MMC	Mitomycin S	Intravenous injection	antitumor antibiotic
mitoxantrone hydrochloride	MIT	Novantrone	Intravenous injection	antitumor antibiotic
methotrexate	MTX	methotrexate	Intravenous injection	antifolic