Non-Interventional Study Protocol
A5481115

Descriptive Analyses of Clinical Characteristics and Treatment Patterns of Breast Cancer Patients Initiating Palbociclib (Ibrance®) Treatment in Japan by using MDV database

Statistical Analysis Plan
(SAP)

Version: 4.0

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TABLE OF CONTENTS

1 AMENDMENTS FROM PREVIOUS VERSION(S)

Amendment number	Date	SAP section(s) changed	Summary of amendment(s)	Reason
1	26 December 2019	2.1 Study design 10.1 Appendix 1: Data derivation details	Removal of the first exclusion criteria: Diagnosis of a second primary malignancy anytime during the study period according to the protocol amendment version 3.0	Broaden the population of palbociclib users considering that the presence of other cancer type may not influence study exposure and outcomes
		2.1 Study design 2.2 Study objectives 5.1 Efficacy / effectiveness endpoint(s) 7.2 Statistical analysis 10.1 Appendix 1: Data derivation details	Addition of objective 8 (To describe the frequency of blood test after administration of palbociclib) and corresponding amendments	To describe the frequency of blood test for palbociclib users to examine the occurrence of adverse effects
		10.3 Appendix 3: Diagnosis and procedure codes used in this study	Addition of code used for identifying blood test	Additional study objective: To describe the frequency of blood test for palbociclib users to examine the occurrence of adverse effects
		10.4 Appendix 4: List of tables and figures	Adding the list of tables and figures	Revision of list of tables and figures
2	16 November 2020	7.2 Statistical analysis	Restricting the definition of Palbociclib lines	Restricting the analysis to the first Palbociclib lines would facilitate the interpretation. A sufficient follow-up from Palbociclib line initiation to assess outcomes would be required.
3	17 June 2021	2 Introduction 2.1 Study design 2.2 Study objectives 4.4 Subgroups 5.1 Efficacy/Effectiveness endpoints 7.2 Statistical analyses 10.1 Appendix 1: Data derivation details 10.4 Appendix 4: List of tables and figures	Addition to Inclusion criteria. #3 Diagnosis of secondary malignant neoplasm based on ICD-10 (C77.x, C78.x, C79.x) Addition of objectives to reveal the demographic and clinical characteristics of ABC patients and to analyze endocrine based therapy for ABC patients	To exclude adjuvant endocrine therapy clearly from endocrine therapy for metastatic setting owing to the addition of the objectives To describe treatment paradigm changes with the launch of new treatment option, CDK4/6 inhibitor.

2 INTRODUCTION

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. 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.

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%. 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. According to The Japanese Breast Cancer Society Clinical Practice Guidelines for Breast Cancer 2018, 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+). Endocrine therapy is the main stream of the treatment for HR+ patients. 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). The choice of primary endocrine therapy for HR+/HER2- advanced breast cancer patients is often due to postoperative adjuvant endocrine therapy performed in the past, possible side effects, progression free period of pretreatment drugs and menopausal status of patients are considered and determined.

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 longer with palbociclib plus letrozole than with placebo plus letrozole in the initial treatment of postmenopausal women with estrogen receptor (ER)+/HER2- advanced breast cancer [the 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]. 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.

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).

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. Thus retrieving data from the real world setting for palbociclib is necessary 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 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- advanced breast cancer (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.

2.1 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. This study will describe the patient demographic and clinical characteristics, real-world treatment patterns including line of therapy and type of endocrine therapy combined with palbociclib, use of antibiotics and/or G-CSF, and the frequency of blood test. The algorithm to define the first line treatment for advanced breast cancer is described in appendix 1.

Setting

The 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	APR 2008 - DEC 2018
Second Year	APR 2008 – AUG 2019
Third Year	APR 2008 – DEC 2020
Fourth Year	APR 2008 – OCT 2021
Fifth Year	APR 2008 – OCT 2022

Study population

Breast cancer patients in Japan recorded in MDV database after December 2008 will be selected for the study. MDV data will be extracted for each patient from the first data record up to the latest record available. The latest surgery or the first metastasis record will be set as a baseline to determine breast cancer treatment lines. Patient data period will be defined as the period from the first patient data record to the latest available patient data record. Patients meeting all of the following criteria will be selected for analysis.

✧ Inclusion criteria

1) Diagnosis of breast cancer based on International statistical classification of diseases and related health problems 10th revision (ICD-10) (C50.xx)

Presence of any breast cancer related record in DiseaseData (identified using *Icd10code* codes C50) with confirmed diagnosis (*UtagaiFlg*=0) within patient data period

2) Received at least one prescription of endocrine therapy drugs during the index period

Presence of at least one prescription record of endocrine therapy (identified using *Receiptcode* as listed in Appendix 3 in treatment sheet) in ActData within the patient data period

3) Diagnosis of secondary malignant neoplasm based on ICD-10 (C77.x, C78.x, C79.x)

Presence of any metastasis related record in DiseaseData (identified using *Icd10code* codes in metastasis sheet) with confirmed diagnosis (*UtagaiFlg*=0) within patient data period

✧ Exclusion criteria

1) Received at least one prescription of anti-HER2 therapy (Trastuzumab, Trastuzumab emtansine, Pertuzumab, and Rapachinibutoshiru acid hydrate) during the index period

Presence of at least one prescription record of anti-HER2 treatment (identified using *Receiptcode* as listed in Appendix 3 in treatment sheet) in ActData within the patient data period

◆ The algorithm for identifying the first-line treatment for breast cancer is as follows:

1) Patient with any breast cancer related record in DiseaseData (identified using *Icd10code* C50) with confirmed diagnosis (*UtagaiFlg*=0) within patient data period

2) Patient with at least one prescription record of endocrine therapy (identified using *Receiptcode* as listed in Appendix 3 in treatment sheet) in ActData within the patient data period

3) Patient without any prescription record of anti-HER2 treatment (identified using *Receiptcode* as listed in Appendix 3 in treatment sheet) in ActData within the patient data period

4) Patient meeting the following criteria for any of the four subpopulations as defined below (see section 4.4 for details):

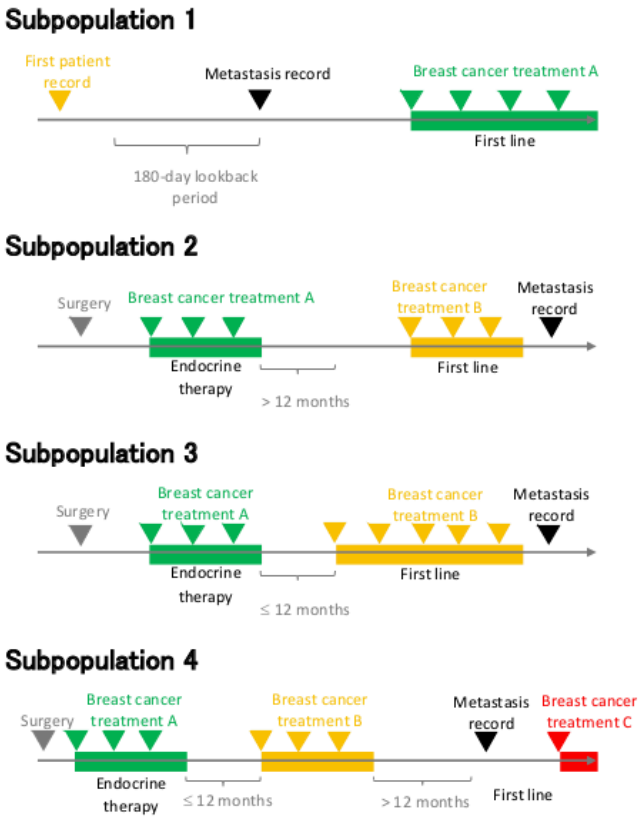
➢ Subpopulation 1: De novo metastatic breast cancer patients

➢ Subpopulation 2: Patients with metastatic breast cancer with breast cancer surgery and a first treatment line starting after at least 12 months after the first endocrine therapy

➢ Subpopulation 3: Patients with metastatic breast cancer with breast cancer surgery and a first treatment line starting within less than 12 months after a subsequent breast cancer treatment regimen (first endocrine therapy excluded)

- Subpopulation 4: Patients with metastatic breast cancer with breast cancer surgery and a first treatment line starting after at least 12 months after a subsequent breast cancer treatment regimen (first endocrine therapy excluded)

Figure 1. Examples of patterns for each subpopulation



Subsequent therapies

Patients with a first-line treatment for breast cancer will be considered as the analysis population. Subsequent therapies (identified using the algorithm below) after the first-line treatment will be defined as the second line, third line, and so on, in a sequential manner.

- For identifying subsequent therapies, the following algorithm will be used:

1. Medical record for breast cancer treatment prescription based on *Receiptcode* (Appendix 3) will be identified after metastasis record date (based on *FromDate*) or last surgery (based on *ActDate*), as mentioned above.

2. The first subsequent therapy will be defined at the first breast cancer treatment prescription record date (*ActDate*), and the initiation date will be set at the corresponding date.

3. Combinations (based on general name as listed in Appendix 3 in treatment sheet) of breast cancer treatments will be identified within a time-window from initiation date to initiation date + 30 days

4. End of the first subsequent therapy will be set as any of the earliest among the following criteria:

   a) Gap period of at least 120 days between two subsequent breast cancer treatment prescription records in the first subsequent therapy (based on general name as listed in Appendix 3 in treatment sheet): The end of the subsequent therapy will be set as the date of the latest record before the gap + 120 days

   b) Presence of a breast cancer treatment not in the first subsequent therapy (based on general name as listed in Appendix 3 in treatment sheet): the earliest date of a new breast cancer treatment prescription record – 1 days will be defined as the end of the first subsequent therapy

   c) End of the study period

   d) Last patient data record

   Duration will be calculated as the difference between the end of the first subsequent therapy - first breast cancer treatment prescription record date +1 day.

5. Subsequent therapies will be identified as follows

   a) The subsequent therapy will be defined at the first breast cancer treatment prescription record date (*ActDate*) after the end of the previous subsequent therapy, and the initiation date will be set at the corresponding record date.

   b) Combinations (based on general name as listed in Appendix 3 in treatment sheet) of breast cancer treatments will be identified within a time-window from initiation date to initiation date + 30 days

   c) End of the subsequent therapy will be set as any of the earliest among the following criteria:

- ✧ Gap period of at least 120 days between two subsequent breast cancer treatment prescription records in the subsequent therapy (based on general name as listed in Appendix 3 in treatment sheet): The end of the subsequent therapy will be set as the date of the latest record before the gap + 120 days
- ✧ Presence of a breast cancer treatment not in the subsequent therapy (based on general name as listed in Appendix 3 in treatment sheet): the earliest date of a new breast cancer treatment record – 1 days will be defined as the end of the subsequent therapy
- ✧ End of the study period
- ✧ Last patient data record

d) Repeat 5) until the last breast cancer treatment prescription record

Duration will be calculated as the difference between the end of the subsequent therapy - the first breast cancer treatment prescription record date after the end of the previous subsequent +1 day.

Subsequent therapy algorithm was based on a reported algorithm used on existing claims database (Carroll et al., 2017). Briefly, examples are described in the diagram below.

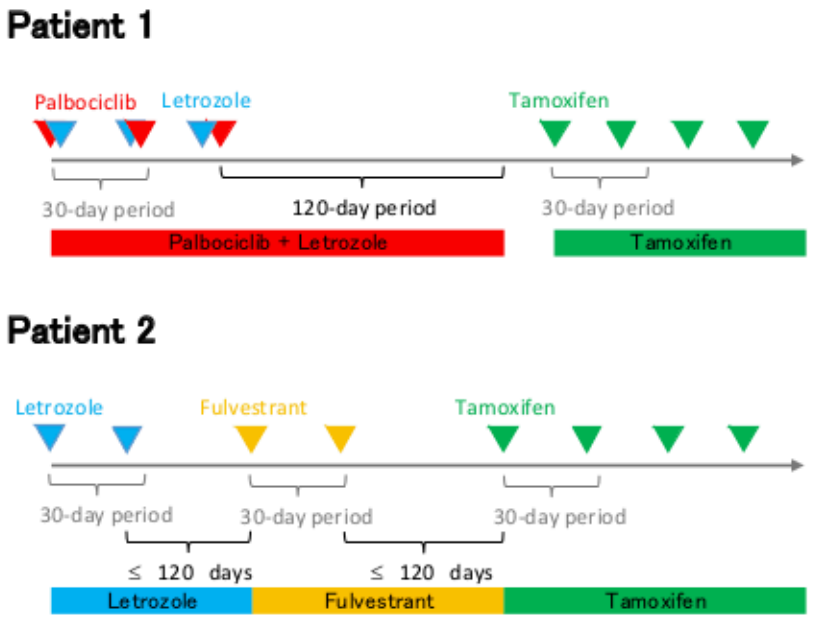


Figure 2. Examples of treatment sequence patterns

Data source

MDV Database is based on health claims data and administrative data or DPC (Diagnosis Procedure Combination) data from over 300 Japanese acute hospitals.

The database is released and maintained by Medical Data Vision Inc. The data contained in the database includes anonymized patient identifier, age, gender, diagnosis, medical procedures, prescriptions, inpatient/outpatient status, and laboratory data. Data collected from 2008 will be used in this study. Definitions of the variables in MDV datasets are indicated in the definition form Non-English Text _20210521.xlsx .

Treatment/cohort labels

Not applicable

2.2 STUDY OBJECTIVES

The main 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 (December 15, 2017). More specifically, Medical Data Vision (MDV) database will be utilized to achieve the following research objectives:

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

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

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

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

Objective 5: To evaluate TTF of subsequent therapy after end of palbociclib treatment

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

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

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

Objective 9: To characterize the demographic and clinical characteristics of ABC patients at the initiation of endocrine treatment for ABC

Objective 10: To describe the treatment patterns of each line of endocrine therapy for ABC patients

Objective 11: To evaluate TTF of endocrine therapy for ABC patients

Objective 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

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

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

3 HYPOTHESES AND DECISION RULES

3.1 STATISTICAL HYPOTHESES

This is a descriptive retrospective observational study using claims database without any specific hypothesis.

3.2 STATISTICAL DECISION RULES

For statistical tests, the statistical significance level will be 0.05 (two-sided). Analysis will be performed using SAS Release 9.4 or later (SAS Institute, Inc., Cary, NC), and R version 3.4.0 or later (The R Foundation for Statistical Computing).

4 ANALYSIS SETS/POPULATIONS

4.1 FULL ANALYSIS SET

Analysis dataset will be defined as any patient meeting inclusion and exclusion criteria (see section 2.1) and with identified first treatment line for breast cancer.

4.2 SAFETY ANALYSIS SET

Not applicable

4.3 OTHER ANALYSIS SET

Not applicable

4.4 SUBGROUPS

In this study, analysis population will be divided into subgroups as described below.

Subpopulation 1

- Any metastasis record (identified using *Icd10code* as listed in Appendix 3 in meta sheet) in DiseaseData within the patient data period

Metastasis record date will be identified using the variable *FromDate* at the first metastasis record.

- Absence of breast cancer surgery record (identified using *KubunCode* as listed in Appendix 3 in surgery sheet) in ActData within the patient data period

- 180 day-lookback period available before the first metastasis record

The difference between the metastasis record date and the date of the earliest record available is at least equal to 180 days.

- At least one breast cancer treatment prescription record after the first metastasis record (identified using *Receiptcode* as listed in Appendix 3 in treatment sheet) in ActData, and no breast cancer treatment prescription record in the 180 day-lookback period
  The breast cancer treatment after the first metastasis record will be defined as the first-line treatment.

The first line will be determined using the algorithm of subsequent therapies as described further below.

Subpopulation 2

- Any metastasis record (identified using *Icd10code* as listed in Appendix 3 in meta sheet) in DiseaseData within the patient data period

- Breast cancer surgery record (identified using *KubunCode* as listed in Appendix 3 in surgery sheet) in ActData within the patient data period

- Adjuvant endocrine therapy*, defined as the first subsequent endocrine therapy record (identified based on general name as listed in Appendix 3. in treatment sheet) with start date within 365 days from the last breast cancer surgery record (identified using *KubunCode* as listed in Appendix 3 in surgery sheet)

*Please refer to the section corresponding to the algorithm of treatment sequences.

- Initiation of another breast cancer treatment subsequent therapy after the endocrine therapy with a gap of at least 12 months (365 days) between the end of the endocrine therapy and the start of the other breast cancer treatment subsequent therapy.
  The latter will be defined as the first-line treatment.

Subpopulation 3

- Any metastasis record (identified using *Icd10code* as listed in Appendix 3 in meta sheet) in DiseaseData within the patient data period
- Breast cancer surgery record (identified using *KubunCode* as listed in Appendix 3 in surgery sheet) in ActData within the patient data period
- Adjuvant endocrine therapy*, defined as a the first subsequent endocrine therapy record (identified based on general name as listed in Appendix 3 in treatment sheet) with start date within 365 days from the last breast cancer surgery record (identified using *KubunCode* as listed in Appendix 3 in surgery sheet)

  *Please refer to the section corresponding to the algorithm of treatment sequences
- No gap of 12 months or more between subsequent therapies after the end of the adjuvant endocrine therapy.
  The first-line treatment will be defined as the breast cancer treatment sequence next to the adjuvant endocrine therapy.

The following patients will not be included in the analysis since the true first-line treatment among these individuals would be difficult to assess:

- ✧ Patients with the same hormonal therapy in both adjuvant endocrine therapy and the first-line treatment
- ✧ Patients with Letrozole in adjuvant endocrine therapy, and Anastrozole in the first-line treatment
- ✧ Patients with Anastrozole in adjuvant endocrine therapy, and Letrozole in the first-line treatment

Subpopulation 4

- Any metastasis record (identified using *Icd10code* as listed in Appendix 3 in meta sheet) in DiseaseData within the patient data period

- Breast cancer surgery record (identified using *KubunCode* as listed in Appendix 3 in surgery sheet) in ActData within the patient data period

- Adjuvant endocrine therapy*, defined as a the first subsequent endocrine therapy record (identified based on general name as listed in Appendix 3 in treatment sheet) with start date within 365 days from the last breast cancer surgery record (identified using *KubunCode* as listed in Appendix 3 in surgery sheet)

  *Please refer to the section corresponding to the algorithm of subsequent therapy.

- Initiation of second subsequent therapy next to first subsequent therapy after adjuvant endocrine therapy with a gap of at least 12 months between the end of first subsequent therapy and start of the second subsequent therapy. The second subsequent therapy next to the gap of at least 12 months will be defined as the first-line treatment. If several gaps are identified, only the first one will be considered.

5 ENDPOINTS AND COVARIATES

Endpoints, patient demographic and clinical characteristics, and exposures are described below. Exposure will be defined as each cancer treatment line (see section 2.1).

5.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

Definition of endpoints, and patient demographic and clinical characteristics are indicated in the table below.

Table 1. Definitions of exposures

Variable	Role	Operational definition
Palbociclib line	Exposure	Treatment line will be identified using the algorithm described in section 2.1. Among treatment line, palbociclib treatment lines will be identified based on general name as listed in Appendix 3. Each treatment line will be characterized using start date and end date of the treatment line. When considering combinations with endocrine treatment, the following drugs will be considered and identified using receiptcodes as listed in Appendix 3: anastrozole, exemestane, fulvestrant, letrozole, medroxyprogesterone, tamoxifen, toremifene.
Chemotherapy line	Exposure	Treatment line will be identified using the algorithm described in section 2.1. A chemotherapy line (single or as combination) will be identified. Each treatment line will be characterized using general name, and start date and end date of the treatment line.
Endocrine therapy line	Exposure	Treatment line will be identified using the algorithm described in section 2.1. An endocrine therapy line

Variable	Role	Operational definition
		(single or as combination) will be identified. Each treatment line will be characterized using general name, and start date and end date of the treatment line.
Targeted therapy line	Exposure	Treatment line will be identified using the algorithm described in section 2.1. A targeted therapy line (single or as combination) will be identified. Each treatment line will be characterized using general name, and start date and end date of the treatment line.
Blood test date	Exposure	Blood test identified using *receiptcode* for laboratory test (Appendix 3) Note: The number of blood test date will be calculated based on the number of unique *ActDate*.

Table 2. Definitions of endpoints

Variable	Role	Operational definition
Age at the first line for advanced breast cancer	Target population of palbociclib (Demographic/Clinical characteristics)	Age recorded at the start of the first line
Age at palbociclib initiation	Target population of palbociclib (Demographic/Clinical characteristics)	Age recorded at the start of the first palbociclib line
Age at endocrine therapy initiation	Target population of endocrine therapy (Demographic/Clinical characteristics)	Age recorded at the start of the endocrine therapy (at first line, second line, and third line, respectively)
Gender	Target population of palbociclib (Demographic/Clinical characteristics)	Gender recorded at the start of the first palbociclib line
Gender (endocrine therapy)	Target population of endocrine therapy (Demographic/Clinical characteristics)	Gender recorded at the start of the endocrine therapy (at first line, second line, and third line, respectively)
Weight	Target population of palbociclib (Demographic/Clinical characteristics)	*Weight* recorded in FF1Data within the period 180 days - the first palbociclib line start date to the first palbociclib line start date The value of the latest record will be considered.

Variable	Role	Operational definition
Weight (endocrine therapy)	Target population of endocrine therapy (Demographic/Clinical characteristics)	*Weight* recorded in FF1Data within the period 180 days - the endocrine therapy start date to the endocrine therapy start date (first line, second line, and third line, respectively) The value of the latest record will be considered.
Height	Target population of palbociclib (Demographic/Clinical characteristics)	*Height* recorded in FF1Data within the period 180 days - the first palbociclib line start date to the first palbociclib line start date The value of the latest record will be considered.
Height (endocrine therapy)	Target population of endocrine therapy (Demographic/Clinical characteristics)	*Height* recorded in FF1Data within the period 180 days - the endocrine therapy start date to the endocrine therapy start date (first line, second line, and third line, respectively) The value of the latest record will be considered.
BMI	Target population of palbociclib (Demographic/Clinical characteristics)	BMI will be calculated using the following formula: BMI=(weight)/(height/100)^2 If either weight or height is zero or missing, BMI will be considered as missing.
BMI (endocrine therapy)	Target population of endocrine therapy (Demographic/Clinical characteristics)	BMI will be calculated using the following formula: BMI=(weight)/(height/100)^2 If either weight(endocrine therapy) or height(endocrine therapy) is zero or missing, BMI will be considered as missing. Note: BMI for endocrine therapy at first line, second line and third line will be identified, respectively. However, the weight and height are recorded only at hospitalization, and the measurement at the same timepoint may be used for all the lines.
Charlson comorbidity index	Target population of palbociclib (Demographic/Clinical characteristics)	Calculation of Charlson comorbidity index will be performed by summing up weights for particular *Icd10code* identified at the start date of the first palbociclib line using the based on *DataMonth*. To exclude a suspected disease, only disease records with “Utagaiflg” coded as 0 will be considered. ICD-10 codes for the corresponding diseases and their respective weights will be indicated in the excel file “Appendix 3” in “Charlson” sheet. [Reference] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for

Variable	Role	Operational definition
		defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005 Nov;43(11):1130-9.
Charlson comorbidity index (endocrine therapy)	Target population of endocrine therapy (Demographic/Clinical characteristics)	Similarly as above, the calculation of Charlson comorbidity index will be performed by summing up weights for particular *Icd10code* identified at the start date of the endocrine therapy (at first line, second line, and third line, respectively) using the based on *DataMonth*.
Cancer stage	Target population of palbociclib (Demographic/Clinical characteristics)	Cancer stage will be determined based on *uicct*, *uiccn*, and *uiccm* in FF1Data within the period 180 days - the first palbociclib line start date to the first palbociclib line start date Stage will be classified based on MDV data categories.
Cancer stage (endocrine therapy)	Target population of endocrine therapy (Demographic/Clinical characteristics)	Cancer stage will be determined based on *uicct*, *uiccn*, and *uiccm* in FF1Data within the period 180 days - the first endocrine therapy start date to the first endocrine therapy start date Stage will be classified based on MDV data categories.
Palbociclib daily dose	Target population of palbociclib (Demographic/Clinical characteristics)	Palbociclib daily dose will be identified at the first palbociclib prescription record within the corresponding palbociclib line using *Amount* of the corresponding receipt record multiplied by the dose corresponding to the receiptcode as indicated in Appendix 3 in treatment sheet.
Index year	Target population of palbociclib (Demographic/Clinical characteristics)	Year corresponding to the start date of the first palbociclib line
Index year (endocrine therapy)	Target population of endocrine therapy (Demographic/Clinical characteristics)	Year corresponding to the start date of the first endocrine therapy
Treatment duration of palbociclib	Time to treatment failure of palbociclib	For each palbociclib treatment line, the duration will be calculated as the difference between the corresponding palbociclib end date – start date +1 days. However, if latest patient record or the end of the study period occurs before end date, the duration

Variable	Role	Operational definition
		will be censored at the corresponding date. Date of the censore will be defined as "end date".
Treatment duration of endocrine therapy	Time to treatment failure of endocrine therapy	For each endocrine therapy, the duration will be calculated as the difference between the corresponding endocrine therapy (first line, second line, and third line, respectively) end date – start date +1 days. However, if latest patient record or the end of the study period occurs before end date, the duration will be censored at the corresponding date. Date of the censore will be defined as "end date".
Status for termination of palbociclib line	Time to treatment failure of palbociclib	For each palbociclib line, the status for treatment termination will be classified as follows: 1. Appearance of a new breast cancer treatment and no discontinuation of all breast cancer treatments: any new breast cancer treatment record within 120 day window from the end of palbociclib line 2. Treatment gap (>120 days) of all breast cancer treatment: at least 120 day gap after palbociclib line end date 3. Discontinuation of all breast cancer treatments: no breast cancer treatment in palbociclib line present in the subsequent line 4. Patient disenrollment: palbociclib line end date corresponding to the last patient record date 5. End of study period: palbociclib line end date corresponding to the end of the study period (2021/4)
Status for termination of endocrine therapy	Time to treatment failure of endocrine therapy	For each endocrine therapy, the status for treatment termination will be classified as follows: 1. Appearance of a new breast cancer treatment and no discontinuation of all breast cancer treatments: any new breast cancer treatment record within 120 day window from the end of endocrine therapy 2. Treatment gap (>120 days) of all breast cancer treatment: at least 120 day gap after endocrine therapy end date 3. Discontinuation of all breast cancer treatments: no breast cancer treatment in endocrine

Variable	Role	Operational definition
		therapy present in the subsequent line 4. Patient disenrollment: endocrine therapy end date corresponding to the last patient record date End of study period: endocrine therapy end date corresponding to the end of the study period (2021/4)
Subsequent therapy after end of palbociclib: breast cancer treatment	Treatment pattern of subsequent therapy after end of palbociclib	For each treatment line next to palbociclib line, breast cancer treatment(s) will be determined using General name as indicated in the Appendix 3.
Subsequent therapy after end of endocrine therapy: breast cancer treatment	Treatment pattern of subsequent therapy after end of endocrine therapy	For each treatment line next to endocrine therapy, breast cancer treatment(s) will be determined using General name as indicated in the Appendix 3.
Subsequent therapy after end of palbociclib: breast cancer treatment category combination	Treatment pattern of subsequent therapy after end of palbociclib	For each treatment line next to palbociclib line, breast cancer treatment category combination will be determined using categories as indicated in the Appendix 3. The categories are defined as follows: chemotherapy, endocrine therapy, CDK 4/6 inhibitor, mTOR inhibitor, PI3K inhibitor.
Subsequent therapy after end of endocrine therapy: breast cancer treatment category combination	Treatment pattern of subsequent therapy after end of endocrine therapy	For each treatment line next to endocrine therapy, breast cancer treatment category combination will be determined using categories as indicated in the Appendix 3. The categories are defined as follows: chemotherapy, endocrine therapy, CDK 4/6 inhibitor, mTOR inhibitor, PI3K inhibitor.
Treatment duration of post-palbociclib treatment	Time to treatment failure of subsequent therapy after end of palbociclib	For each treatment line next to palbociclib line, the duration will be calculated as mentioned in section 2.1. If a patient has no treatment line with palbociclib or does not present subsequent line after the line with palbociclib, the patient will be excluded from the analysis.
Treatment duration of post-endocrine therapy	Time to treatment failure of subsequent therapy after end of endocrine therapy	For each treatment line next to endocrine therapy, the duration will be calculated as mentioned in section 2.1. If a patient has no treatment line with endocrine treatment or does not present subsequent line after the line with endocrine treatment, the patient will be excluded from the analysis.
Antibiotic use during	Use of antibiotics and/or G-	Presence of antibiotic prescription record with

Variable	Role	Operational definition
treatment with palbociclib	CSF during treatment with palbociclib	L03A1 ATC code within the period from the start date to the end date of a palbociclib treatment line
Antibiotic use during treatment with endocrine therapy	Use of antibiotics and/or G-CSF during treatment with endocrine therapy	Presence of antibiotic prescription record with L03A1 ATC code within the period from the start date to the end date of an endocrine therapy
G-CSF use during treatment with palbociclib	Use of antibiotics and/or G-CSF during treatment with palbociclib	Presence of G-CSF prescription record with J01 or J02 ATC codes within the period from the start date to the end date of a palbociclib treatment line
G-CSF use after administration of an endocrine therapy	Use of antibiotics and/or G-CSF after administration of an endocrine therapy	Presence of G-CSF prescription record with J01 or J02 ATC codes within the period from the start date to the end date of an endocrine therapy
Endocrine therapies before administration of palbociclib as mBC treatment	Target population of palbociclib (Demographic/Clinical characteristics)	Number of different types of endocrine therapies (as indicated in *Category 2* in treatment sheet in Appendix 3) in the subsequent therapies prior to palbociclib line
Duration of endocrine therapy	Target population of palbociclib (Demographic/Clinical characteristics)	Duration of the endocrine therapy will be calculated as end date of endocrine therapy – start date of endocrine therapy +1 day.
LHRH agonist	Target population of palbociclib (Demographic/Clinical characteristics)	Presence of any record corresponding to LHRH agonist within the first line, identified using *Receiptcode* (as indicated in LHRH sheet in Appendix 3) Each of the following will be identified: -Leuprorelin -Goserelin -Leuprorelin or Goserelin
LHRH agonist (endocrine therapy)	Target population of endocrine therapy (Demographic/Clinical characteristics)	Presence of any record corresponding to LHRH agonist within the first endocrine therapy, identified using *Receiptcode* (as indicated in LHRH sheet in Appendix 3) Each of the following will be identified: -Leuprorelin -Goserelin -Leuprorelin or Goserelin
Frequency of blood test	To describe the frequency of blood test during treatment with palbociclib	The number of blood test record with *ActDat*e occurring within a treatment line, identified using

Variable	Role	Operational definition
		Labocode (as indicated in Test sheet in Appendix 3)
First blood test	To describe the frequency of blood test during treatment with palbociclib	The earliest (based on *ActDate*) blood test record as identified using *Labocode* (as indicated in Test sheet in Appendix 3) during a palbociclib treatment line.
First blood test timing from initial treatment	To describe the frequency of blood test during treatment with palbociclib	First blood test timing from initial treatment will be calculated as the following difference (in days): First blood test date – palbociclib treatment initiation
Adjuvant treatment duration	To characterize the demographic and clinical characteristics of ABC patients at the initiation of treatment with palbociclib	Duration of the first subsequent endocrine therapy (identified based on general name as listed in Appendix 3 in treatment sheet) with start date within 365 days from the last breast cancer surgery record (identified using *KubunCode* as listed in Appendix 3 in surgery sheet) as follows: Duration = End date – start date + 1 days Stratification will be performed based on the following criteria: >730 days or ≤730 days
Lookback period duration	Target population of palbociclib (Demographic/Clinical characteristics)	For patients in subpopulation 1, the difference between the first metastasis record date and the date of the earliest record available. Patients will be stratified as follows: more than 12 months (365 days), 12 months (365 days) or less

5.2 SAFETY ENDPOINTS
Not applicable

5.3 OTHER ENDPOINTS
Not applicable

5.4 COVARIATES
Not applicable

6 HANDLING OF MISSING VALUES
Missing values is expected when identifying variables based on hospitalization records. However, since analysis using such variables would be descriptive only, no missing data imputation will be performed.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

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.

7.2 STATISTICAL ANALYSES

Only Palbociclib lines meeting the following conditions will be considered for the analyses1-5, 7, and 8. :

- First in time Palbociclib line
- At least a minimum of 3 month-period (90 days) of the follow-up in MDV database available from the initiation of Palbociclib line (i.e the date of latest record available – Palbociclib initiation date +1 ≥ 90 days)

Only patients who have treatment lines meeting the following conditions will be considered for the analyses9-14 :

- Initiated endocrine therapy for ABC setting as first line
- At least a minimum of 3 month-period (90 days) of the follow-up in MDV database available from the initiation of endocrine therapy as first line for ABC setting (i.e the date of latest record available – endocrine therapy initiation date +1 ≥ 90 days)

The following excluded patients will be descriptively summarized (frequencies and percentages among subpopulation 3, as described in section 4.4):

- ✧ Patients with the same hormonal therapy in both adjuvant endocrine therapy and the first-line treatment
- ✧ Patients with Letrozole in adjuvant endocrine therapy, and Anastrozole in the first-line treatment
- ✧ Patients with Anastrozole in adjuvant endocrine therapy, and Letrozole in the first-line treatment

Patient disposition and overall line sequences will be graphically presented using sunburst diagram.

It is to be noticed that all tables and figures to be produced are listed in Appendix 4.

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

Demographic and clinical characteristics (as listed in Table 2) will be descriptively summarized for all patients initiating palbociclib. The start date of the first palbociclib line will be used as a baseline to identify patient characteristics (as mentioned in Table 2). Moreover, similarly, characteristics of patients initiating a second palbociclib line, third line, and so on, will be descriptively summarized (provided data are sufficient).

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

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 (as first-line, second-line, and so on) divided by the total number of patients initiating any breast cancer treatment line (as first-line, second-line, and so on, respectively) will be calculated with considering whether palbociclib is prescribed from first treatment or added after >30 days from first treatment day of initial endocrine therapy. Results will be presented as a bar plot according to the breast cancer treatment line (first-line, second-line, and so on). Moreover, the percentage of each endocrine treatment type used in combination with palbociclib (as defined in Table 1), will be calculated. The number of patients initiating palbociclib line (as first-line, second-line, and so on) will be set as the denominator .

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

Time to treatment failure of palbociclib is defined as the time from the start date of first palbociclib line to end date. Time to treatment failure of palbociclib will be censored at patient disenrollment or end of study period (see Table 2 for details). Duration will be calculated in days. Moreover, Kaplan-Meier analysis will be performed to analyze time to treatment failure, and Kaplan-Meier curves will be presented. Analysis will be stratified by treatment line position (e.g first line, second line, and so on). Also, log rank test with a significance of 5% will be performed to assess the difference between treatment line distributions.

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

For the line of therapy after palbociclib treatment, the proportion of each breast cancer treatment in the subsequent therapy after palbociclib will be calculated, as the number of patients having the corresponding breast cancer treatment (as defined in Table 2) in the subsequent therapy line divided by the total number of patients with a subsequent therapy after palbociclib line. Moreover, the proportion of each treatment line regimen (including

breast cancer treatment category combinations, as mentioned in Table 2) will be calculated in a similar manner. Additionally, the same analysis will be performed after stratification by the position of palbociclib line (first line, second line, and so on).

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

For the subsequent therapy after palbociclib, a similar analysis to time to treatment failure of palbociclib will be performed. Analysis will be stratified by treatment line position (e.g first line, second line, and so on). Also, log rank test with a significance of 5% will be performed to assess the difference between line groups.

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

Within each specific time intervals 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 with any corresponding line start date (as first line, second line, and so on) within the specified time interval divided by the total number of patients with any line start date (as first line, second line, and so on) within the same interval. Therapies will be defined as follows, based on *Receiptcode* definitions (as indicated in Appendix 3): chemotherapy, endocrine therapy, CDK 4/6 inhibitor, mTOR inhibitor, PI3K inhibitor. Sensitivity analysis will be performed using the following time intervals: 365 days or 180 days.

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

The proportion of patients prescribed antibiotics and the proportion of patients prescribed G-CSF will be calculated as the number of patients prescribed the corresponding treatment at a palbociclib line (as defined in Table 2) divided by the total number of patients initiating palbociclib line. Additionally, stratified analysis will be performed considering palbociclib line position (as first line, second line, and so on).

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

Distribution and descriptive statistics of first blood test timing from initial treatment (as defined in Table 2) stratified by presence of palbociblib in the corresponding treatment line will be provided for treatment line starting after palbociclib launch and with termination within 1 year after palbociclib launch.

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

Demographic and clinical characteristics (as listed in Table 2) will be descriptively summarized for all patients initiating a first endocrine therapy. The start date of the first endocrine therapy will be used as a baseline to identify patient characteristics (as mentioned in Table 2). Moreover, similarly, among patients initiating endocrine treatment as first line, characteristics of patients initiating another endocrine therapy as a second line or third line will be descriptively summarized (if provided data are sufficient).

10. To describe the treatment patterns of each line of endocrine therapy for ABC patients
Treatment pattern of endocrine therapy will be assessed based on the percentage of patients initiating an endocrine therapy, as first-line, second-line, and so on. Results will be presented as a bar plot according to the breast cancer treatment line (first-line, second-line, and so on). Moreover, the percentage of each endocrine treatment type for each treatment line including type of therapy combined with endocrine therapy (as defined in Table 1), will be calculated. The number of patients initiating an endocrine therapy (as first-line, second-line, and so on) will be set as the denominator .

11. To evaluate TTF of endocrine therapy for ABC patients
Time to treatment failure of endocrine therapy is defined as the time from the start date of a line of therapy including an endocrine therapy to end date. Time to treatment failure of endocrine therapy will be censored at patient disenrollment or end of study period (see Table 2 for details). Duration will be calculated in days. Moreover, Kaplan-Meier analysis will be performed to analyze time to treatment failure, and Kaplan-Meier curves will be presented. Analysis will be stratified by treatment line position (e.g first line, second line, and so on). Also, log rank test with a significance of 5% will be performed to assess the difference to assess the difference between lines of therapy (1st line vs. 2nd line).

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
For the line of therapy after endocrine therapy, the proportion of each breast cancer treatment in the subsequent therapy after endocrine therapy will be calculated, as the number of patients having the corresponding breast cancer treatment (as defined in Table 2) in the subsequent therapy line divided by the total number of patients with a subsequent therapy after endocrine therapy. Moreover, the proportion of each treatment line regimen (including breast cancer treatment category combinations, as mentioned in Table 2) will be calculated in a similar manner. Additionally, the same analysis will be performed after stratification by the position of endocrine therapy (first line, second line, and so on).

13. To evaluate TTF of subsequent therapy after end of endocrine therapy for ABC patients
For the subsequent therapy after the end of endocrine therapy, a similar analysis to time to treatment failure of endocrine therapy will be performed. Analysis will be stratified by treatment line position (e.g first line, second line, and so on). Also, log rank test with a significance of 5% will be performed to assess the difference between line groups.

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

The proportion of endocrine therapies with prescription of antibiotics and the proportion of endocrine therapies with prescription of G-CSF will be calculated as the number of endocrine therapies with prescription of the corresponding treatment (as defined in Table 2) divided by the total number of endocrine therapies. Additionally, the same analysis will be performed after stratification by the position of endocrine therapy (first line, second line, and so on).

Additional analyses

- TTF and treatment patterns prior a palbociclib line as a second line

The number of patients having a palbociclib line as a second line and time to treatment failure of Palbociclib will be assessed as described in 3., and stratified by duration of the first line (6 months (180 days) or less, More than 6 months (180 days) and less than 12 months (365 days), 12 months (365 days) or more). The same analysis will be performed by restricting to patients with an endocrine therapy as first line. Treatment pattern of prior line of palbociclib as second line will be evaluated as 2., and stratification will be performed using prior therapy duration (6 months (180 days) or less, More than 6 months (180 days) and less than 12 months (365 days), 12 months (365 days) or more).

- TTF and treatment pattern of a subsequent therapy after a palbociclib line as first line

Patterns of subsequent therapies after a palbociclib line will be presented based on the following treatment categories: all therapies, abemaciclib/palbociclib, everolimus, endocrine monotherapies, chemotherapy. Using these categories, median TTF for palbociclib and the subsequent line will be presented. Similarly as 2., treatment pattern of the subsequent therapy after palbociclib as first line will be evaluated, but stratification will be performed using palbociclib line duration (6 months (180 days) or less, more than 6 months (180 days) and less than 12 months (365 days), 12 months (365 days) or more). Moreover, the following line patterns and their proportions (the denominator will correspond to the total number of patients with a palbociclib line as first line) will be summarized:

  - Palbociclib line as first line and abemaciclib line as a subsequent therapy
  - Palbociclib line as first line and palbociclib line as a subsequent therapy
  - Palbociclib line as first line and abemaciclib line as second or later line
  - Palbociclib line as first line and palbociclib line as second or later line

Finally, for patients having a palbociclib line as first line and abemaciclib line as a subsequent therapy, the duration of both palbociclib and abemaciclib line will be displayed by patient. Additionally, the dose change within the palbociclib line will displayed (125 mg, 100 mg, 75 mg, or others).

- TTF of Palbociclib line after dose reduction

Time to treatment failure of palbociclib will be analyzed as describe in 2. focusing on the following Palbociclib lines:

- Palbociclib lines with an initial dose of 125 mg, with no dose reduction occurring within 3 months from line initiation, and with a duration of at least 3 months
- Palbociclib lines with an initial dose of 125 mg, with a dose reduction (to 100 mg or 75 mg) occurring within 3 months from line initiation, and with a duration of at least 3 months
- Palbociclib lines with an initial dose of either 100 mg or 75 mg

- Dose reduction patterns in older patients

The number, the proportion of palbociclib lines for each combination of initial and final dose (125 mg, 100 mg, 75 mg, others) and the proportion of lines with dose reduction will be provided in patients aged 65 or older, and those aged 75 or older. Additionally, among these later, trends in palbociclib dose reduction by cycle (i.e every 4 weeks) will be provided.

- Trend in initial dosing of palbociclib treatment lines over 6 month windows from the beginning of the study period

The first-in-time record of palbociclib for each patient, regardless of inclusion/exclusion criteria, will be identified using *Amount* of the corresponding receipt record multiplied by the dose corresponding to the receiptcode as indicated in Appendix 3 in treatment sheet. The number and the percentages of patients initiating palbociclib lines with different dose (125 mg, 100 mg, 75 mg, others) will be summarized over 6 month windows from the beginning of the study period.

7.2.1 Safety Analyses

Not applicable

7.2.2 Summary of Analyses

Not applicable

8 LIST OF TABLES AND TABLE SHELLS

Table 1. Definitions of exposures

Table 2. Definitions of endpoints

Figure 1. Examples of patterns for each subpopulation

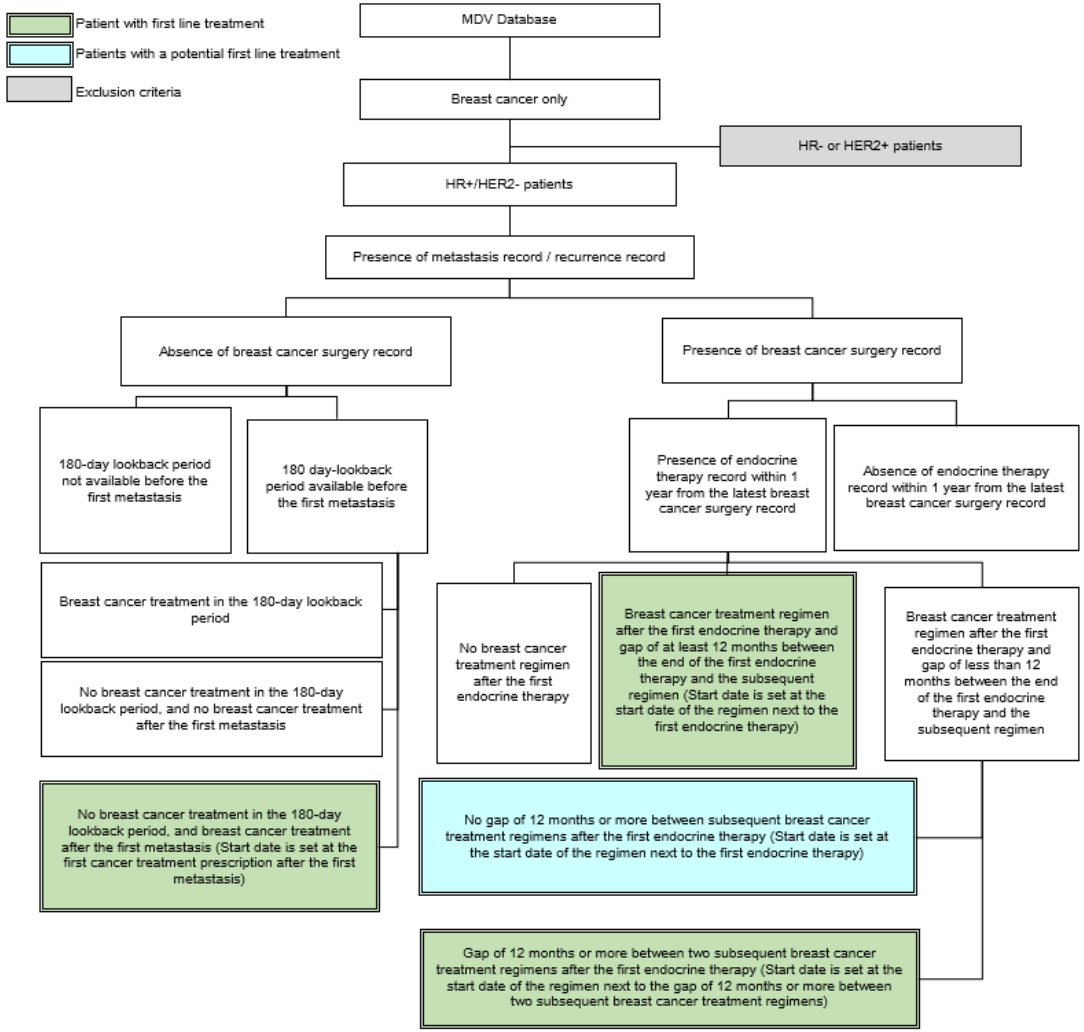
Figure 2. Examples of treatment sequence patterns

9 REFERENCES

Carroll NM, Burniece KM, Holzman J, McQuillan DB, Plata A, Ritzwoller DP, Algorithm to identify systemic cancer therapy treatment using structured electronic data. JCO Clinical Cancer Informatics. 2017. DOI: 10.1200/CCI.17.00002

10 APPENDICES

10.1 APPENDIX 1: DATA DERIVATION DETAILS



10.2 APPENDIX 2: ADDITIONAL STATISTICAL METHODOLOGY DETAILS

Not applicable

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

Diagnosis and procedure codes used in the study are listed in the following stand alone document: codedefinitions.xlsx.

10.4 APPENDIX 4: LIST OF TABLES AND FIGURES

Title
Figure 1. Patient disposition*
Figure 2. Line sequences*
Table 1. Population characteristics - Demographic and clinical characteristics (Overall)
Table 2. Population characteristics - Demographic and clinical characteristics (By line position)
Figure 3a. Treatment pattern of palbociclib - Proportion of patients initiating palbociclib line*
Figure 3b. Treatment pattern of palbociclib - Proportion of patients with palbociclib add-on next to the first endocrine therapy
Figure 4. Treatment pattern of palbociclib - Percentage of endocrine treatment combination among palbociclib lines
Table 3. Time to treatment failure of palbociclib - Median duration of palbociclib line
Figure 5. Time to treatment failure of palbociclib - Kaplan-Meier curve of palbociclib line duration (Overall)
Figure 6. Time to treatment failure of palbociclib - Kaplan-Meier curve of palbociclib line duration (By line position)
Figure 7. Treatment pattern of subsequent therapy after palbociclib - Proportion of each breast cancer treatment for the subsequent therapy after palbociclib*
Figure 8. Treatment pattern of subsequent therapy after palbociclib - Proportion of each breast cancer treatment category combination for the subsequent therapy*
Table 4. Time to treatment failure of subsequent therapy after palbociclib - Median duration of subsequent therapy after palbociclib*
Figure 9. Time to treatment failure of subsequent therapy after palbociclib - Kaplan-Meier curve of the line duration of the subsequent therapy after palbociclib*
Figure 10. Time to treatment failure of subsequent therapy after palbociclib - Kaplan-Meier curve of the line duration of the subsequent therapy after palbociclib (By line position)*
Figure 11. Changes in treatment pattern (365-day time-window)*

Figure 12. Changes in treatment pattern (180-day time window)*
Table 5. Use of antibiotics after administration of palbociclib
Table 6. Use of G-CSF after administration of palbociclib
Table 7. Status for termination of palbociclib line
Table 8. Treatment combinations for 1st and 2nd lines*
Table 9. Treatment combinations for subsequent therapy after palbociclib*
Table 10. Type of censoring by line position
Figure 13. Distribution of palbociclib among line positions
Table 11. Treatment combinations for 1st and 2nd lines (First line in 2015)*
Table 12. Treatment combinations for 1st and 2nd lines (First line in 2016)*
Table 13. Treatment combinations for 1st and 2nd lines (First line in 2017)*
Table 14. Treatment combinations for 1st and 2nd lines (First line in 2018)*
Table 15. Number of patients by treatment line and period with respect to Palbociclib market launch (1 year window)*
Table 16. Number of patients by treatment line and period with respect to Palbociclib market launch (6 months window)*
Table 17. Initial and final palbociclib doses (mg), and dose reduction within a same palbociclib line
Figure 14. Palbociclib line by line position*
Table 18. Palbociclib line duration by initial and final palbociclib doses (mg) within a same palbociclib line
Table 19. Frequency of blood tests within lines in after launch period stratified by presence of palbociclib*
Figure 15. Concomitant endocrine therapies (premenopausal therapies)
Figure 16. Percentage of palbociclib line subsequent to a chemotherapy (by type of chemotherapy)
Table 20. Top 5 anti-cancer drug regimens among lines without palbociclib in the period within 1 year after palbociclib market launch*
Table 21. Charlson comorbidity index by initial and final palbociclib doses (mg) within a same palbociclib line
Table 22. Use of pegfilgrastim within palbociclib line with G-CSF
Table 23. Presence of chemotherapy before palbociclib line
Table 24. Number of chemotherapy medications before palbociclib line
Figure 17. Distribution of the first test after palbociclib line initiation (in days)
Table 25. The number of lines with the first test at 14 days after palbociclib line initiation
Figure 18. Distribution of the first test timing after palbociclib line initiation (in days) for patients without any test within 14 days

Table 45. Population characteristics - Demographic and clinical characteristics (By line position) – Endocrine therapy
Figure 28. Treatment pattern of endocrine therapy - Proportion of patients initiating endocrine therapy
Figure 29. Distribution of endocrine therapy among line positions
Figure 30. Treatment pattern of endocrine therapy - Percentage of endocrine treatment combination among endocrine therapies
Table 46. Time to treatment failure of endocrine therapy - Median duration of endocrine therapies
Figure 31. Time to treatment failure of endocrine therapy - Kaplan-Meier curve of endocrine therapy duration (Overall)
Figure 32. Time to treatment failure of endocrine therapy - Kaplan-Meier curve of endocrine therapy duration (By line position)
Figure 33. Time to treatment failure of endocrine therapy - Kaplan-Meier curve of endocrine therapy duration (Overall) stratified by period
Figure 34. Time to treatment failure of endocrine therapy - Kaplan-Meier curve of endocrine therapy duration stratified by period and by line position
Table 47. Status for termination of endocrine therapy
Table 48. Type of censoring by line position – Endocrine therapy
Figure 35. Treatment pattern of subsequent therapy after endocrine therapy - Proportion of each breast cancer treatment for the subsequent therapy after endocrine therapy
Figure 36. Treatment pattern of subsequent therapy after endocrine therapy - Proportion of each breast cancer treatment category combination for the subsequent therapy
Table 49. Time to treatment failure of subsequent therapy after endocrine therapy - Median duration of subsequent therapy after endocrine therapy
Figure 37. Time to treatment failure of subsequent therapy after endocrine therapy - Kaplan-Meier curve of the line duration of the subsequent therapy after endocrine therapy
Figure 38. Time to treatment failure of subsequent therapy after endocrine therapy - Kaplan-Meier curve of the line duration of the subsequent therapy after endocrine therapy (By line position)
Table 50. Use of antibiotics after administration of endocrine therapy
Table 51. Use of G-CSF after administration of endocrine therapy
Table 52. Number of lines and time to treatment failure for palbociclib and endocrine therapy lines stratified by GAP from adjuvant and duration of adjuvant treatment - Patients with a surgery record
Table 53. Number of lines and time to treatment failure for palbociclib and endocrine therapy lines stratified by duration of the lookback period - Patients without any surgery record

Figure 39. Median duration of palbociclib line and subsequent therapy
Figure 40. Duration of palbociclib line and subsequent abemaciclib line for individual patients
Figure 41. Palbociclib dose change before abemaciclib line
Table 54. Number or lines and time to treatment failure of palbociclib as second line stratified by duration of the first line
Table 55. Number of lines and time to treatment failure of palbociclib as second line stratified by duration of endocrine therapy as first line
Figure 42. Proportion of each breast cancer treatment for the prior therapy of palbociclib as second line, stratified by duration of the first line
Figure 43. Proportion of each breast cancer treatment category for the prior therapy of palbociclib as second line, stratified by duration of the first line
Figure 44. Proportion of each breast cancer treatment of the subsequent therapy after palbociclib line as first line, stratified by duration of palbociclib line
Figure 45. Proportion of each breast cancer treatment category of the subsequent therapy after palbociclib line as first line, stratified by duration of palbociclib line
Table 56. Number and proportions of abemaciclib and palbociclib line patterns after palbociclib line as first line
Table 57. Time to treatment failure of palbociclib line according to initial dose and dose reduction - Median duration of palbociclib line
Figure 46. Time to treatment failure of palbociclib line according to initial dose and dose reduction - Kaplan-Meier curve of the line duration of palbociclib line
Table 58. Initial and final palbociclib doses (mg), and dose reduction within a same palbociclib line in patients aged 65 or older
Table 59. Initial and final palbociclib doses (mg), and dose reduction within a same palbociclib line in patients aged 75 or older
Figure 47. Trend in palbociclib line dose reduction in patients aged 65 or older
Figure 48. Trend in palbociclib line dose reduction in patients aged 75 or older
Table 60. Trend in initial dosing of palbociclib treatment lines over 6 month windows from the beginning of the study period

*: Not restricted to the first palbociclib line and no minimum of 3 month-period (90 days) available from the initiation of Palbociclib line required