NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A Retrospective Non-interventional Study of Breast Cancer Patients Diagnosed With HR+/HER2- Locally Advanced or Metastatic Breast Cancer Treated With Palbociclib in Denmark
Protocol number	A5481176
Protocol version identifier	Final Protocol Version 1.0
Date	09 December 2021
Active substance	L01XE33 - palbociclib
Medicinal product	Ibrance (palbociclib)
Research question and objectives	The objective is to retrospectively describe and assess clinical and demographical characteristics, treatment patterns in a real-world (RW) setting of patients with HR+/HER2- (hormone receptor positive/human epidermal growth factor receptor 2 negative) locally advanced or metastatic breast cancer receiving palbociclib in combination treatment. *Primary objectives:* Progression free survival (PFS) and Time on Treatment (ToT) of patients receiving palbociclib in combination with aromatase inhibitor (AI) *Secondary objectives:* • Demographic charactersitics of the patients • Disease specific characteristics • PFS and ToT of palbociclib in combination with fulvestrant • Overall survival (OS) of patients receiving palbociclib in combination with AI *(with censoring by 01 May 2022 and also reported after 6, 12 and 24 months of palbociclib treatment (landmark))* • OS of patients receiving palbociclib in combination with fulvestrant *(with censoring by 01 May 2022 and also reported after 6, 12 and 24 months (landmark))* • First subsequent post-palbociclib treatment upon progression
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AI	Aromatase inhibitor
a/MBC	Advanced metastatic breast cancer
CDK	Cyclin-dependent kinase
CDK4	Cyclin Dependent Kinase 4
CDK6	Cyclin Dependent Kinase 6
CI	Confidence interval
CPR	Centrale Personregister – CPR is the registry that holds the personal ID numbers that every Danish citizen has
DBCG	Danish Breast Cancer Group
DC50	ICD-10 code for patients with breast cancer
E2F	A group of genes that encodes a family of transcription factors in higher eukaryotes
EC	European Commission
EMA	European Medicines Agency
ER+	Estrogen Receptor-positive
FDA	Food and Drug Administration
FSFV	First subject first visit
G1 phase	Growth 1 phase
GDPR	General Data Protection Regulation
HR	Hormone receptor; hazard ratio
HR+	Hormone receptor positive
HER2	Human epidermal growth factor receptor 2
HER2-	HER2 negative
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICMJE	International Committee of Medical Journal Editors
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
LSLV	Last subject last visit
MBC	Metastatic breast cancer
NIS	Non-Interventional Study
OS	Overall survival
PFS	Progression free survival
Rb	Retinoblastoma protein
RCT	randomized controlled trials
RW	Real-World
RWE	Real-World Evidence
S phase	Synthesis phase
SAP	Statistical Analysis Plan
ToT	Time on Treatment
USA	United States of America

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD MD, MSc	PPD	PPD	PPD PPD
PPD , MSc, PhD	PPD	PPD	PPD PPD
PPD , MD, PhD	PPD	PPD	PPD PPD
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4. ABSTRACT

Title
A Retrospective Non-interventional Study of Breast Cancer Patients Diagnosed With HR+/HER2- Locally Advanced or Metastatic Breast Cancer Treated With Palbociclib in Denmark.

Authors
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Rationale and background
There is a need for additional and updated real-world evidence (RWE) about the cyclin-dependent kinase 4/6(CDK4/CDK6) inhibitors in a real-world setting. In Denmark, access to the DBCG clinical registry is unique and feasible. Thus collecting clinical and pathological data from patients from all regions of Denmark will add on to the existing clinical evidence. The project aims at collecting restrospective clinical effectiveness data and treatment pattern data on palbociclib.

Research question and objectives
The objective is to retrospectively describe and assess clinical and demographical characteristics, treatment patterns in a real-world (RW) setting of patients with HR+/HER2- locally advanced or metastatic breast cancer receiving palbociclib in combination treatment.

Primary objectives:
- PFS of patients receiving palbociclib in combination with AI
- ToT of patients receiving palbociclib in combination with AI

Secondary objectives:
- Demographic charactersitics of the patients who have received palbociclib
  - Split into different age groups (below 50, 50 -70, and above 70 years of age)
- Disease specific characteristics of the patients who have received palbociclib
  - Type, number and location of metastases (visceral vs non-visceral)
  - Surgery
  - Type and number of adjuvant treatment
  - De novo (primary metastatic breast cancer [MBC])
  - Recurrent MBC
  - Median time from initial breast cancer diagnosis (incidence date) to relapse
- PFS of patients receiving palbociclib in combination with fulvestrant
- ToT with palbociclib in combination with fulvestrant
- OS in patients receiving palbociclib in combination with AI *(with censoring by 01 May 2022 and also reported after 6, 12 and 24 months of palbociclib treatment (landmark))*

- OS in patients receiving palbociclib in combination with fulvestrant *(with censoring by 01 May 2022 and also reported after 6, 12 and 24 months of palbociclib treatment (landmark))*
- First subsequent post-palbociclib treatment upon progression

Study design
The study is designed as a secondary data collection Non-Interventional Study (NIS) based on retrospective data from an existing registry. The study is a single-arm study only focusing on patients treated with palbociclib in Denmark.

Population
Patients with HR+/HER2- locally advanced or metastatic breast cancer treated with palbociclib (1st or 2nd line) (01 January 2017- 31 December 2020).

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

1. Patients with breast cancer (International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10]: ICD-10 code for patients with breast cancer [DC50])
2. A diagnosis of HR+/HER2- locally advanced or metastatic breast cancer
3. Initiated treatment with palbociclib as either 1st or 2nd line treatment between 01 January 2017 and 31 December 2020
4. Inclusion date: Date of relapse/stage IV disease/progression leading to initiation of palbociclib+AI/progression leading to initiation of palbociclib+fulvestrant

Variables and outcomes *(a detailed overview of the variables is listed in section 9.3)*
- Diagnosis (ICD-10 code: DC50) *(exposure/inclusion)*
- Treatment with palbociclib *(exposure/inclusion)*
- Date of birth
- Date of breast cancer diagnosis
- Occurrence of metastases
- Type of metastases (visceral vs. non-viseral)
- Number of metastases sites
- Location of metastases
- Surgery
- De Novo (primary MBC)
- Breast cancer disease duration – median time from initial breast cancer diagnosis (incidence date) to relapse
- Date of relapse
- Date for treatment initiation with palbociclib
- Date for treatment stop with palbociclib
- ToT (palbociclib) *(outcome)*

- Reasons to discontinuation with palbociclib
- PFS *(outcome)*
- Date of death
- OS *(outcome)*
- Post-palbociclib treatment (first subsequent treatment post-palbociclib)

Data sources
This study will be based on the DBCG registry. No other Danish healthcare registries will be included.

Study size
It is estimated that the total population of palbociclib-treated breast cancer patients with HR+/HER2- locally advanced or metastatic breast cancer included in the DBCG registry constitutes of 1,500 patients in Denmark.

Data analysis
Descriptive statistics, including stratification on sub-groups. In the PFS and OS analyses, Kaplan-Meier survival distribution functions will be estimated. Besides an OS analysis with censoring at 01 May 2022, supplementary OS analyses will be made after 6, 12 and 24 months of palbociclib treatment (landmark cut-off time points). A separate Statistical Analysis Plan (SAP), including shell tables, will be developed prior to data analysis.

Milestones

Final Protocol: 17 December 2021
Final Statistical Analysis Plan: 31 January 2022
Start of data collection (first subject first visit [FSFV] – database study, historic data): 01 February 2022
Data setup: 01 February 2022
Data analyses: 01 February-01 August 2022
End of data collection (last subject last visit [LSLV] – database study, historic data): 01 August 2022
DBCG Final study report: 30 September 2022
Manuscript ready for submission: 15 December 2022

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Final Protocol	17 December 2021
Final Statistical Analysis Plan	31 January 2022
Start of data collection (FSFV – database study, historic data)	01 February 2022
Data setup	01 February 2022
Data analyses	01 February – 01 August 2022
End of data collection (LSLV – database study, historic data)	01 August 2022
DBCG Final study report	30 September 2022
Manuscript ready for submission	15 December 2022

7. RATIONALE AND BACKGROUND

The discovery and development of CDK4/CDK6 inhibitors have revolutionized the paradigm of therapeutic management of HR+ MBC worldwide. The most common cancer globally is breast cancer (1). In Denmark, breast cancer is the most frequent cancer in women, with approximately 4,700 new cases per year; and the 5 year OS is estimated to be 86%. To date roughly 64,000 women are living with the breast cancer diagnosis. It is estimated that roughly 20% of the patients initially diagnosed with breast cancer will at some stage in their life experience a relapse of the disease (loco-regional or distant metastasis). The median OS of metastatic breast cancer is between 2-3 years however 25% of the patients can attain an OS of 5 years. The incidence of loco-regional or metastatic estrogen receptor-positive (ER+)/HER2- breast cancer in Denmark is therefore estimated to be roughly 650 patients yearly (2).

Cyclin-dependent kinases (CDKs) (are essential regulatory players in the controlled cell cycle trajectory, a process needed for the division of cells in the body. This cell cycle is a series of events which are tightly controlled and regulated. This cell cycle machinery however can be deregulated if the CDKs responsible for driving the cell cycle become hyperactive resulting in an uncontrolled proliferation of cells. This hyperactivity of CDKs resulting in uncontrolled cell proliferation is a well-recognized hallmark of malignancy (3). Targeting and inhibition of the cell cycle machinery ie, the CDK's has therefore been of great interest in the past decade and led finally to the therapeutic development of the pharmacologic inhibitors known as CDK4/CDK6 inhibitors. These inhibitors hinder the transition from growth 1 (G1) phase to synthesis (S) phase by inhibiting the phosphorylation of retinoblastoma protein (Rb) and a group of genes that encodes a family of transcription factors in higher eukaryotes (E2F) release. This results therefore in the arrest at G1 phase resulting in inhibition of tumor cell growth (4-7).

The first cell cycle inhibitor was palbociclib which was approved by Food and Drug Administration (FDA) on the basis of the Phase 2 study PALOMA-1 (8). This study showed doubling of the PFS from 10.2 to 20.2 months when a combination of palbociclib and letrozole was given to the HR+/HER2- advanced breast cancer patients. These significant results were later confirmed in a Phase 3 study PALOMA-2 as well (9). This approval was followed by the other two CDK4/CDK6 inhibitors, ribociclib and abemaciclib. In Denmark these targeted therapeutic agents were incorporated in the clinical practice since 2016 (10).

The introduction of CDK4/CDK6 inhibitors has permanently transformed the therapeutic management of HR+ MBC worldwide. The three CDK4/CDK6 inhibitors palbociclib, ribociclib, and abemaciclib are approved with a combination of AI or with fulvestrant. Abemaciclib also has the indication of monotherapy therapy of pre-treated patients.

To date, several Phase 2 and 3 randomized controlled trials (RCTs) have evaluated CDK4/CDK6 inhibitors in the treatment of HR+/HER2- advanced metastatic breast cancer (a/MBC). Palbociclib was evaluated in three registrational trials with different patient populations: PALOMA-1 (11), PALOMA-2 (3) and PALOMA-3 (12,13). For palbociclib,

the Phase 3 trial PALOMA-2 demonstrated a median PFS of 24.8 vs. 14.5 months, respectively, for patients treated with palbociclib or placebo in addition to letrozole (hazard ratio [HR] 0.58; $p < 0.001$). After a median follow-up of approximately 38 months, median PFS was 27.6 months for palbociclib-letrozole and 14.5 months for letrozole (HR 0.563; $P < 0.0001$) (14).

PALOMA-3 (fulvestrant with/without palbociclib) included both pre-menopausal (goserelin added for premenopausal women) and post-menopausal women with HR+/HER2- MBC who had relapsed or progressed during prior endocrine treatment, and there was no limit on no of prior endocrine therapies (2nd line and plus setting). Overall, the addition of palbociclib resulted in an improvement in PFS from 4.6 months to 9.5 months (HR 0.46; $p < 0.001$) (12,13).

Ribociclib was evaluated in the three trials, Phase 3 MONALEESA-2 (15) , MONALEESA-3 (16) and MONALEESA-7 (17). Abemaciclib was evaluated in MONARCH 1 (18), MONARCH 2 (19) and MONARCH 3 (20).

Randomization and blinding are considered to be the gold standard for determining the effect of a treatment in randomized controlled clinical trials. However due to strict protocol-specified definition of inclusion criteria, populations in the randomized trials does not always represent patients treated in clinical practice. For example patients with wider ranges of disease severity and age, taking a broader range of concomitant medications, and with more and varying comorbidities are not always fully represented in clinical trials (21). Less than 5% of adult patients with cancer participate in clinical trials (22) hence there is a need to expand our knowledge by collecting more RWE data from the clinical practice.

Therefore, real-world data are increasingly being used to understand the safety and effectiveness of new drug regimens in actual clinical practice where patients populations are heterogenous (21,23). Although the definition of RWE is evolving, most associate RWE with data derived from medical practice among heterogeneous sets of patients in real-life settings, such as insurance claims data and clinical data from electronic health records (24). RW data can also be defined as data relating to patient health status or the delivery of health care routinely collected from a variety of sources, such as the electronic health records and administrative data (21)

The first comprehensive systematic literature review of RWE studies on CDK4/CDK6 inhibitors in the treatment of HR+/HER2- a/MBC was carried out by Harbeck et al. (25). Their work identified 114 studies between 2015–2019, 85 of which were only presented at conferences. The results on efficacy and safety of CDK4/CDK6 inhibitors complemented the results seen in randomized clinical trials. However most of the published studies were conducted in United States of America (USA). Hence there is a need to look at RWE data for CDK4/CDK6 inhibitors in the treatment of HR+/HER2- a/MBC from a local perspective (25).

A comprehensive retrospective observational analysis of electronic health records within the Flatiron Health Analytic Database was carried out with palbociclib (26). A total of 1430 patients with ≥ 3 months of follow-up received palbociclib plus letrozole or letrozole alone in the first-line setting between 03 February 2015, and 28 February 2019. Real-world PFS and OS were analyzed. The results showed that plus letrozole was associated with longer PFS than letrozole alone in a heterogeneous population and among various patient subgroups. In the adjusted analysis to balance patient characteristics between arms, palbociclib combination treatment was associated with significantly longer median PFS compared to letrozole alone (20.0 vs 11.9 months; HR, 0.58; 95% confidence interval [CI], 0.49–0.69; P < 0.0001).These results complement the results from the randomized Phase 3 study PALOMA-2 where the hazard ratio was = 0.58 (95% CI: 0.46–0.72; two-sided P < 0.001) (26).

Compared to existing RWE studies the present study will with access to the national DBCG clinical registry allow us to analyse patient data for a total country population with no selection bias as all patients are included. Thus collecting clinical and pathological RW data from patients from all regions of Denmark via the DBCG registry will add on to the existing pool of RWE.

8. RESEARCH QUESTION AND OBJECTIVES

In general, the overall objective is using data from the Danish DBCG registry to retrospectively describe and assess clinical and demographical characteristics, treatment patterns in a RW setting of patients with HR+/HER2- locally advanced or metastatic breast cancer receiving palbociclib in combination treatment. The project will look at both 1st and 2nd line patients.

The results of the study will provide valuable insights to supplement the results from the randomized clinical trials as well as the existing RWE published.

Primary objectives:

- PFS of patients receiving palbociclib in combination with AI
- ToT of patients receiving palbociclib in combination with AI

Secondary objectives:

- Demographic characteristics of the patients who have received palbociclib
  - Split into different age groups (below 50 years, 50-70, and above 70 years of age)
- Disease specific characteristics of the patients who have received palbociclib
  - Type, number and location of metastases (visceral vs. non-visceral)
  - Surgery
  - Type and number of adjuvant treatment
  - De novo (primary MBC)
  - Recurrent MBC
  - Median time from initial breast cancer diagnosis (incidence date) to relapse
- PFS of patients receiving palbociclib with palbociclib in combination with fulvestrant
- ToT with palbociclib in combination with fulvestrant
- OS in patients receiving palbociclib in combination with AI *(with censoring by 01 May 2022 and also reported after 6, 12 and 24 months of palbociclib treatment (landmark)*
- OS in patients receiving palbociclib in combination with fulvestrant *(with censoring by 01 May 2022 and also reported after 6, 12 and 24 months of palbociclib treatment (landmark)*
- First subsequent post-palbociclib treatment upon progression

Following the inclusion criteria (see section 9.2.1 below) the analyses will be performed on the overall population of palbociclib-treated patients with HR+/HER2- locally advanced or metastatic breast cancer.

In addition, some of the research questions above will be addressed on specific sub-groups in terms of age (grouped into below 50, 50-70, and above 70 years of age) as well as patients with visceral disease (defined as metastases in the organs, eg, lung, liver). See section 9.5.1 for further details.

As stated, the research questions will be addressed and analysed using the DBCG registry (see section 9.1 for a description of the registry).

8.1. Definitions

PFS is defined as the date of relapse or stage IV disease (index date) to progression or death, whichever occurs first.

- Patients will be censored for PFS by 31 December 2020
- Progression of disease is based on scans and blood testing results

ToT is defined as date of palbociclib treatment start to date of treatment stop with palbociclib.

OS is defined as the date of relapse or stage IV disease (index date) until death of any cause

- Patients will be censored for OS by 01 May 2022
- Overall survival will also be reported after 6, 12 and 24 months *(landmark cut-off time points)*

9. RESEARCH METHODS

9.1. Study design

The study is designed as a secondary data collection NIS based on retrospective data from an existing registry focusing on HR+/HER2- locally advanced or metastatic breast cancer treated with palbociclib. The study is a single-arm study only focusing on patients treated with palbociclib in Denmark.

The study is purely descriptive and explorative. No formal hypotheses will be tested in the study.

Since the establishment in 1976, the DBCG has maintained a clinical registry for early breast cancer patients in Denmark in which surgeons, pathologists, medical geneticists and oncologists report data regarding diagnosis, treatment and follow-up of breast cancer. This is a unique clinical registry. This well-established breast cancer registry (1976) managed by DBCG was expanded in 2017 to include retrospective and prospective clinical and pathological data on breast cancer patients with a relapse. This includes both the primary MBC (De Novo) and recurrent MBC.

The DBCG registry focusing on relapses which the study will be based is one of several DBCG registries. It is estimated that end of 2021 the DBCG registry will include all Danish patients with locally advanced or metastatic breast cancer. The data and records in the registry are based on systematic review following a standard case report form of all electronic patient records of patients diagnosed with locally advanced or metastatic breast cancer.

The data collection and the ongoing populating of the DBCG registry are performed by healthcare professionals in the DBCG secretariat and are conducted independently of this study. Compared to other exhaustive national Danish patient registries, the DBCG registry contains detailed clinical and pathological data about the treatment patterns of patients with

HR+/HER2- locally advanced or metastatic breast cancer. Thus, the registry is an important and well-suited source to address the research questions (See section 8).

The present NI-Study will only use and rely on the existing data in the DBCG registry and no additional data will be collected as part of the study, as well as no review of medical records will be made. Therefore, the present NI-Study is defined as a retrospective secondary data collection study, where all data needed for the analysis exist as structured data by the time of study start. This also means that there are no human review of unstructured data conducted as part of the protocol.

9.2. Setting

In the DBCG registry, patients with HR+/HER2- locally advanced or metastatic breast cancer treated with palbociclib will be identified. Palbociclib was approved by the European Commission (EC) and European Medicines Agency (EMA) in November 2016. Hence, the study period will be 2017-2020. A follow-up on patients until 01 May 2022 in terms of the estimation of OS will be made.

The CDK4/CDK6 inhibitors ribociclib and abemaciclib were approved later (2018 and 2020, respectively) and data regarding these treatments are currently not included in the registry. The study will only include patients treated with palbociclib.

9.2.1. Inclusion criteria

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

1. Patients with breast cancer (ICD-10: DC50)
2. A diagnosis of HR+/HER2- locally advanced or metastatic breast cancer
3. Initiated treatment with palbociclib as either 1st or 2nd line treatment between 01 January 2017 and 31 December 2020
4. Inclusion date: Date of relapse/stage IV disease/progression leading to initiation of palbociclib+AI/progression leading to initiation of palbociclib+fulvestrant

9.2.2. Exclusion criteria

There are no exclusion criteria for this study.

9.3. Variables

The main variables included in the study are the following:

Table 1. List of variables

Variable	Role	Data source(s)	DBCG variable(s)
Diagnosis (ICD-10 code: DC50)	Exposure/Inclusion	DBCG registry	Not applicable
Treatment with palbociclib	Exposure/Inclusion	DBCG registry	RE201, RE201A
Date of birth	Baseline characteristic	DBCG registry	Based on M1
Date of breast cancer diagnosis	Baseline characteristic	DBCG registry	Not applicable
Occurrence of metastases	Baseline characteristic	DBCG registry	RE220-RE227
Type of metastases (visceral vs non-visceral)	Baseline characteristic	DBCG registry	RE220-RE227
Number of metastases sites	Baseline characteristic	DBCG registry	RE220-RE227
Location of metastases	Baseline characteristic	DBCG registry	RE10-18 + 80-81, 117-119, 219-222
Surgery	Baseline characteristic	DBCG registry	RE19
De Novo (primary MBC)	Baseline characteristic	DBCG registry	Calculated
Breast cancer disease duration – median time from initial breast cancer diagnosis (incidence date) to relapse	Baseline characteristic	Estimated via DBCG registry registrations	Based on variables listed in this table
Date of relapse	Baseline characteristic	DBCG registry	RE1-RE3
Date for treatment initiation with palbociclib	Baseline characteristic	DBCG registry	RE203-RE205
Date for treatment stop with palbociclib	Baseline characteristic	DBCG registry	RE206-RE208
Post-palbociclib treatment (first subsequent treatment post-palbociclib)	Baseline characteristic	DBCG registry	RE24, RE24A, RE33, RE33A, RE42, RE42A, RE69, RE69A
Reasons to discontinuation with palbociclib	Baseline characteristic	DBCG registry	RE209, RE209A
Death date	Baseline characteristic	DBCG registry	Not applicable
PFS *(see section 8.1 for definition)*	Outcome	Estimated via DBCG registry	Based on variables listed in this table
ToT with palbociclib *(see section 8.1 for definition)*	Outcome	Estimated via DBCG registry registrations	Based on variables listed in this table
OS *(see section 8.1 for definition)*	Outcome	Estimated via DBCG registry registrations	Based on variables listed in this table *(overall and after 6, 12 and 24 months of palbociclib treatment (landmark times))*

9.4. Data sources

This study will be based solely on the DBCG registry. No other Danish healthcare registries will be included. The DBCG registry also includes information on death.

9.5. Study size

It is estimated that the total population of palbociclib-treated patients with HR+/HER2- locally advanced or metastatic breast cancer included in the DBCG registry constitutes of 1,500 patients since the introduction of palbociclib in Denmark (from 01 January 2017 to 31 December 2020).

9.5.1. Sub-groups

In addition, the primary objective (PFS, ToT) as well as some of the secondary objectives (OS and first subsequent post-palbociclib treatment) will be addressed for the following sub-groups such as those below provided sample size is sufficient:

- Specific age groups (below 50 years, 50 -70, and above 70 years of age)
- Patients with visceral disease (defined as metastases in the organs, eg, lung, liver)

9.6. Data management

The Danish Breast Cancer Group hosts the DBCG registry and all analyses will be performed by DBCG's biostatistical researchers following this protocol and a pre-specified SAP. Pfizer will not have access to data at the individual level – only summary data in tables produced by DBCG as part of the discussion of results and reporting.

The individual-level patient data in the registry are well-structured, of high quality, and in a ready-to-analyse format. Data will be analysed using SAS software.

9.7. Data analysis

In general, some research questions will be addressed via descriptive statistics, including stratification on sub-groups. In the PFS and OS analyses, Kaplan-Meier survival distribution functions will be estimated, implying that statistics on median survival expectedly will be available. Overall survival will be estimated for all patients with a censoring of data by 01 May 2022, ie, why the maximum follow-up period for the first treated palbociclib patient 01 January 2017 will be close to 5.5 years. In Kaplan-Meier landmark analyses OS will furthermore be analysed and reported after 6, 12 and 24 months from treatment initiation.

A separate SAP, including shell tables, will be developed prior to data analysis. The SAP will be dated, filed, and maintained by the sponsor. The SAP will also include precise definitions of the sub-groups. 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.

9.8. Quality control

DBCG's biostatistical researchers will compile the full data set and perform the analyses. The researchers will follow generally accepted methods as well as DBCG's internal guidelines for data analysis.

The study involves analyses of individual data. DBCG's biostatistical researchers will, however, only have access to data in de-personalized form (by encrypted personal identification codes). Pfizer will not have access to any individual data in the project, only the summary data produced by DBCG's biostatistical researchers.

Furthermore, the study design, literature, decisions on data analysis, interpretation of the results of the study, as well as reporting (manuscript) will be only discussed in the project group (see list of responsible parties in section 3).

The study though will as a Non-Interventional Study with Pfizer as sponsor, collaborator and part of the project group have to use certain templates, incl. the present protocol template and a template for the SAP, etc. Furthermore, the study has to follow certain review stages by the sponsor such as a technical protocol review and a review of the final scientific manuscript prior to submission to a scientific journal.

9.9. Strengths and limitations of the research methods

Naturally, this study has both strengths and limitations.

DBCG has provided a long history of compiling and maintaining registry data since the past 40 years. The data from DBCG has been part of both national and international studies. In addition the data collected by DBCG have been published in more than 430 peer-reviewed papers (27).

And has been part of several meta-analyses conducted by Early Breast Cancer Triallists' Collaborative Group (28-29). The extension of this registry to include relapsed patients nationwide is therefore a very unique feature of this registry. To collect relapse data about MBC patients has been a challenge in many countries.

The DBCG registry holds the most detailed and comprehensive information about patients diagnosed with HR+/HER2- locally advanced or metastatic breast cancer, implying that, compared to other Danish healthcare registries, new and more detailed results can be presented. Furthermore, the study is a study carried out at the population level, which makes the study and its results as complete and generalizable as possible and minimizes the risk of selection bias.

At the same time, since this study only involves data from the DBCG registry, the completion and validity of the analyses rely 100% on the quality and validity of the data in the registry.

The study does furthermore only include the data available in the DBCG registry and only data of a quantitative nature. More qualitative data and outcomes following the treatment of the breast cancer patients will though not be included.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, or publications, or in any other disclosures except where required by law. As described, DBCG's biostatistical researchers will have access only to data in de-personalized form (encrypted personal identification codes (CPR)). Pfizer will not have access to any individual data in connection with the project but only the summary data produced by DBCG's biostatistical researchers.

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)

Approval from the Danish Data Protection Agency is not necessary for this type of study. However, in accordance with General Data Protection Regulation (GDPR) the study will be reported via Pactius to the Capital Region of Denmark's research list.

Approval from an ethics committee is not required by Danish law since a retrospective database study does not involve collection of or research on biological material.

No other approvals from IRBs or IECs are necessary under Danish law.

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 will follow generally accepted research practices described 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 (30).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Besides a study report presenting the results, a manuscript for a scientific article will be written and submitted to an international peer-reviewed journal. Authorship of the article manuscripts will follow the requirements set by the International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). All members of the project group as described in section 3 of this protocol, including external members and Pfizer employees, fulfilling these requirements with respect to the article manuscripts are offered co-authorship of the scientific article.

The study and its results will also be disclosed at the ClinicalTrials.gov website.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting 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.

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14. LIST OF TABLES

Table 1. List of variables (see section 9.3).

15. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Not applicable.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.