NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Impact of age and comorbidities on treatment outcomes of first-line treatment with palbociclib in combination with an aromatase inhibitor (AI) in patients diagnosed with HR+/HER2 - metastatic breast cancer – Danish Non-Interventional Study
Protocol number	A5481188
Protocol version identifier	Version 3.0
Date	17 February 2025
Active substance	L01XE33 – Palbociclib
Medicinal product	Ibrance (palbociclib)
Research question and objectives	The objective is to investigate the outcomes (progression free survival (PFS) and overall survival (OS)) of first-line treatment with palbociclib in combination with an aromatase inhibitor (AI) in hormone receptor positive (HR+) or human epidermal growth factor receptor (HER2) metastatic breast cancer (mBC) patients in Denmark. These patients consist of endocrine sensitive, endocrine resistant as well as de novo patients. Primary objectives: - PFS of all mBC patients receiving palbociclib + AI as first-line treatment - OS of all mBC patients receiving palbociclib + AI as first-line treatment Secondary objectives: Age subgroup analyses: - Age distribution in full data set of mBC patients receiving palbociclib + AI as first-line treatment - PFS/OS of all mBC patients below 65 years of age, 65-74 years of age and 75+ years of age, respectively, receiving palbociclib + AI as first-line treatment Comorbidity subgroup analyses (Charlson Comorbidity Index (CCI)) is used as a data source for comorbidity and comorbidity burden): - PFS/OS in the full data set of mBC patients receiving palbociclib + AI as first-line treatment split into CCI point scores of 0, 1, 2, and 3 or higher (3+) - PFS/OS in the full data set of mBC patients receiving palbociclib + AI as first-line treatment split into number of comorbidities (none, one, and two or more) - PFS/OS in the full data set of mBC patients receiving palbociclib+AI as first line treatment split into type of comorbidity – with focus on five main groups: Cardiac disease, Vascular disease, Metabolic disease, Psychiatric disease, Blood and lymphatic system.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC	Advanced Breast Cancer
AE	Adverse event
AI	Aromatase Inhibitor
a/MBC	Advanced metastatic breast cancer
BC	Breast Cancer
C50	ICD-10 code for patients with breast cancer
CCI	Charlson Comorbidity Index
CDK	Cyclin-dependent kinase
CDK4	Cyclin Dependent Kinase 4
CDK6	Cyclin Dependent Kinase 6
CNS	Central Nervous System
CPR	Centrale Person Register – registry that holds the personal ID numbers that every Danish citizen has
CV	Cardiovascular
DBCG	Danish Breast Cancer Group
EC	Ethical Committee
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSFV	First subject first visit
GDPR	General Data Protection Regulation
HIV/AIDS	Human Immunodeficiency Virus / Acquired ImmunoDeficiency Syndrome
HR	Hazard ratio
HR+	Hormone receptor positive, including estrogen receptor positive (ER+)
HER2	Human epidermal growth factor receptor 2
HER2-	HER2 negative
ICD-10	International Classification of Diseases and Related Health Problems, 10th Revision
ICMJE	International Committee of Medical Journal Editors
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
LOT	Line of Treatment
LPR	National Patient Registry (Landspatientregistret)
LSLV	Last subject last visit
MBC	Metastatic breast cancer
NI-Study	Non-Interventional Study
OS	Overall survival
PFS	Progression free survival
RCT	randomized controlled trials
RW	Real-World
RWE	Real-World Evidence
SAP	Statistical Analysis Plan
US	United States of America

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title

Impact of age and comorbidities on treatment outcomes of first-line treatment with palbociclib in combination with an aromatase inhibitor (AI) in patients diagnosed with HR+/HER2 – metastatic breast cancer – Danish Non-Interventional Study. Protocol version 3.0, February 17th, 2025.

Authors

PPD, MD, MSc; PPD, MSc; PPD, MSc, PhD; PPD, MSc, Pfizer Denmark; PPD, MD, PhD; and PPD, MD, Danish Breast Cancer Group and Rigshospitalet.

Rationale and background

Randomized controlled trials (RCT) may have limitations with patients in daily practice being more heterogeneous than in the RCTs. Metastatic breast cancer (mBC) patient populations include, like the rest of the population, more elderly patients as well as patients with comorbidities besides their cancer disease. However elderly and patients with comorbidities have been underrepresented in RCTs due to strict in- and exclusion criteria, and therefore the outcome of treatment with CDK4/CDK6, incl. palbociclib, is unclear from these RCTs. Studies using real-world (RW) data of the patients in actual daily clinical practice can address the question of effectiveness and safety in these more heterogenous patient populations. A number of RW-evidence (RWE) studies – many from the US – found significant improvements in OS and PFS for HR+/HER2- mBC patients treated with palbociclib+AI compared to AI alone. In a Danish setting though, limited evidence on the effectiveness of palbociclib in older mBC patients with comorbidities is available. As an update and extension of the Garly *et al.* study, the present study therefore aims to investigate the use and effectiveness of palbociclib+AI as first-line treatment in subgroups of elderly patients as well as patients with comorbidities having HR+/HER2- mBC.

All first-line mBC patients consist of endocrine resistant, endocrine sensitive and de novo patients. As in Garly et al. endocrine resistant patients are defined as recurrent patients with advanced disease within 12 months of completing adjuvant endocrine therapy or during adjuvant endocrine therapy. Endocrine sensitive patients are defined as recurrent patients with advanced disease after 12 months of completing adjuvant endocrine therapy, recurrent patients who received no adjuvant endocrine therapy or patients with de novo, advanced breast cancer. De novo patients are defined as newly metastatic patients.

Research question and objectives

The objective is to retrospectively investigate the outcomes (overall PFS and OS) of first-line treatment with palbociclib in combination with an AI in key subgroups of mBC patients in Denmark focusing on age and comorbidity burden.

- Primary objectives:
  - PFS of all mBC patients receiving palbociclib + AI as first-line treatment
  - OS of all mBC patients receiving palbociclib + AI as first-line treatment

Secondary objectives:

- Age subgroup analyses:
  - Age distribution in the full data set of mBC patients receiving palbociclib + AI as first-line treatment
  - PFS and OS in mBC patients below 65 years of age, 65-74 years of age and 75+ years of age, respectively, receiving palbociclib+AI as first-line treatment.

- Comorbidity subgroup analyses (CCI) is used as a data source for comorbidity and expression of comorbidity burden):
  - PFS and OS in the full data set of mBC patients receiving palbociclib + AI as first-line treatment split into CCI point scores of 0, 1, 2, and 3 or higher (3+)
  - PFS and OS in the full data set of mBC patients receiving palbociclib + AI as first-line treatment split into number of comorbidities (no comorbidity, one comorbidity, and two or more comorbidities)
  - PFS and OS in the full dataset of mBC patients receiving palbociclib + AI as first-line treatment split into type of comorbidity – focus on five main groups: Cardiac disease, Vascular disease, Metabolic disease, Psychiatric disease, Blood and lymphatic system.

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 HR+/HER2- mBC patients treated with palbociclib in combination with an AI as first-line treatment in Denmark.

Population

The full dataset consists of endocrine sensitive, endocrine resistant and de novo HR+/HER2- mBC patients treated with palbociclib as first-line treatment (01 January 2017- 31 December 2021). Patients will be censored for OS and PFS by 1st February 2024.

Inclusion criteria

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

1. Patients with breast cancer (ICD-10: C50)
2. A diagnosis of HR+/HER2- locally advanced or metastatic breast cancer
3. Endocrine sensitive endocrine resistant or *de novo* mBC patient
4. Initiated treatment with palbociclib as first-line treatment (palbociclib + AI) between 1 January 2017 and 31 December 2021
5. Inclusion date: Date of relapse/stage IV disease/progression leading to initiation of palbociclib + AI

Variables (see section 9.3 for additional details)

- Diagnosis (ICD-10 code: C50) *(exposure/inclusion)*
- Treatment with palbociclib

- Date of birth
- Date of breast cancer diagnosis
- Occurrence of metastases
- Visceral status (visceral and non-visceral)
- Bone only
- Metastatic sites (liver, lung, central nervous system (CNS), lymph nodes)
- *De Novo* (primary mBC)
- Date of relapse
- Date for treatment initiation with palbociclib
- Date for treatment stop with palbociclib
- Charlson Comorbidity Index (CCI) (point scores of 0, 1, 2, and 3 or higher (3+)) at start of palbociclib treatment
- Number of comorbidities at start of palbociclib treatment
- Types of comorbidities at start of palbociclib treatment (Cardiac disease, Vascular disease, Metabolic disease, Psychiatric disease, Blood and lymphatic system)
- Death date
- PFS (*outcome*)
- OS (*outcome*)

Data sources
This study will be based on the Danish Breast Cancer Group (DBCG) registry and the National Patient Registry (LPR) with respect to the comorbidities.

Study size
It is estimated that the total population of first-line palbociclib-treated breast cancer patients with HR+/HER2- mBC included in the DBCG registry from the period 2017-2021 constitutes of 580 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. Censoring for OS and PFS analyses will be 1st February 2024. A separate Statistical Analysis Plan (SAP), including shell tables, will be developed prior to data analysis.

Milestones

• Final Protocol	29 February 2024
• Final Statistical Analysis Plan	5 March 2024
• Start of data collection (FSFV – database study)	6 March 2024
• Data setup	6 March 2024
• End of data collection (LSLV – database study)	19 April 2024
• Data analyses	22 April – July 2024
• DBCG Final study report	01 August 2024
• Manuscript ready for submission	31 August 2024

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
3.0	17 February 2025	Substantial	3. Responsible Parties 4. Abstracts	Added Daniel Sloth Hauberg as a Principal Investigator of the Protocol	Since PPD has left Pfizer, PPD has taken over the responsibility as NI study lead responsible for protocol amendments
	17 February 2025		4. Abstracts	Update of Abstract title	Updated title with correct protocol version number and date
	17 February 2025		4. Abstracts 8.1 Definitions 9.2 Setting 9.8 Data Analysis	Update of OS and PFS censoring date	Due to additional follow-up data available, the censoring date has been changed from 31st December 2023 to 1st February 2024

6. MILESTONES

Milestone	Planned date
Final Protocol	29 February 2024
Final Statistical Analysis Plan (SAP)	5 March 2024
Start of data collection (FSFV – database study, historic data)	6 March 2024
Data setup	6 March 2024
End of data collection (LSLV – database study, historic data)	19 April 2024
Data analyses	22 April –July 2024
DBCG Final study report	01 August 2024
Manuscript ready for submission	31 August 2024

7. RATIONALE AND BACKGROUND

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

The introduction of CDK4/CDK6 inhibitors has revolutionized the paradigm of therapeutic management of HR+ mBC worldwide. The most common cancer globally is breast cancer (4). 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 in Denmark are living with a breast cancer diagnosis with 20% of them experiencing a relapse of the disease at some stage in their life.

The three CDK4/CDK6 inhibitors palbociclib, ribociclib, and abemaciclib are approved in combination with AI or with fulvestrant. To date, several Phase 2 and 3 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 (5), PALOMA-2 (2) and PALOMA-3 (6,7). Ribociclib was evaluated in three trials, Phase 3 MONALEESA-2 (8), MONALEESA-3 (9) and MONALEESA-7 (10). Abemaciclib was evaluated in MONARCH 1 (11), MONARCH 2 (12) and MONARCH 3 (13).

Specifically, 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). Patients receiving palbociclib and letrozole had numerically longer OS compared to placebo and letrozole (median OS was 53.9 months versus 51.2 months), but the results were not statistically significant (HR= 0.956; *P*=0.3378) (15).

RCTs remain the gold standard in the scientific evidence hierarchy to show efficacy of drugs. However, it is also well established that despite being randomized such studies may have limitations such as homogenous patient populations which often do not reflect the clinical picture encountered in the heterogeneous real-world. Both patient-related and disease-related variables can impact the prognosis of metastatic breast cancer patients. Some variables are sites of metastatic involvement, tumor subtypes, burden of disease, and patient comorbidities (16). In addition, many patients have co-existing comorbidities, when they are diagnosed with cancer, especially the elderly patients (17). The number of elderly cancer patients has increased due to the aging population through the past many years (18). International studies show that 20-35% of breast cancer (BC) patients have one or more comorbidities at the time of their BC diagnosis (19). In Danish women diagnosed with early breast cancer, the share of patients with comorbidities has been shown to be around 16-20% (20-23).

Studies using RW data of the patients in actual daily clinical practice can address the question of effectiveness and safety in more heterogenous patient populations compared to the study populations in RCTs (24-25).

According to the systematic literature review by Harbeck et al. a number of RW-evidence (RWE) studies on CDK4/CDK6 inhibitors in the treatment of HR+/HER2- mBC has been carried out (26). The majority of these studies confirmed the efficacy and safety of CDK4/CDK6 inhibitors as found in RCTs (26). A retrospective observational analysis of electronic health records within the US Flatiron Health Analytic Database of patients treated with palbociclib plus letrozole by DeMichele *et al*., confirmed the results of the PALOMA-2 RCT study (27). Similarly, Rugo *et al*. utilizing Flatiron data on 2888 patients with HR+/HER2− mBC treated with first-line palbociclib+AI versus AI alone found a median OS of 49.1 months in the palbociclib group and 43.2 months in the AI group (HR= 0.76; $P < 0.0001$) and median PFS of 19.3 months and 13.9, respectively (HR= 0.70; $P < 0.0001$) (28). RWE on Danish patients treated with palbociclib utilizing data from the DBCG national clinical registry have recently been published showing a median OS of 56.9 months and PFS of 31.3 months in the first-line, endocrine sensitive, AI group (29).

Despite the high incidence of breast cancer in the elderly population, elderly patients have been less frequently included in the RCTs, resulting in an evidence gap with respect to the treatment outcome for this patient group. The Alliance for Clinical Trials in Oncology found in an analysis of the breast cancer trials conducted that < 20% of the trial participants were ≥ 65 years of age and < 10% were ≥ 70 years of age (30). Also, in the three PALOMA trials the majority of the included patients were younger than 65 years of age, and only 9.5% were ≥75 years of age (31).

Some studies have tried to address this unmet need and lack of evidence in RCTs regarding the elderly population by utilizing data from the US Flatiron database. Brufsky *et al*. found significant improvements in OS (43.0 vs 32.4 months, HR=0.66, p=0.0007) and PFS (20.0 vs 15.0 months, HR=0.72, p=0.0021) for HR+/HER2- mBC patients aged ⩾ 75 years treated with palbociclib + AI compared with AI alone (32). In another study Rugo *et al.* found significant improvements in PFS (22.2 vs 15.8 months; HR=0.59, p<0.0001) for patients with mBC aged ⩾65 years treated with palbociclib + letrozole versus letrozole alone (33).

Strict inclusion and exclusion criteria in clinical trials also restricts inclusion of patients with certain comorbidities. However, a study on US patients revealed that more than half (62%) of the patients with newly diagnosed HR+/HER2- mBC had at least one preexisting cardiovascular (CV) comorbidity at the time of BC diagnosis, and among those aged 65 years or older it was 87%, and of those with preexisting CV comorbidity, 53% were prescribed medication with a risk of QTc prolongation (34). Again, there is an unmet need and lack of evidence from the RCTs on the effectiveness of CDK4/CDK6 inhibitors in the treatment of HR+/HER2- a/mBC in comorbid patient populations. The impact of comorbidities on palbociclib effectiveness has recently been studied in a number of real-world observational studies from the US. The POLARIS study, which included 1,250 patients receiving palbociclib in routine clinical practice in US and Canada, showed that patients had a median of 2 comorbidities at baseline (range 0-9) (35). The study found that patients in real-life receiving palbociclib in first line of therapy (1LOT) or ⩾ 2LOT with CCI score of 2 or lower tended to have longer PFS and OS than those with CCI score of 3 or higher. Similarly, patients with cardiac disorders in the 1LOT as well as blood and lymphatic disorders in the ≥ 2LOT had shorter PFS. For the other comorbidity subgroups in the study comparable clinical outcomes were found (35). Another new real-world effectiveness study confirmed that patients with HR+/HER2- mBC, who had cardiovascular disease as comorbidity, when receiving palbociclib + AI as first-line therapy obtained significant prolonged OS (40.7 vs 26.5 months, HR=0.732, p=0.0476) and significant

improved PFS (20.0 vs 12.5 months, HR=0.679, *p*=0.0070) compared to similar patients only receiving AI alone (36).

In a Danish setting, limited evidence is available on older metastatic breast cancer patients with comorbidities and the effectiveness of treatment with palbociclib in these subgroups of the Danish mBC patients. As an update and extension of the Garly et al. study (29), the present study therefore aims to investigate the use and effectiveness of palbociclib + AI as first-line treatment in all HR+/HER2- mBC patients in Denmark, as well as in subgroups of elderly patients and those with comorbidities.

All first-line mBC patients consist of endocrine resistant, endocrine sensitive and de novo patients. As in Garly et al. (29) endocrine resistant patients are defined as recurrent patients with advanced disease within 12 months of completing adjuvant endocrine therapy or during adjuvant endocrine therapy. Endocrine sensitive patients are defined as recurrent patients with advanced disease after 12 months of completing adjuvant endocrine therapy, recurrent patients who received no adjuvant endocrine therapy or patients with de novo, advanced breast cancer. De novo patients are defined as newly metastatic patients. The study data will be based on the DBCG clinical database as the previous study by Garly *et al*. (29).

The study will, as a RWE study, follow and comply with the recent specific GROW guidance for reporting oncology RWE studies in peer-reviewed journals presented at ESMO 2023 (37).

8. RESEARCH QUESTION AND OBJECTIVES

The overall objective is to retrospectively investigate the outcomes (overall PFS and OS) of first-line treatment with palbociclib in combination with an AI in key subgroups of mBC patients in Denmark focusing on age and comorbidity burden.

Primary objectives:

- PFS of all mBC patients receiving palbociclib in combination with AI as first-line treatment
- OS of all mBC patients receiving palbociclib in combination with AI as first-line treatment

Secondary objectives:

- *Age subgroup analyses:*
  - Age distribution in the full data set of mBC patients receiving palbociclib + AI as first-line treatment
  - PFS and OS in mBC patients below 65 years of age, 65-74 years of age and 75+ years of age, respectively, receiving palbociclib + AI as first-line treatment

- *Comorbidity subgroup analyses* (Charlson Comorbidity Index (CCI) (38) is used as a data source for comorbidity and comorbidity burden – comorbidities at start of palbociclib treatment):
  - PFS and OS in the full dataset of mBC patients receiving palbociclib + AI as first-line treatment split into CCI point scores of 0, 1, 2, and 3 or higher (3+)

- PFS and OS in the full dataset of mBC patients receiving palbociclib + AI as first-line treatment split into number of comorbidities (no comorbidity, one comorbidity, and two or more comorbidities)
- PFS and OS in the full dataset of mBC patients receiving palbociclib + AI as first-line treatment split into type of comorbidity – focus on five main groups: Cardiac disease, Vascular disease, Metabolic disease, Psychiatric disease, Blood and lymphatic system.

Following the inclusion criteria (see section 9.2.1 below) the analyses will be performed on the full data set of patients with HR+/HER2- locally advanced or metastatic breast cancer treated with palbociclib + AI as first-line treatment.

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 1st February 2024
- Progression of disease is based on scans and blood testing results

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 1st February 2024

9. RESEARCH METHODS

9.1. Study Design

The study is designed as a secondary data collection NI-Study. Retrospective data will be collected from an existing registry - the DBCG registry. The focus of this study will be on HR+/HER2- locally advanced or metastatic breast cancer treated with palbociclib. The study is a single-arm study 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 (39,40). 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 on which the study will be based is one of several DBCG registries. All Danish patients with locally advanced or metastatic breast cancer are included in the DBCG registry. 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 of the present study and has previously been used to analyze treatment outcomes for all first- and second-line palbociclib patients in Denmark (29).

The present NI-Study will therefore rely on data in the DBCG registry, as well as data from the National Patient Registry (comorbidity data). No additional data will be collected as part of the study, furthermore 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 is no human review of unstructured data conducted as part of the protocol.

9.2. Setting

In the DBCG registry, all HR+/HER2- locally advanced or mBC patients treated with palbociclib in combination with AI as first-line treatment will be identified. Palbociclib was approved by the European Commission and European Medicines Agency (EMA) in November 2016. Hence, the study period will be from 1 January 2017 and to 31 December 2021. A follow-up on patients until 1st February 2024 in terms of the estimation of PFS and OS will be made.

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: C50)
2. A diagnosis of HR+/HER2- locally advanced or metastatic breast cancer
3. Endocrine sensitive, endocrine resistant, or de novo mBC patient
4. Initiated treatment with palbociclib as first-line treatment (palbociclib + AI) between 1 January 2017 and 31 December 2021
5. Inclusion date: Date of relapse/stage IV disease/progression leading to initiation of palbociclib + AI

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.3. Variables

The main variables included in the study are shown in Table 1.

Table 1. Variables in the study

Variable	Role	Data source(s)	DBCG variable(s)
Diagnosis (ICD-10 code: C50)	Exposure/Inclusion	DBCG registry	Not applicable
Treatment with Palbociclib	Exposure/Inclusion	DBCG registry	RE201, RE201A
Date of birth	Baseline	DBCG registry	Based on M1
Date of breast cancer diagnosis	Baseline	DBCG registry	Not applicable
Occurrence of metastases	Baseline	DBCG registry	RE220-RE227
Visceral status (visceral and non-visceral – visceral defined as metastases in the organs, e.g., lung, liver))	Baseline	DBCG registry	RE220-RE227
Bone only	Baseline	DBCG registry	RE14
Metastatic sites (liver, lung, CNS, lymph nodes)	Baseline	DBCG registry	RE10-18 + 80-81, 117-119, 219-222
De Novo (primary mBC)	Baseline	DBCG registry	Calculated
Date of relapse	Baseline	DBCG registry	RE1-RE3
Date for treatment initiation with palbociclib	Baseline	DBCG registry	RE203-RE205
Date for treatment stop with palbociclib	Baseline	DBCG registry	RE206-RE208
Charlson Comorbidity Index (CCI) – point scores of 0, 1, 2, and 3 or higher (3+) (calculated at start of palbociclib treatment)	Baseline	National Patient Registry (LPR) data used to define CCI in DBCG registry	Not applicable
Number of comorbidities (calculated at start of palbociclib treatment)	Baseline	National Patient Registry (LPR) data used to define CCI in DBCG registry	Not applicable
Types of comorbidities (Cardiac disease, Vascular disease, Metabolic disease, Psychiatric disease, Blood and lymphatic system) (calculated at start of palbociclib treatment)	Baseline	National Patient Registry (LPR) data used to define CCI in DBCG registry	Not applicable
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
OS *(see section 8.1 for definition)*	Outcome	Estimated via DBCG registry registrations	Based on variables listed in this table

9.4. Charlson Comorbidity Index (CCI) and comorbidities

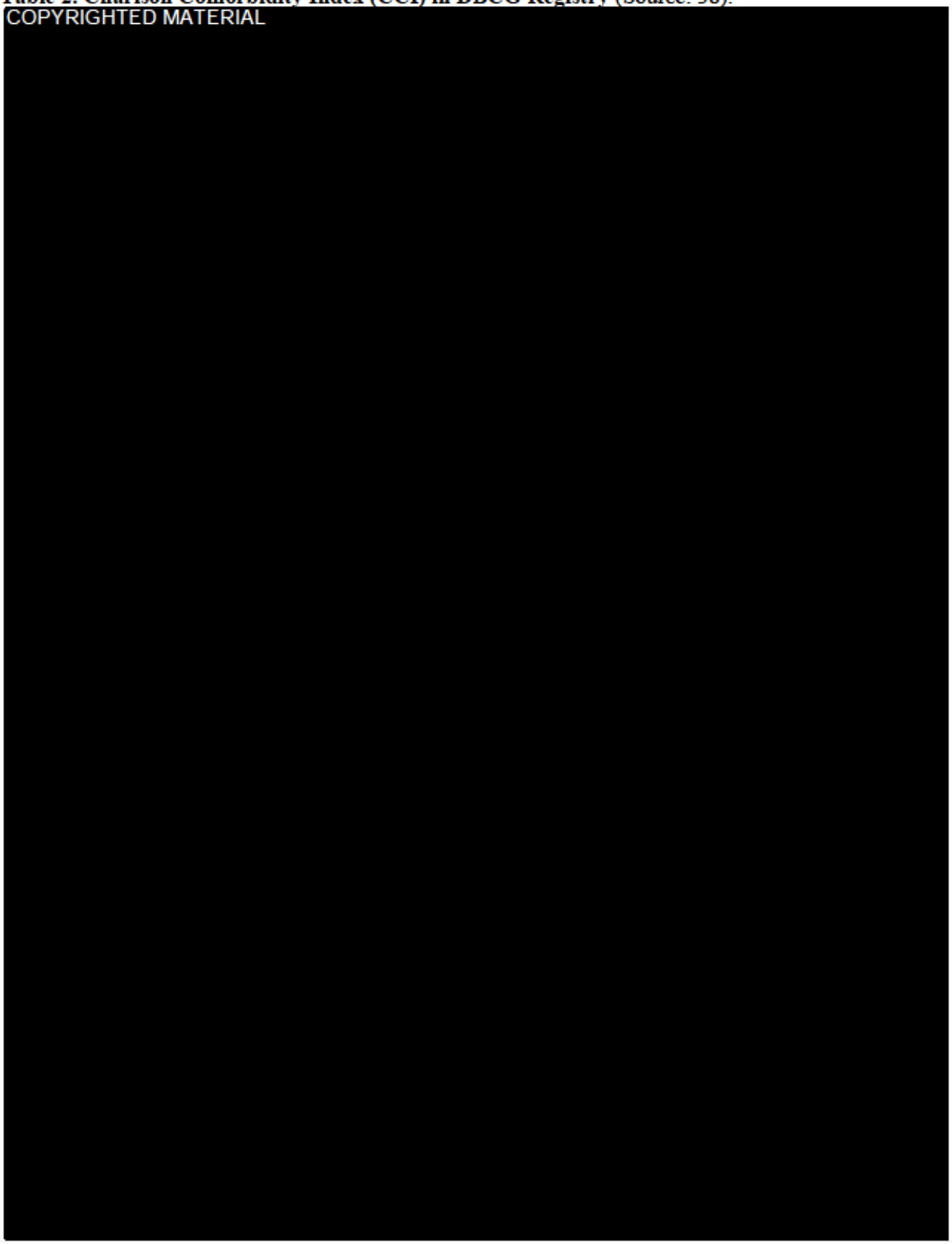
The Charlson Comorbidity Index (CCI) is used as the data source for comorbidity in the study.

The data in the DBCG database for the CCI are originally drawn from the LPR. The National Patient Registry has disease data on all patients requiring a hospital contact, i.e. outpatient and inpatient, which means that ICD-codes (today ICD-10 classification) of patients diseases are recorded. In CCI all comorbidities, excluding the specific cancer type under investigation, are included as comorbidities, and included in the overall CCI score. In the present study this means that breast cancer in itself (ICD-10: C50x) is not included, but other cancer-types and tumors are. Data on comorbidities in patients are recorded and calculated at start of their palbociclib treatment, i.e. how many and which comorbidities are present at the time the mBC patient gets palbociclib, and what is the associated CCI score at this time?

With the Charlson Comorbidity Index an overall CCI-score can be calculated for each patient. For each comorbidity recorded for the patient a score between 0 and 6 is assigned depending on the comorbidity and whether it is part of the CCI. All scores are then summed up at the end for each patient. The higher the CCI score the more severe the comorbidity status.

The CCI instrument used in the study is shown below in Table 2.

Table 2. Charlson Comorbidity Index (CCI) in DBCG Registry (Source: 38).



In the present study the CCI score is grouped into four groups as defined below:

- Patients with a **CCI score of 0** defines patients with no comorbidity besides the breast cancer disease.
- Patients with a **CCI score of 1** defines patients with one comorbidity of the type with a score of 1, e.g., myocardial infarction or diabetes mellitus.
- Patients with a **CCI score of 2** defines patients with two comorbidities each having a score of 1 or one comorbidity alone with a CCI score of 2, e.g., diabetes mellitus with organ damage or a solid tumor besides breast cancer disease.
- Patients with a **CCI score of 3 or higher (3+)** defines patients with severe comorbidity/ies having one comorbidity with a CCI score of 6, e.g., Human Immunodeficiency Virus/Acquired ImmunoDeficiency Syndrome (HIV/AIDS), or two or more comorbidities each with CCI scores of 1-2. These comorbidities are also besides the patients' breast cancer disease.

Again, the higher the CCI score the more severe the comorbidity status for the patient, leaving those with a CCI score of 3 or higher (CCI 3+) as patients being most impacted by their comorbidities.

Besides using the CCI score for subgroup analyses of the treatment outcomes (PFS and OS), the number of comorbidities is also used for subgroup analyses and calculated from the CCI. Patients are split into three comorbidity groups – no comorbidity, one comorbidity and two or more comorbidities. Splitting the subgroup analysis according to number of comorbidities per patient puts equal weight on all comorbidities.

In the third subgroup analyses of the treatment outcomes (PFS and OS) comorbidities are categorized into five main disease groups: Cardiac disease, Vascular disease, Metabolic disease, Psychiatric disease, Blood and lymphatic system. Recording of these will also come from the CCI.

9.5. Data Sources

This study will be based on the DBCG registry and the National Patient Registry (LPR) with respect to the comorbidities. No other Danish healthcare registries will be included.

9.6. Study Size

The study focusses on all HR+/HER2- locally advanced mBC patients (endocrine sensitive, endocrine resistant or de novo) that have received palbociclib in combination with AI as first-line treatment in the inclusion period 1 January 2017 to 31 December 2021.

It is estimated that the total population of palbociclib-treated patients following these inclusion criteria in the DBCG registry constitutes 580 patients overall.

Subgroup analyses of this patient population will be made based on age and comorbidity status as described in section 8 above.

9.7. 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-analyze format. Data will be analyzed using SAS software.

9.8. Data Analysis

In general, the research questions will be addressed via descriptive statistics, including stratification on subgroups. In the PFS and OS analyses, Kaplan-Meier survival distribution functions will be estimated, implying that statistics on median survival expectancy will be available. Overall survival will be estimated for all patients with a censoring of data by 1st February 2024, ie, why the maximum follow-up period for the first treated palbociclib patient 1 January 2017 will be 7 years and one month.

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 subgroups. 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.

9.9. 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).

This NI-Study with Pfizer as sponsor, collaborator, and part of the project group, will have to use certain templates, incl. the present protocol template and a template for the SAP, etc. Furthermore, the study must 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.

9.10. Limitations of the Research Methods

This study has both strengths and limitations.

DBCG has a long history of compiling and maintaining registry data for 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 632 peer-reviewed papers (29,41).

And have been part of several meta-analyses conducted by Early Breast Cancer Triallists' Collaborative Group (42,43). The extension of this registry to include relapsed patients nationwide is therefore a unique feature of this registry and was previously utilized in the study by Garly *et al.* (30). Collecting 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 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 thus not be included.

9.11. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

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 a deidentified/anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves deidentified/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)/ Ethics Committee (EC)

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 follow generally accepted research practices described in *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* (44).

Furthermore, the study will comply with the recent *ESMO GROW* guidance for reporting oncology real-world evidence (37).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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. The chosen target manuscript for submission of the manuscript is decided in consensus by the project group (see group in section 3).

Authorship criteria 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, as well as others involved from DBCG in the present study, all fulfilling these requirements with respect to the manuscripts should be

offered co-authorship of the scientific article. First drafts of the manuscript should be made available to all co-authors for their obligation to comment on the manuscript as co-author. All co-authors should approve the final manuscript prior to submission to the agreed journal.

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

15. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.