Non-Interventional Study Protocol
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A retrospective non-interventional study of breast cancer patients diagnosed with HR+ / HER2- locally advanced or metastatic breast cancer treated with palbociclib in Denmark

Statistical Analysis Plan
(SAP)

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable.

2 INTRODUCTION

The discovery and development of CDK (cyclin-dependent kinases) 4/6 inhibitors have revolutionised the paradigm of therapeutic management of hormone receptor-positive (HR+) metastatic breast cancer (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%. Currently, approx. 64,000 women are living with a breast cancer diagnosis. It is estimated that approx. 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 HR+/Human epidermal growth factor receptor 2-negative (HER2-) breast cancer in Denmark is estimated to be around 500 *patients yearly [2]..*

The first cell-cycle inhibitor was palbociclib, which was approved by the FDA on the basis of the phase 2 study PALOMA-1 [3]. *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 the phase 3 study PALOMA-2 as well [4]. This approval was followed by the other two CDK4/6 inhibitors ribociclib and abemaciclib. In Denmark, these targeted therapeutic agents were incorporated into the clinical practice from 2016 onwards* [5]. *The introduction of CDK4/6 inhibitors has permanently transformed the therapeutic management of HR+ MBC worldwide. The three CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib are approved for either with a combination of aromatase inhibitor (AI) or with fulvestrant.*

2.1 STUDY RATIONALE

To date, several Phase II and III randomised controlled trials (RCTs) have evaluated CDK4/6 inhibitors in the treatment of HR+/HER2- advanced breast cancer/MBC. Randomisation and blinding are considered to be the gold standard for determining the effect of a treatment in randomised controlled clinical trials. However, due to strict protocol-specified definition of inclusion criteria, populations in the randomised trials do not always represent patients treated in clinical practice. Therefore, real-world data (RWD) are increasingly being used to understand the safety and effectiveness of new drug regimens in actual clinical practice where patient populations are heteregenous[6,7].

However, there is a need for additional and updated real-world evidence (RWE) about the CDK4/6 inhibitors in a real-world setting. Most RWE studies on CDK4/6 inhibitors published to date are studies conducted in the USA. Hence, there is a need for

national/European data for CDK4/6 inhibitors in the treatment of HR+/HER2- advanced breast cancer/MBC.
In Denmark, access to the Danish Breast Cancer Group (DBCG) clinical register 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 to collect retrospective clinical effectiveness data and treatment pattern data on palbociclib.

Compared to existing RWE studies, this study will, through its access to the national DBCG clinical register, 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 RWD from patients from all regions of Denmark via the DBCG register will add on to the existing pool of RWE.

Thus, the overall objective is to use data from the Danish DBCG register to retrospectively describe and assess clinical and demographical characteristics and treatment patterns in a real-world setting of patients with HR+/HER2- locally advanced or metastatic breast cancer receiving palbociclib in combination treatment.

Note: in this document, any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

2.2 STUDY DESIGN

The study is designed as a secondary data collection Non-Interventional Study (NIS) based on retrospective data from the DBCG clinical register. The study is a single-arm study focusing only on patients treated with palbociclib in Denmark.

Study population

Patients registered in the DBCG register with HR+/HER2- locally advanced or metastatic breast cancer and treated with palbociclib (first- or second-line) (1 January 2017 to 31 December 2020).
It is estimated that the total population included in the DBCG register consists of 1,500 patients in Denmark.

Data source

The entire study will be undertaken among patients registered in the DBCG clinical register. *That is, the study will be based solely on the DBCG register. No other Danish healthcare registers will be included. The DBCG register also includes information on death.*

Since its establishment in 1976, the DBCG has maintained a clinical register 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 register. This well-established breast cancer register

(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 register focusing on relapses, which the study will be based on, is one of several DBCG registries. It is estimated that by the end of 2021, the DBCG register will include all Danish patients with locally advanced or metastatic breast cancer. The data and records in the register 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 population of the DBCG register 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 register contains detailed clinical and pathological data about the treatment patterns of patients with HR+/HER2- locally advanced or metastatic breast cancer.

Treatment/cohort labels

As stated, this study focuses only on the cohort of patients with HR+/HER2- locally advanced or metastatic breast cancer treated with palbociclib.

2.3 STUDY OBJECTIVES

In general, the overall objective is to use data from the Danish DBCG register to retrospectively describe and assess clinical and demographical characteristics and treatment
patterns in a real-world setting of patients with HR+/HER2- locally advanced or metastatic breast cancer receiving palbociclib in combination treatment. The project will include both first- and second-line patients.

The primary objective is to estimate
- *Progression-Free Survival (PFS) and*
- *Time on Treatment (ToT)*

of patients receiving Palbociclib in combination with aromatase inhibitor (AI).

Details regarding primary and secondary endpoints are described in section 5.

3 HYPOTHESES AND DECISION RULES

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

4 ANALYSIS SETS/POPULATIONS

As stated, this study includes the population of patients with HR+/HER2- locally advanced or metastatic breast cancer treated with palbociclib identified in the DBCG register.

The inclusion and exclusion criteria are specified below.

Inclusion criteria

To be eligible for inclusion in the study, patients must meet the following criteria:

- *Patients with breast cancer (ICD10: DC50)*
- *A diagnosis of HR+/HER2- locally advanced or metastatic breast cancer*
- *Initiated treatment with palbociclib as either 1st or 2nd line treatment between 01 January 2017 and 31 December 2020*
- *Inclusion date: Date of relapse/stage IV disease/progression leading to initiation of palbociclib+AI/progression leading to initiation of palbociclib+fulvestrant*

Exclusion criteria

There are no exclusion criteria for this study.

4.1 SUBGROUPS

For the population of patients with HR+/HER2- locally advanced or MBC treated with palbociclib, results will also be presented for the following subgroups:

- *Patients younger than 50 years*
- *Patients aged 50-70 years*
- *Patients older than 70 years*
- *Patients with visceral disease (defined as metastases in the organs, e.g., lung, liver)*
- *Patients without visceral disease (defined as metastases in the organs, e.g., lung, liver)*

5 ENDPOINTS AND VARIABLES

The primary endpoints of the study are:

- *Progression-Free Survival (PFS) of patients receiving palbociclib in combination with aromatase inhibitor (AI)*
- *Time on Treatment (ToT) of patients receiving palbociclib in combination with AI*

The secondary endpoints are:

- *PFS of patients receiving palbociclib in combination with Fulvestrant*
- *ToT with palbociclib in combination with Fulvestrant*
- *Overall Survival (OS) in patients receiving palbociclib in combination with AI*
- *Overall Survival (OS) in patients receiving palbociclib in combination with Fulvestrant*
- *First subsequent post-palbociclib treatment upon progression*

- *Results in terms of disease-specific descriptive statistics describing the patients who have received Palbociclib:*
  - *Type, number and location of metastases (visceral vs. non-visceral)*
  - *Surgery*
  - *Type and number of adjuvant treatment(s)*
  - *De novo (primary MBC)*
  - *Recurrent MBC*
  - *Median time from initial breast cancer diagnosis (incidence date) to relapse (only relevant for recurrent MBC)*

5.1 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 (ICD10 code: DC50)	Exposure/Inclusion criteria	DBCG register	-
Treatment with palbociclib	Exposure/Inclusion criteria	DBCG register	RE201, RE201A
Date of birth	Baseline characteristic	DBCG register	Based on M1
Date of breast cancer diagnosis	Outcome	DBCG register	-
Occurrence of metastases	Characteristics	DBCG register	RE220-RE227
Type of metastases	Characteristics	DBCG register	RE220-RE227
Number of metastases sites	Characteristics	DBCG register	RE220-RE227
Location of metastases	Characteristics	DBCG register	RE10-18 + 80-81, 117-119, 219-222
Surgery	Characteristics	DBCG register	RE19
De Novo (primary MBC)	Characteristics	DBCG register	Calculated
Breast cancer disease duration – median time from initial breast cancer diagnosis (incidence date) to relapse	Estimated outcome	Estimated via DBCG register registrations	Based on variables listed in this table
Date of relapse	Outcome	DBCG register	RE1-RE3
Date for treatment initiation with palbociclib	Outcome	DBCG register	RE203-RE205

Date for treatment stop with palbociclib	Outcome	DBCG register	RE206-RE208
Time on Treatment (ToT) with Palbociclib	Estimated outcome	Estimated via DBCG register registrations	Based on variables listed in this table
Reasons to discontinuation with palbociclib	Outcome	DBCG register	RE209, RE209A
Progression Free Survival (PFS)	Estimated outcome	Estimated via DBCG register registrations	Based on variables listed in this table
Post-palbociclib treatment (first subsequent treatment post-palbociclib)	Outcome	DBCG register	RE24, RE24A, RE33, RE33A, RE42, RE42A, RE69, RE69A
Death date	Outcome	DBCG register/Danish Cause of Death Register	-
Overall Survival (OS)	Estimated outcome	Estimated via DBCG register registrations	Based on variables listed in this table

6 HANDLING OF MISSING VALUES

The study will only include patients for whom there are complete registrations in the DBCG register. Thus, decisions on handling of missing values is not relevant.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

As stated, the study is a single-arm study and will be purely descriptive and explorative. No formal hypotheses will be tested.

In general, this study will provide two types of outcomes

1. Outcomes on PFS, ToT and OS
2. Descriptive statistics on the population having palbociclib

7.1 DEFINITIONS

Incidence date	The date of the initial breast cancer diagnosis
Index date	The date of relapse or stage IV disease
Progression Free Survical (PFS)	The time from the date of relapse or stage IV disease (index date) to progression or death, whichever occurs first. Patients will be censored 31 December 2020. Progression of disease is based on scans and blood testing results.
Overall Survival (OS)	The time from index date to death og any cause.
Time on Treatment (ToT)	The date of palbociclib treatment start to date of treatment stop with palbociclib. ToT is estimated on the basis of variables RE203-RE205 and RE206-RE208 in the DBCG database
Visceral disease	Defined as metastases in the organs, i.e., liver, lung, ascites, pleural effusion, and metastases in the central nervous system. Visceral disease is based on the variable *Location of metastases* (RE10-18 + 80-81, 117-119, 219-222) in the DBCG database

7.2 STATISTICAL ANALYSES

In the PFS, ToT and OS, Kaplan-Meier survival distribution functions will be estimated. Hence, if possible median PFS, ToT and OS as well as interquartile ranges (IQR) will be estimated. Unadjusted Kaplan Meier curves will be presented to illustrate time-to-event (PFS, ToT or OS).
For OS, OS-rates (%) at 6, 12 and 24-months (landmarks) will be estimated.

For the descriptive statistics, numbers and percentages will be provided and presented in tables, including cross tabulations (see section 8 for presentation of tables shells).

For

- 'all patients' vs. 'patients younger than 50 years'
- 'all patients' vs. 'patients aged 50-70 years'
- 'all patients' vs. 'patients older than 70 years'

statistical test (e.g. χ^2-test) for differences in:

- 'types of metastaces' (visceral, non-visceral or both)
- 'surgery' (yes or no)

will be performed.

All data analysis will be executed using statistical software such as SAS or Rstudio.

8 LIST OF TABLES AND TABLE SHELLS

This section presents an overview of the table shells.

Table 2. Descriptive statistics

Population	Subgroup	Outcome	Result
All included patients	-	Number of patients	N (100%)
		Age	Median, mean and st. deviation
All included patients	Patients younger than 50 years	Number of patients	N (%)
	Patients aged 50-70 years	Number of patients	N (%)
	Patients older than 70 years	Number of patients	N (%)
All included patients	Patients with visceral disease	Number of patients	N (%)
		Age	Median, mean and st. deviation
	Patients without visceral disease	Number of patients	N (%)
		Age	Median, mean and st. deviation
All included patients	Primary MBC	Number of patients	N (%)
		Age	Median, mean and st. deviation
	Recurrent MBC	Number of patients	N (%)
		Age	Median, mean and st. deviation

Table 3. Disease-specific descriptive statistics.

Population	Subgroup	Outcome	Result
All included patients	-	Type of metastases	Visceral: N (%) Non-visceral: N (%) Both: N (%)
		Number of metastases	0: N (%) 1: N (%) 2: N (%) >2: N (%)
		Location of metastases	Skin: N (%) Bone: N (%) Lung: N (%) Liver: N (%) CNS: N (%) Other: N (%)
		Surgery	Yes: N (%) No: N (%)
		Adjuvant treatment*	Type 1: Median number of treatments of type 1: Type 2: Median number of treatments of type 2:
All included patients	Patients younger than 50 years	Type of metastases	Visceral: N (%) Non-visceral: N (%) Both: N (%)
		Number of metastases	0: N (%) 1: N (%) 2: N (%) >2: N (%)
		Location of metastases	Skin: N (%) Bone: N (%) Lung: N (%) Liver: N (%) CNS: N (%) Other: N (%)
		Surgery	Yes: N (%) No: N (%)
		Adjuvant treatment*	Type 1: Median number of treatments of type 1: Type 2: Median number of treatments of type 2:

	Patients aged 50-70 years	Type of metastases	Visceral: N (%) Non-visceral: N (%) Both: N (%)
		Number of metastases	0: N (%) 1: N (%) 2: N (%) >2: N (%)
		Location of metastases	Skin: N (%) Bone: N (%) Lung: N (%) Liver: N (%) CNS: N (%) Other: N (%)
		Surgery	Yes: N (%) No: N (%)
		Adjuvant treatment*	Type 1: Median number of treatments of type 1: Type 2: Median number of treatments of type 2:
	Patients older than 70 years	Type of metastases	Visceral: N (%) Non-visceral: N (%) Both: N (%)
		Number of metastases	0: N (%) 1: N (%) 2: N (%) >2: N (%)
		Location of metastases	Skin: N (%) Bone: N (%) Lung: N (%) Liver: N (%) CNS: N (%) Other: N (%)
		Surgery	Yes: N (%) No: N (%)
		Adjuvant treatment*	Type 1: Median number of treatments of type 1: Type 2: Median number of treatments of type 2:

All included patients	Visceral metastases	Type of MBC	Primary MBC: N (%) Recurrent MBC: N (%)
		Number of metastases	0: N (%) 1: N (%) 2: N (%) >2: N (%)
		Location of metastases	Skin: N (%) Bone: N (%) Lung: N (%) Liver: N (%) CNS: N (%) Other: N (%)
		Surgery	Yes: N (%) No: N (%)
		Adjuvant treatment*	Type 1: Median number of treatments of type 1: Type 2: Median number of treatments of type 2:
	Non-visceral metastases	Type of MBC	Primary MBC: N (%) Recurrent MBC: N (%)
		Number of metastases	0: N (%) 1: N (%) 2: N (%) >2: N (%)
		Location of metastases	Skin: N (%) Bone: N (%) Lung: N (%) Liver: N (%) CNS: N (%) Other: N (%)
		Surgery	Yes: N (%) No: N (%)
		Adjuvant treatment*	Type 1: Median number of treatments of type 1: Type 2: Median number of treatments of type 2:
		Time from initial breast cancer diagnosis (incidence date) to relapse	Median time

* The result may be more than 2 types of adjuvant treatment.

Table 4. Progression Free Survival (PFS)*

Endpoint	Population	Subgroup	Outcome	Result
Primary	Included patients treated with palbociclib in combination with AI	-	PFS	Median and IQR
Primary	Included patients treated with palbociclib in combination with AI	Patients younger than 50 years	PFS	Median and IQR
		Patients aged 50-70 years	PFS	Median and IQR
		Patients older than 70 years	PFS	Median and IQR
Primary	Included patients treated with palbociclib in combination with AI	Patients with visceral disease	PFS	Median and IQR
		Patients without visceral disease	PFS	Median and IQR
Secondary	Included patients treated with palbociclib in combination with Fulvestrant	-	PFS	Median and IQR
Secondary	Included patients treated with palbociclib in combination with Fulvestrant	Patients younger than 50 years	PFS	Median and IQR
		Patients aged 50-70 years	PFS	Median and IQR
		Patients older than 70 years	PFS	Median and IQR
Secondary	Included patients treated with palbociclib in combination with Fulvestrant	Patients with visceral disease	PFS	Median and IQR
		Patients without visceral disease	PFS	Median and IQR

Table note: * Following definition of PFS in section 7.1.

Table 5. Time on Treatment (ToT)*

Endpoint	Population	Subgroup	Outcome	Result
Primary	Included patients treated with palbociclib in combination with AI	-	ToT	Median and IQR
Primary	Included patients treated with palbociclib in combination with AI	Patients younger than 50 years	ToT	Median and IQR
		Patients aged 50-70 years	ToT	Median and IQR
		Patients older than 70 years	ToT	Median and IQR
Primary	Included patients treated with palbociclib in combination with AI	Patients with visceral disease	ToT	Median and IQR
		Patients without visceral disease	ToT	Median and IQR
Secondary	Included patients treated with palbociclib in combination with Fulvestrant	-	ToT	Median and IQR
Secondary	Included patients treated with palbociclib in combination with Fulvestrant	Patients younger than 50 years	ToT	Median and IQR
		Patients aged 50-70 years	ToT	Median and IQR
		Patients older than 70 years	ToT	Median and IQR
Secondary	Included patients treated with palbociclib in combination with Fulvestrant	Patients with visceral disease	ToT	Median and IQR
		Patients without visceral disease	ToT	Median and IQR

Table note: * Following definition of ToT in section 7.1.

Table 6. Overall Survival (OS)*

Endpoint	Population	Subgroup	Outcome	Result
Secondary	Included patients treated with palbociclib in combination with AI	-	OS	Median and IQR OS-rates (%) at 6, 12 and 24-months
Secondary	Included patients treated with palbociclib in combination with AI	Patients younger than 50 years	OS	Median and IQR OS-rates (%) at 6, 12 and 24-months
		Patients aged 50-70 years	OS	Median and IQR OS-rates (%) at 6, 12 and 24-months
		Patients older than 70 years	OS	Median and IQR OS-rates (%) at 6, 12 and 24-months
Secondary	Included patients treated with palbociclib in combination with AI	Patients with visceral disease	OS	Median and IQR OS-rates (%) at 6, 12 and 24-months
		Patients without visceral disease	OS	Median and IQR OS-rates (%) at 6, 12 and 24-months
Secondary	Included patients treated with palbociclib in combination with Fulvestrant	-	OS	Median and IQR OS-rates (%) at 6, 12 and 24-months
Secondary	Included patients treated with palbociclib in combination with Fulvestrant	Patients younger than 50 years	OS	Median and IQR OS-rates (%) at 6, 12 and 24-months
		Patients aged 50-70 years	OS	Median and IQR OS-rates (%) at 6, 12 and 24-months
		Patients older than 70 years	OS	Median and IQR OS-rates (%) at 6, 12 and 24-months
Secondary	Included patients treated with palbociclib in combination with Fulvestrant	Patients with visceral disease	OS	Median and IQR OS-rates (%) at 6, 12 and 24-months
		Patients without visceral disease	OS	Median and IQR OS-rates (%) at 6, 12 and 24-months

Table note: * Following definition of OS in section 7.1.

For PFS, ToT and OS (Table 4-6), unadjusted Kaplan Meier curves will be presented.

Table 7. First subsequent post-palbociclib treatment upon progression

Endpoint	Population	Subgroup	Outcome	Result
Secondary	All included patients treated	-	Treatment*	Type 1: Number of patients treated wtih type 1: Type 2: Number of patients treated wtih type 2:
Secondary	All included patients treated	Patients younger than 50 years	Treatment*	Type 1: Number of patients treated wtih type 1: Type 2: Number of patients treated wtih type 2:
		Patients aged 50-70 years	Treatment*	Type 1: Number of patients treated wtih type 1: Type 2: Number of patients treated wtih type 2:

		Patients older than 70 years	Treatment*	Type 1: Number of patients treated wtih type 1: Type 2: Number of patients treated wtih type 2:
Secondary	All included patients treated	Patients with visceral disease	Treatment*	Type 1: Number of patients treated wtih type 1: Type 2: Number of patients treated wtih type 2:
		Patients without visceral disease	Treatment*	Type 1: Number of patients treated wtih type 1: Type 2: Number of patients treated wtih type 2:

Table note: * The result may be more than 2 types of treatment. “No subsequent treatment” is also possible.

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