Non-Interventional Study

A5481188

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

Statistical Analysis Plan

(SAP)

Version: 1.0

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Date: 1-Mar-2024

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AI	Aromatase Inhibitor
CCI	Charlson Comorbidity Index
CDK4	Cyclin Dependent Kinase 4
CDK6	Cyclin Dependent Kinase 6
CI	Confidence interval
DBCG	Danish Breast Cancer Group
DC50	ICD-10 code for patients with breast cancer
EC	European Commission
EMA	European Medicines Agency
HR	Hormone receptor; hazard ratio
HR+	Hormone receptor positive, including estrogen receptor positive (ER+)
HER2	Human epidermal growth factor receptor 2
HER2-	HER2 negative
LOT	Line of Treatment
mBC	Metastatic breast cancer
NIS	Non-Interventional Study
OS	Overall survival
PFS	Progression free survival
RCT	randomized controlled trials
RW	Real-World
RWE	Real-World Evidence

2. RATIONALE AND BACKGROUND

Strict inclusion and exclusion criteria in clinical trials restricts inclusion of elderly patients as well as patients with certain comorbidities. With this there is an unmet need. The impact of comorbidities on palbociclib effectiveness has recently been studied in a number of real-world observational studies from the US.

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 (3), the present study therefore aims to investigate the use and effectiveness of palbociclib in all HR+/HER2- mBC patients in Denmark, as well as in subgroups of elderly patients and those with comorbidities. The study data will be based on the DBCG clinical database as the previous study by Garly et al. (3).

3. STUDY OBJECTIVES AND HYPOTHESES

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

3.1. Primary objectives *(all patients)*

- *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*

3.2. 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) (4) is used as a data source for comorbidity and comorbidity burden – comorbidities at the start of palbociclib treatment):*
  - *PFS and OS in the full data set of mBC patients receiving palbociclib + AI as first-line treatment split into Charlson Comorbidity Index (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 data set 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.*

4. RESEARCH METHODS

4.1. Study design

The study is designed as a secondary data collection non-interventional study (NIS). Retrospective data will be collected from an existing registry - the Danish Breast Cancer Group (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.

4.2. Study population

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 (EC) 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 31 December 2023 in terms of the estimation of PFS and OS will be made. The study will only include patients treated with palbociclib+AI as first-line treatment.

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. *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 data: Data of relapse/stage IV disease/progression leading to initiation of palbociclib+AI*

Exclusion Criteria

There are no exclusion criteria for this study.

4.2.1. Subgroups

Besides presenting results for all mBC patients treated with palbociclib in combination with AI patients as first-line treatment results for different subgroups split by age and comorbidities as well as disease-specific characteristics will also be presented.

These subgroups of HR+/ HER2 negative mBC patients are:

- *Patients below 65 years of age*
- *Patients 65-74 years of age*
- *Patients 75+ years of age*
- *Patients split by comorbidity severity score (CCI; 0, 1, 2, and 3 or higher (3+))*
- *Patients split by number of comorbidities (0, 1, 2+)*
- *Patients split in types of comorbidities (Cardiac disease, Vascular disease, Metabolic disease, Psychiatric disease, Blood and lymphatic system)*
- *Patients with or without visceral disease*
- *Bone only patients*
- *Endocrine resistant, endocrine sensitive or de novo patients*

4.3. Variables

The main variables included in the study are the following:

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*	*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*
Endocrine resistant (recurrent pts with advanced disease within 12 months of completing adjuvant endocrine therapy or during adjuvant endocrine therapy)	*Baseline*	*DBCG registry*	*Calculated*
Endocrine sensitive (recurrent pts with advanced disease after 12 months of completing adjuvant endocrine therapy, recurrent pts who received no adjuvant endocrine therapy)	*Baseline*	*DBCG registry*	*Calculated*
De Novo (primary mBC – newly metastatic)	*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 data used to define CCI in DBCG registry*	*Not applicable*
Number of comorbidities (calculated at start of palbociclib treatment)	*Baseline*	*National Patient Registry 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) (at start of palbociclib treatment)	*Baseline*	*National Patient Registry data used to define CCI in DBCG registry*	*Not applicable*
Death date	*Baseline charac.*	*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*

4.4. Data sources

This study will be based on the DBCG clinical database and the National Patient Registry (LPR) with respect to the comorbidities. Data from the DBCG clinical database and the National Patient Registry will be combined by the personal identification codes (CPR)) that every Danish citizen has.

4.5. Sample size and power calculations

The study is purely descriptive and explorative. No formal hypotheses will be tested in the study. Calculation of sample size is therefore not applicable.

The expected and estimated total study population with the *focus on all Danish mBC patients (endocrine sensitive, endocrine resistant or de novo) that have received palbociclib in combination with AI as first-line therapy. 580 patients will be included from 1 January 2017 to 31 December 2021.*

Subgroup analyses of this patient population will be made based on age and comorbidity.

4.6. Missing Data

The study will only include patients for whom there are complete registrations in the DBCG register. However, should missing data occur, no imputation will be made, and all statistics will be calculated with non-missing values. Counts and percentages of missing values will be presented in the tables where applicable.

4.7. Statistical methodology and analyses

The study is a single-arm study and will be purely descriptive and explorative. No formal hypotheses will be tested.

This study will provide two types of outcomes:

1. Outcomes on PFS and OS of patients treated with palbociclib+AI as first-line (population and subpopulations (Age and Comorbidity) (Appendix A, Table 3 and 4))
2. Descriptive statistics on the population/subpopulations treated with palbociclib+AI (Appendix A, Table 1 and 2)

4.7.1. Index date and follow-up

Definitions of the incidence data and the index date of the first-line treated palbociclib + AI patients shown together with the definition of the treatment outcomes (PFS and OS), as well as definition of visceral disease can be found in the table below.

Incidence date	The date of the initial breast cancer diagnosis.
Index date	The date of relapse or stage IV disease.
Progression Free Survival (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 2021. Progression is based on radiological, clinical, and biochemical examination from the treating departments.
Overall Survival (OS)	The time from index date to death at any cause.
Visceral disease	Defined as metastases in the organs, e.g., lung, liver. Visceral disease is based on the variable Location of metastases (RE10-18 + 80-81, 117-119, 219-222) in the DBCG database.

For the PFS and OS outcomes for the full palbociclib first-line population (primary analyses) as well as each subpopulation (secondary analyses), as presented below, Kaplan-Meier survival distribution functions with 95% confidence intervals will be estimated. Hence, if possible median PFS and OS as well as interquartile ranges (IQR) will be estimated. Unadjusted Kaplan Meier curves will be presented to illustrate time-to-event (PFS or OS).

For the descriptive statistics, numbers and percentages will be provided and presented in tables, including cross tabulations (see section 6 for presentation of tables shells).

All data analysis will be executed using the statistical software R-studio.

4.7.2. Primary analyses

As primary analyses (descriptive) of PFS and OS will be estimated for all Danish mBC patients receiving palbociclib as first-line treatment in combination with AI. PFS will be estimated for all patients until either a physician-assessed disease progression occurred, death or until data cut-off by 31 December 2023. OS will be estimated for all patients with a censoring of data by 31 December 2023 as the last day of data capture in the study.

4.7.3. Secondary analyses

Similar to the primary analyses, univariate analyses of PFS and OS for subgroups (age and comorbidity) of all mBC patients having palbociclib + AI as first-line treatment will be made and with the same definitions and timelines for their estimation.

These subgroups of HR+/ HER2 negative mBC patients are:

Age-groups

- Patients below 65 years of age
- Patients 65-74 years of age
- Patients 75+ years of age

Statistical test of differences in baseline characteristics as well as the PFS and the OS outcomes between each of these age subgroups compared to all first-line palbociclib patients the Shapiro-Wilk test of normality and the Wilcoxon rank sum will be applied.

Comorbidities as measured by Charlson Comorbidity Index (CCI)

- Patients split by comorbidity severity score (CCI; 0, 1, 2, and 3 or higher (3+))
- Patients split by number of comorbidities (0, 1, 2+)
- Patients split in types of comorbidities (Cardiac disease, Vascular disease, Metabolic disease, Psychiatric disease, Blood and lymphatic system)

Statistical test of differences in baseline characteristics as well as the PFS and the OS outcomes between each of these comorbidity groups will be performed, e.g. using the chi-square test).

And finally various disease-specific characteristics of the mBC patients having palbociclib + AI as first-line treatment.

- Patients with or without visceral disease
- Bone only patients
- Endocrine resistant, endocrine sensitive or de novo patients

Similar statistical test of difference as for the two other subgroups will be made for the disease-specific characteristics.

4.7.4. Post-hoc analyses

Not applicable.

5. REFERENCES

1. Tripathy D, Blum JL, Karuturi MS, McCune S, Kurian S, Moezi MM, Anderson DM, Wang Y, Montelongo MZ, Zhang Z, Gauthier E, Rocque E; Impact of comorbidities on real-world patient-reported outcomes of patients with hormone receptor positive human epidermal growth factor 2 negative (HR+/HER2–) advanced breast cancer enrolled in the POLARIS trial. ESMO 2023 373P. https://oncologypro.esmo.org/meeting-resources/esmo-congress/impact-of-comorbidities-on-real-world-rw-clinical-outcomes-of-patients-pts-with-hormone-receptor-positive-human-epidermal-growth-factor-2-negat.

2. Brufsky A, Liu X, Li B, McRoy L, Chen C, Makari D, Layman R, Rugo H; Real-world effectiveness of palbociclib plus aromatase inhibitors (AI) in metastatic breast cancer patients with cardiovascular diseases. SABCS 2023 PO1-17-05. 2023 SABCS Abstract Report-12-1-23 (atgproductions.net).

3. Garly R, Berg T, Jensen MB, Knoop A, Volmer L, Glavicic V, Khan H, Poulsen PB, Olsen J, Kümler I. A Retrospective, Non-Interventional Study of Breast Cancer Patients Diagnosed With ER+/HER2 Negative, Locally Advanced or Metastatic Breast Cancer Treated with Palbociclib in Denmark. Acta Oncologica 2023;1-8. https://doi:10.1080/0284186X.2023.2194030.

4. DMCG.dk Benchmarking Consortium. Rapport om canceroverlevelse i Danmark 1995-2012. https://www.dmcg.dk/siteassets/arsberetninger-og-udgivelser/benchmarking-consortium/a_forsider___metoder_10_11_2014.pdf

6. APPENDICES

6.1. Appendix A: Table shells

This section presents an overview of the table shells.

Table 1. Descriptive statistics. All mBC patients having palbociclib as first-line treatment in combination with AI

Population	Subgroup	Outcome	Result
All included patients (first-line treated with palbociclib+AI)	All patients	Number of patients (all)	N (100%)
		Age	Median, mean and standard deviation
All included patients (first-line treated with palbociclib+AI)	Patients below 65 years of age	Number of patients	N (%)
	Patients 65-74 years of age	Number of patients	N (%)
	Patients 75+ years of age	Number of patients	N (%)
All included patients (first-line treated with palbociclib+AI)	Comorbidities 1 - patients split into severity of comorbidities as measured by CCI (0, 1, 2, 3 or higher (3+))	Number of patients with a CCI score of 0, 1, 2, 3 or higher (3+), respectively	N (%) in each group
		Age	Median, mean and standard deviation
	Comorbidities 2 - patients split into number of comorbidities (0, 1, 2+)	Number of patients with 0, 1, or 2+ comorbidities, respectively	N (%) in each group
		Age	Median, mean and standard deviation
	Comorbidities 3 - patients split into type of comorbidities (Cardiac disease, Vascular disease, Metabolic disease, Psychiatric disease, Blood and lymphatic system)	Number of patients with specific type of comorbidity	N (%) in each group
		Age	Median, mean and standard deviation
All included patients (first-line treated with palbociclib+AI)	*Patients with visceral disease*	*Number of patients*	*N (%)*
		Age	Median, mean and standard deviation
	Patients without visceral disease	*Number of patients*	*N (%)*
		Age	Median, mean and standard deviation
All included patients (first-line treated with palbociclib+AI)	*Patients bone only*	*Number of patients*	*N (%)*
		Age	Median, mean and standard deviation
	Endocrine resistant patients	*Number of patients*	*N (%)*

		Age	Median, mean and standard deviation
	Endocrine sensitive patients	*Number of patients*	*N (%)*
		Age	Median, mean and standard deviation
	De Novo patients (primary mBC)	*Number of patients*	*N (%)*
		Age	Median, mean and standard deviation

Table 2. Disease-specific descriptive statistics. All mBC patients having palbociclib as first-line treatment in combination with AI

Population	Subgroup	Outcome	Result
All included patients (first-line treated with palbociclib+AI)	All patients	Type of metastases	Visceral: N (%) Non-visceral: N (%) Both: N (%)
		Number of metastases	0: N (%) 1: N (%) 2: N (%) >2: N (%)
		Metastatic site	Skin: N (%) Bone: N (%) Lung: N (%) Liver: N (%) CNS: N (%) Other: N (%)
All included patients (first-line treated with palbociclib+AI)	Patients below 65 years of age	Type of metastases	Visceral: N (%) Non-visceral: N (%) Both: N (%)
		Number of metastases	0: N (%) 1: N (%) 2: N (%) >2: N (%)
		Metastatic site	Skin: N (%) Bone: N (%) Lung: N (%) Liver: N (%) CNS: N (%) Other: N (%)
	Patients 65-74 years of age	Type of metastases	Visceral: N (%) Non-visceral: N (%) Both: N (%)
		Number of metastases	0: N (%) 1: N (%) 2: N (%) >2: N (%)
		Metastatic site	Skin: N (%) Bone: N (%) Lung: N (%) Liver: N (%) CNS: N (%) Other: N (%)
	Patients 75+ years of age	Type of metastases	Visceral: N (%) Non-visceral: N (%) Both: N (%)

		Number of metastases	0: N (%) 1: N (%) 2: N (%) >2: N (%)
		Metastatic site	Skin: N (%) Bone: N (%) Lung: N (%) Liver: N (%) CNS: N (%) Other: N (%)
All included patients (first-line treated with palbociclib+AI)	Comorbidities 1 - patients split into severity of comorbidities as measured by CCI (0, 1, 2, 3 or higher (3+))	Type of metastases	Visceral: N (%) Non-visceral: N (%) Both: N (%)
		Number of metastases	0: N (%) 1: N (%) 2: N (%) >2: N (%)
		Metastatic site	Skin: N (%) Bone: N (%) Lung: N (%) Liver: N (%) CNS: N (%) Other: N (%)
	Comorbidities 2 - patients split into number of comorbidities (0, 1, 2+)	Type of metastases	Visceral: N (%) Non-visceral: N (%) Both: N (%)
		Number of metastases	0: N (%) 1: N (%) 2: N (%) >2: N (%)
		Metastatic site	Skin: N (%) Bone: N (%) Lung: N (%) Liver: N (%) CNS: N (%) Other: N (%)
	Comorbidities 3 - patients split into type of comorbidities (Cardiac disease, Vascular disease, Metabolic disease, Psychiatric disease, Blood and lymphatic system)	Type of metastases	Visceral: N (%) Non-visceral: N (%) Both: N (%)
		Number of metastases	0: N (%) 1: N (%) 2: N (%) >2: N (%)
		Metastatic site	Skin: N (%) Bone: N (%) Lung: N (%) Liver: N (%) CNS: N (%) Other: N (%)

Table 3. Progression Free Survival (PFS)*. All mBC patients having palbociclib as first-line treatment in combination with AI

Endpoint	Population	Subgroup	Outcome	Result
Primary	All included patients (first-line treated with palbociclib+AI)	All patients	PFS	Median and IQR
Secondary	All included patients (first-line treated with palbociclib+AI)	Patients below 65 years of age	PFS	Median and IQR
		Patients 65-74 years of age	PFS	Median and IQR
		Patients aged 75+ years of age	PFS	Median and IQR
Secondary	All included patients (first-line treated with palbociclib+AI)	Comorbidities 1 - patients split into severity of comorbidities as measured by CCI (0, 1, 2, 3 or higher (3+))	PFS	Median and IQR
		Comorbidities 2 - patients split into number of comorbidities (0, 1, 2+)	PFS	Median and IQR
		Comorbidities 3 - patients split into type of comorbidities (Cardiac disease, Vascular disease, Metabolic disease, Psychiatric disease, Blood and lymphatic system)	PFS	Median and IQR
Secondary	All included patients (first-line treated with palbociclib+AI)	Patients with visceral disease	PFS	Median and IQR
		Patients without visceral disease	PFS	Median and IQR
Secondary	All included patients (first-line treated with palbociclib+AI)	Patients bone-only	PFS	Median and IQR
		Patients not bone-only	PFS	Median and IQR
Secondary	All included patients (first-line treated with palbociclib+AI)	Endocrine resistant patients	PFS	Median and IQR
		Endocrine sensitive patients	PFS	Median and IQR
		De novo patients	PFS	Median and IQR

Table note: * Following definition of PFS in section 4.7.1.

Table 4. Overall Survival (OS)*. All mBC patients having palbociclib as first-line treatment in combination with AI

Endpoint	Population	Subgroup	Outcome	Result
Primary	All included patients (first-line treated with palbociclib+AI)	All patients	OS	Median and IQR
Secondary	All included patients (first-line treated with palbociclib+AI)	Patients below 65 years of age	OS	Median and IQR
		Patients 65-74 years of age	OS	Median and IQR
		Patients aged 75+ years of age	OS	Median and IQR
Secondary	All included patients (first-line treated with palbociclib+AI)	Comorbidities 1 - patients split into severity of comorbidities as measured by CCI (0, 1, 2, 3 or higher (3+))	OS	Median and IQR
		Comorbidities 2 - patients split into number of comorbidities (0, 1, 2+)	OS	Median and IQR
		Comorbidities 3 - patients split into type of comorbidities (Cardiac disease, Vascular disease, Metabolic disease, Psychiatric disease, Blood and lymphatic system)	OS	Median and IQR
Secondary	All included patients (first-line treated with palbociclib+AI)	Patients with visceral disease	OS	Median and IQR
		Patients without visceral disease	OS	Median and IQR
Secondary	All included patients (first-line treated with palbociclib+AI)	Patients bone-only	OS	Median and IQR
		Patients not bone-only	OS	Median and IQR
Secondary	All included patients (first-line treated with palbociclib+AI)	Endocrine resistant patients	OS	Median and IQR
		Endocrine sensitive patients	OS	Median and IQR
		De novo patients	OS	Median and IQR

Table note: * Following definition of OS in section 4.7.1.

For PFS and OS (Table 3 and 4), unadjusted Kaplan Meier curves will be presented.

6.2. Appendix B: Additional information

None.