

# Palbociclib dose reductions and the effect on clinical outcomes in patients with advanced breast cancer

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## ARTICLE INFO

### Article history:

Received 1 November 2021

Received in revised form

16 November 2021

Accepted 17 November 2021

Available online 17 November 2021

### Keywords:

Palbociclib

Breast cancer

Clinical outcomes

Dose reductions

Older patients

## ABSTRACT

**Background:** This study aimed to provide insights into the real-world use of palbociclib, dose reductions, and drug effectiveness in (older) patients with advanced breast cancer (BC).

**Patients and methods:** Patients with advanced BC treated with palbociclib from 2017 to 2020 were included. The Kaplan-Meier method was used to calculate time to next treatment (TTNT) and overall survival (OS) for patients with or without dose reductions. These clinical outcomes were also compared in subgroup analyses for older patients ( $\geq 70$  years) and younger patients ( $< 70$  years) and for patients discontinuing palbociclib early ( $< 4$  administrations).

**Results:** A total of 598 patients with advanced BC were included, with a median age of 64 years. Palbociclib dose reductions occurred in 33% of all patients. Early discontinuation of palbociclib without dose reductions occurred in 23% of the patients. Patients who required a palbociclib dose reduction were older (median age 67 years vs. 63 years). Patients with dose reductions had a significantly higher TTNT of 16.9 vs. 11.4 months ( $p < 0.001$ ) and median OS of 29.7 vs. 21.9 months ( $p = 0.003$ ) compared to patients without dose reductions. The TTNT in older patients was significantly longer (16.9 vs. 11.6 months,  $p = 0.013$ ) than younger patients, but OS was similar (20.7 vs. 26.7 months,  $p = 0.051$ ).

**Conclusion:** Palbociclib dose reductions occurred in real-world practice similarly to the PALOMA-3 trial. Patients with dose reductions had no poorer outcomes compared to patients not requiring a dose reduction. Older patients treated with palbociclib had more frequent dose reductions, but this did not appear to affect OS.

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## 1. Introduction

The overall survival (OS) of patients with advanced breast

cancer (BC) has improved over the last decades [1]. Since 1970, progression-free survival (PFS) and OS have improved due to the introduction of several new systemic therapies. These therapies include chemotherapy, anti-HER2 directed therapy, aromatase inhibitors, and most recently, the cyclin-dependent kinases 4 and 6 (CDK-4/6) inhibitors [1]. Hormone-positive BC is the most common type of BC and comprises about 80% of all breast cancers [2]. The

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### Abbreviations

BC	breast cancer
CDK-4/6 inhibitors	cyclin-dependent kinases 4 and 6 inhibitors
DBC	Diagnose Behandel Combinatie (Dutch) information system on in-hospital activities
DICA	Dutch Institute for Clinical Auditing
EMA	European Medicines Agency
OS	overall survival
PFS	progression-free survival
RWD	real-world data
SmPC	Summary of Product Characteristics
TTNT	time to next treatment

CDK-4/6 inhibitors are registered for use in hormone-positive, HER2-negative advanced BC patients [3].

The European Medicines Agency (EMA) approved the first CDK-4/6 inhibitor, palbociclib, in 2016. The PALOMA-3 trial showed a significant benefit in median PFS of palbociclib in combination with fulvestrant (9.5 months) after prior endocrine therapy compared to placebo (4.6 months,  $p < 0.0001$ ) [4–6]. The most recent follow-up of the PALOMA-3 trial in 2021 showed an OS benefit of 6.8 months ( $p = 0.0221$ ) [7]. Palbociclib is also registered as first-line treatment combined with aromatase inhibitors (letrozole, anastrozole) [4]. The combination of palbociclib/letrozole was compared to letrozole monotherapy in the PALOMA-2 trial and showed a median PFS of 24.8 months compared to 14.5 months for letrozole monotherapy ( $p < 0.001$ ) [8].

The use of palbociclib in older BC patients has been investigated in a pooled analysis of the PALOMA trials [9]. This study demonstrated a PFS benefit in patients treated with palbociclib regardless of age. The safety profile was comparable, but myelosuppression was more frequent in patients  $\geq 75$  years [9]. A review on the use of targeted therapies described the evidence gap in toxicities and efficacy of these therapies in older patients [10]. Real-world data (RWD) includes information of older patients which are under-represented in phase III clinical trials and can be helpful in daily clinical practice to treat older patients effectively.

The advised initial dose for palbociclib is 125 mg once daily [4]. Reduced doses (100 mg and 75 mg) are recommended in the summary of product characteristics (SmPC) to manage adverse events (AE's) of CTCAE grade 3 or higher [11]. The dose is first reduced to 100 mg/day and then to 75 mg/day, and the complete blood count should be monitored [11]. Primarily, palbociclib toxicity is characterized by gastrointestinal side effects and hematologic toxicity such as neutropenia [12]. Phase III clinical trials did not specifically investigate the efficacy of reduced palbociclib dosages, even though these reductions occur in clinical practice [13]. Older patients could be prone to toxicity because of their comorbidities, comedication use, and higher frailty. This could result in a higher need for dose reductions. A previous review on palbociclib included several real-world studies investigating palbociclib dose modifications, but the real-world effectiveness of such modifications was not described [14].

Clinical outcomes can differ between the real-world population and clinical trial patients due to differences in patient-, tumor-, and treatment characteristics [13]. Furthermore, medication use (treatment patterns, dosing schedules, therapy compliance) can differ from the recommended posology in daily clinical practice. The Dutch Institute for Clinical Auditing (DICA) Medicines project was set up in 2018 to generate RWD from existing data sources to

improve the effective use of medicines in daily clinical practice [15]. RWD provide insights into the use of new medicines and are important as these data provide valuable information on treatment aspects not investigated in clinical trials.

The effect of palbociclib dose reductions on clinical outcomes in advanced BC patients remains unknown. In addition, a previous study showed that older patients treated with palbociclib experience higher toxicity rates [16]. Therefore, this study aimed to provide insights into the real-world use of palbociclib, dose reductions, and drug effectiveness in (older) patients with BC.

## 2. Patients and methods

### 2.1. Data sources

Data were retrieved from the DICA medicines program. In this program, existing data sources are re-used and combined to provide insights into the real-world (systemic) therapy of Dutch patients with cancer and their outcomes. The DICA medicines data consist of administrative and financial files on systemic therapies from the hospital pharmacy, linked to clinical patient- and tumor data registered in DICA quality registries. Furthermore, a third data source, the Dutch *DBC information system* [17], is linked to the other data sources focusing on in-hospital activity information and information on diagnosis and treatment. Survival data are the fourth data source, derived from the Vektis database, a national database that comprises the date of deaths of Dutch citizens [18]. The database contains data starting from 1-1-2017. This study used administrative and financial data, providing detailed information on palbociclib treatment (prescription dates and doses) linked to the *DBC information system*.

### 2.2. Patients

The patients included in this study were treated in clinical practice in one of eight general hospitals participating in the DICA medicines program. Seventy-four hospitals in the Netherlands are treating patients with BC. All patients treated with palbociclib from 01 to 01-2017 to 31-12-2020 were selected. Patients with hormone receptor-positive, HER-2 negative BC without any contraindications are treated with palbociclib in clinical practice. Contraindications for palbociclib include hypersensitivity to palbociclib or any of the excipients or the use of St. John's Wort [11]. Grade 3 and 4 neutropenia and concomitant use of CYP3A4-inhibitors or -inducers are relative contraindications, and use of palbociclib in patients with other comorbidities (i.e., interstitial lung disease, infections, hepatic and renal impairments) should be cautious [11]. Palbociclib treatment was combined with fulvestrant (after failing endocrine therapy) or aromatase inhibitors (first-line therapy).

### 2.3. Data analysis

The patient population was divided into two groups based on prescribed dose reductions. Dose reduction was defined as reducing the dose of palbociclib from 125 mg to 100 mg or 75 mg ( $\geq 20\%$  dose reduction). Separate analyses were performed on patients with an initial treatment dose lower than 125 mg. Furthermore, subanalyses were performed on older patients, defined as patients  $\geq 70$  years. We chose 70 years as an acceptable cut-off point since this is a common cut-off point in geriatric oncology. The International Society of Geriatric Oncology guideline for geriatric assessment in older patients with BC uses 70 years as the cut-off point for geriatric research [19]. Another subanalysis included patients who discontinued early. Early discontinuation was defined as discontinuation before the fourth administration of palbociclib

without dose reduction. Response evaluation often occurs after three treatment courses in daily clinical practice. Differences in OS over the years (2017–2020) and between the two palbociclib treatment combinations (fulvestrant or aromatase inhibitors) were also analyzed.

Descriptive statistics were used to analyze the available baseline patient characteristics from the DICA medicines program database. These included age at diagnosis, gender, and the Charlson comorbidity index (CCI) [20]. The CCI was calculated based on DBC information in the year palbociclib was first prescribed and includes age and a list of different comorbidities such as diabetes, liver disease, malignancies, AIDS, kidney diseases, heart failure, and COPD. The different groups were compared with Pearson's chi-squared test. Comparisons were considered statistically significant for two-sided  $P$ -values  $<0.05$ .

To determine differences in clinical outcomes between patients with or without dose reductions and between older and younger patients, we used time-to-next treatment (TTNT) and OS. The TTNT and OS were estimated using the Kaplan-Meier method with corresponding two-sided 95% confidence intervals (CI). TTNT and survival time were calculated from the date of the first palbociclib prescription to the date of next treatment or date of death, respectively. Patients who did not receive a subsequent treatment or who were alive at the dataset cut-off date were censored on the last date of palbociclib (TTNT) or the last date of any medicine administration (OS), respectively. At this date, the patient was considered alive. The median follow-up time was calculated with the reverse Kaplan-Meier method [21].

Data handling and statistical analyses were performed using the R software system for statistical computing (version 4.1.0.; packages lubridate, tidyr, ggplot2, tableone, ggthemes, survival, survminer) [22].

### 3. Results

#### 3.1. Real-world use of palbociclib

Between 2017 and 2020, a total of 598 BC patients were treated with palbociclib. In 2017, 103 patients were treated with palbociclib; in 2018, 176 patients; in 2019, 175 patients; and in 2020, 144 patients. The median follow-up time for OS of all patients treated with palbociclib was 12.9 months. The median age of the study population was 64 years, ranging from 25 to 92 years. Of all patients, 422 (71%) received palbociclib combined with fulvestrant

and 173 (29%) combined with aromatase inhibitors. The baseline characteristics of the patient population can be found in Table 1. Most patients ( $N = 565$ , 94.5%) started palbociclib treatment with the advised dose of 125 mg. Thirty patients (5%) received a starting dose of 100 mg and 3 patients (0.5%) received a starting dose of 75 mg. In patients who started palbociclib with an initial dose of 100 or 75 mg ( $N = 33$ ), 64% were older than 70 years. Fig. 1 shows the dosing patterns of all patients treated with palbociclib over time. Patients who received a dose reduction did not have a dose increase over time.

#### 3.2. Dose reductions or early discontinuation

Dose reductions occurred in 33% ( $N = 195$ ) of the patients. In 59% ( $N = 116$ ) of the patients with dose reductions, a reduction was required in the first three months after initiation of therapy (Fig. 2). The median time to dose reduction was 69 days (IQR 36–152). Patients who required a dose reduction were older compared to patients without dose reduction, median age of 67 years vs. 63 years ( $p = 0.004$ ), respectively (supplement 1). The CCI did not differ significantly ( $p = 0.526$ ) between the groups (Table 2). Patients with dose reductions had a median TTNT of 16.9 months (95% CI: 15.3–24.1) compared to 11.4 months (95% CI: 9.7–13.9) in patients without dose reductions ( $p < 0.001$ ) (Fig. 3a). The median OS of patients with dose reductions was significantly higher compared to patients without dose reductions (29.7 months (95% CI: 26.7–34.8) vs. 21.9 months (95% CI: 20.3–24.9),  $p = 0.003$ ) (Fig. 3b).

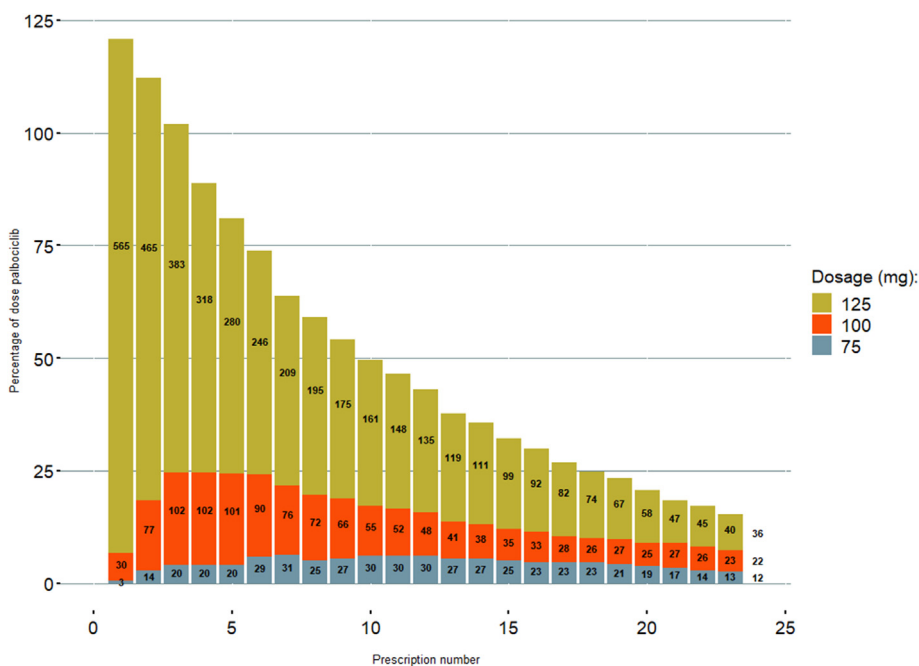
In 136 (23%) of the patients who initially started palbociclib treatment, treatment was discontinued within four courses, without a dose reduction. Another 22 (4%) patients discontinued within four courses and had a dose reduction before discontinuation. There were no significant differences in age ( $p = 0.348$ ) and CCI ( $p = 0.082$ ) between patients who received  $>3$  administrations of palbociclib and patients who discontinued early without dose reduction (supplement 2). The median OS of patients early discontinuing palbociclib was 7.6 months (95% CI: 5.1–11.3) and 28.6 months (95% CI: 25.6–32.2) in patients treated with  $>3$  administrations of palbociclib ( $p < 0.001$ ) (supplement 3).

Median OS of patients without a dose reduction, but who received  $>3$  palbociclib administrations ( $N = 267$ ), was 26.7 months (95% CI: 23.5–33.2) compared to 29.7 months (95% CI: 26.7–34.8) in patients with a dose reduction ( $p = 0.75$ ) (supplement 4).

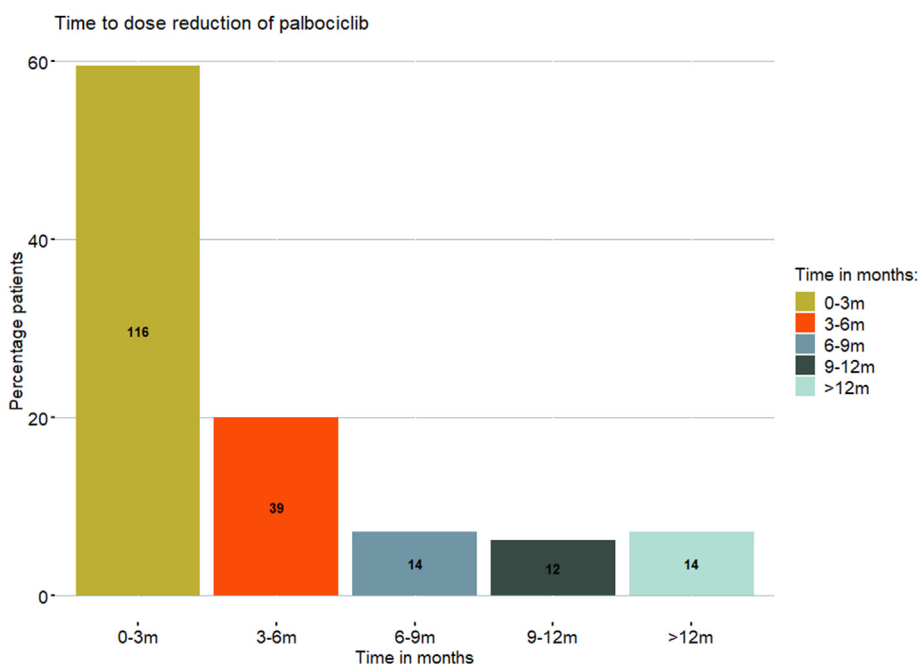
**Table 1**  
Patient- and tumor characteristics of patients treated with palbociclib from 2017 to 2020.

	Categories	Patients
N (total)		598
Year of initiation therapy; n (%)	2017	103 (17.2)
	2018	176 (29.4)
	2019	175 (29.3)
	2020	144 (24.1)
Gender; n (%)	Male	9 (1.5)
	Female	589 (98.5)
Age in years (median [range])		64 [25, 92]
Age in years (category); n (%)	$<70$	409 (68.4)
	$\geq 70$	189 (31.6)
		35 (5.9)
Charlson comorbidity index; n (%)	$\leq 2$	310 (51.8)
	$\geq 3$ and $< 6$	195 (32.6)
	$\geq 6$	58 (9.7)
	Unknown	173 (28.9)
Treatment combination; n (%)	Combination with aromatase inhibitor	422 (70.6)
	Combination with fulvestrant	3 (0.5)
	Unknown	

N = absolute number, The Charlson comorbidity index is measured in the year of first palbociclib administration.



**Fig. 1.** The dosing patterns of palbociclib over the number of prescriptions. \*The numbers in the bars represent the absolute number of patients that were treated with the specific dose of palbociclib per prescription number.



**Fig. 2.** The time to palbociclib dose reduction from start of therapy. \*The numbers in the bars represent the absolute number of patients in which a dose reduction occurred.

**3.3. Use of palbociclib in older patients**

Thirty-two percent of the patients (N = 189) treated with palbociclib were ≥70 years, with a median age of 75 years (IQR: 70–92). In older patients, 39% required a dose reduction, compared to 30% (p = 0.041) in the younger population of <70 years, with a median age of 58 years (IQR: 25–69) (supplement 5). The median treatment duration of palbociclib was not statistically significantly different between patients <70 and ≥ 70 years (7.5 months (IQR: 3.8–14.4) vs. 7.0 months (IQR: 2.9–15.6), p = 0.41) (supplement 6).

A significant difference (p = 0.013) in TTNT was observed between older (16.9 months) and younger patients (11.6 months) (Fig. 4a). The median OS of older patients was not significantly different from younger patients (20.7 vs. 26.7 months, p = 0.051) (Fig. 4b).

**3.4. Differences between study years**

The patient- and tumor characteristics of patients treated with palbociclib in 2017 were similar to those treated in the years after (supplement 7). The median OS did not differ between 2017 and

**Table 2**  
Patient- and tumor characteristics of patients with and without a palbociclib dose reduction.

	Categories	No dose reduction	Dose reduction	P-value
N (total)		403	195	
Year of initiation therapy; n (%)	2017	77 (19.1)	26 (13.3)	0.022
	2018	110 (27.3)	66 (33.8)	
	2019	109 (27.0)	66 (33.8)	
	2020	107 (26.6)	37 (19.0)	
Gender; n (%)	Male	8 (2.0)	1 (0.5)	0.304
	Female	395 (98.0)	194 (99.5)	
Age in years (median [range])		63 [25–88]	67 [36–92]	0.004
Age in years (category); n (%)	<70	287 (71.2)	122 (62.6)	0.041
	≥70	116 (28.8)	73 (37.4)	
Charlson comorbidity index; n (%)	≤2	23 (5.7)	12 (6.2)	0.526
	≥3 and < 6	216 (53.6)	94 (48.2)	
	≥6	129 (32.0)	66 (33.8)	
	Unknown	35 (8.7)	23 (11.8)	
Treatment combination; n (%)	Combination with aromatase inhibitor	115 (28.5)	58 (29.7)	0.422
	Combination with fulvestrant	287 (71.2)	135 (69.2)	
	Unknown	1 (0.2)	2 (1.0)	

N = absolute number, The Charlson comorbidity index is measured in the year of first palbociclib administration.

2020 (supplement 8). Moreover, there was no difference in median OS between patients treated with palbociclib combined with fulvestrant or aromatase inhibitors (supplement 9).

#### 4. Discussion

This study shows that 33% of the BC patients treated with palbociclib required a dose reduction. Most dose reductions were performed within three months (59%) after start of palbociclib and occurred more often in patients ≥70 years. The TTNT was significantly longer in older patients compared to patients <70 years. The OS of older patients did not differ significantly from younger patients despite the more frequent dose reductions.

##### 4.1. Previous research

Previous research on palbociclib dose reductions by Kish et al. in the USA showed a dose reduction rate of 20%, and 12% of the patients started with a lower dose of 100 or 75 mg [14]. The median time to dose reduction was 39 days. In this current study, 33% of the patients required a dose reduction, 5.5% started with a lower dose, and the median time to dose reduction was 69 days. This previous study did not assess clinical benefit because of limited follow-up time. Our study has a longer median follow-up time, possibly resulting in a higher number of dose reductions. In addition, our results are comparable to the number of dose reductions in the registration trials. In the PALOMA-3 trial (palbociclib/fulvestrant), with a median follow-up time of 44.8 months, 34% of the patients had a dose reduction [6]. In the PALOMA-2 trial (palbociclib/letrozole), 36% of the patients had a dose reduction.

Another real-world study, investigating the effectiveness of palbociclib showed there was no efficacy-effectiveness gap in BC patients treated with palbociclib [13]. This study showed fewer dose reductions (22%) but was based on 46 patients treated between 2016 and 2018. We found more dose reductions, in a larger population, with a higher OS for patients with dose reductions. Data on the moment of progressive disease are needed to estimate PFS. TTNT was used as a surrogate for PFS since subsequent treatment is presumably initiated due to progressive disease. This resulted in patients with dose reductions having a longer TTNT than patients without dose reductions. Response to palbociclib

treatment is evaluated three to six months after starting therapy. This could explain the decline in the numbers at risk in the group of patients without dose reduction in the Kaplan-Meier estimate of TTNT (Fig. 3a). Presumably, these patients progressed, palbociclib treatment was discontinued, and subsequent treatment was started, while patients with dose reductions did not progress but experienced toxicity that required lowering the treatment dose. This might have introduced a bias to the analyses, which also affected OS analyses. One-third (33.7%) of the patients without a dose reduction discontinued treatment within three palbociclib courses. We presume that these patients discontinued treatment mainly because of progressive disease. In the PALOMA-3 trial [6], only 4% of the patients discontinued treatment due to an adverse effect, and in the PALOMA-2 trial, the main reason for treatment discontinuation was progressive disease (39%) [8]. Similar OS between patients with or without dose reductions was found when we excluded these early discontinuation patients from the analysis ( $p = 0.75$ ) (supplement 4). This confirms our hypothesis that the outcomes of patients without a dose reduction are strongly affected by this group of patients early discontinuing therapy. Our results suggest that dose reductions do not affect survival outcomes.

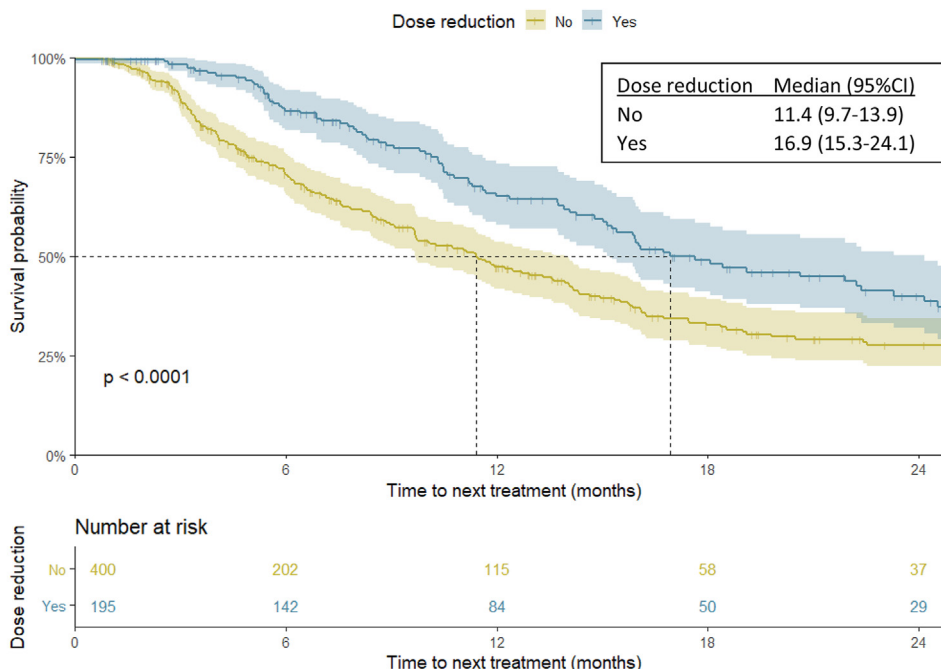
##### 4.2. Older patients

Although we observed more dose reductions in older patients, their clinical outcomes were similar to those of younger patients. Older patients are more prone to toxicity which could explain higher number of dose reductions. The treatment duration of palbociclib in our study was similar between older and younger patients. This contrasts with the pooled analysis of the PALOMA trials, which showed longer treatment duration for older patients (>65 years).

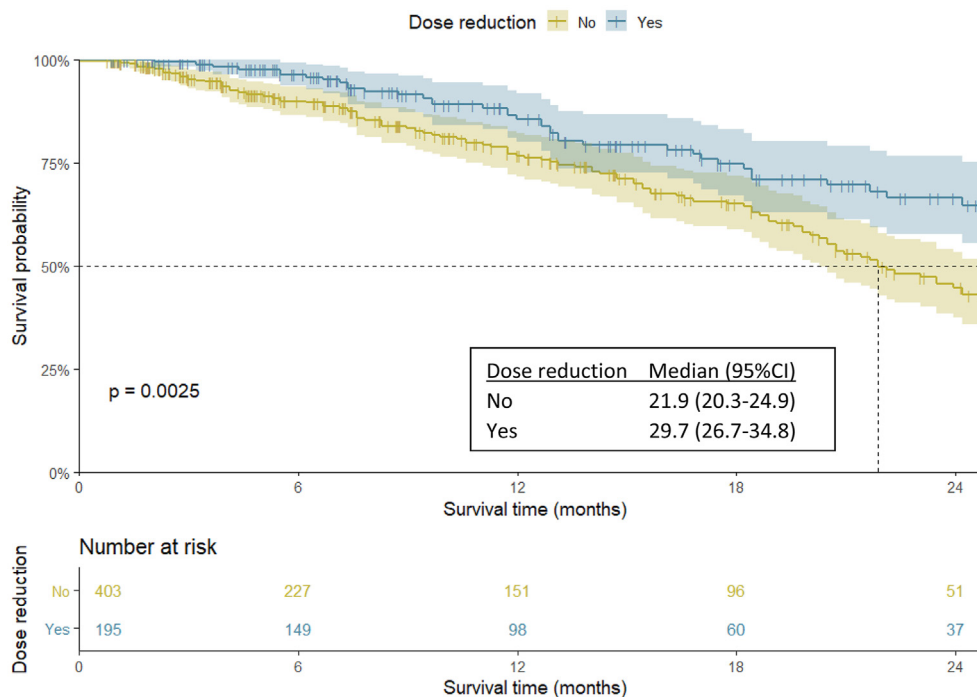
##### 4.3. Real-world data monitors uptake of new medicines

The DICA medicines program collects RWD which can help monitor the uptake of new medicines in clinical practice. Clinical questions on palbociclib dose reductions and treatment in older patients were the basis of this study. Monitoring palbociclib real-world usage showed that the OS of real-world patients is lower than in the PALOMA-3 trial, presumably due to more comorbidities





a) Time to next treatment of BC patients treated with palbociclib with and without a dose reduction.



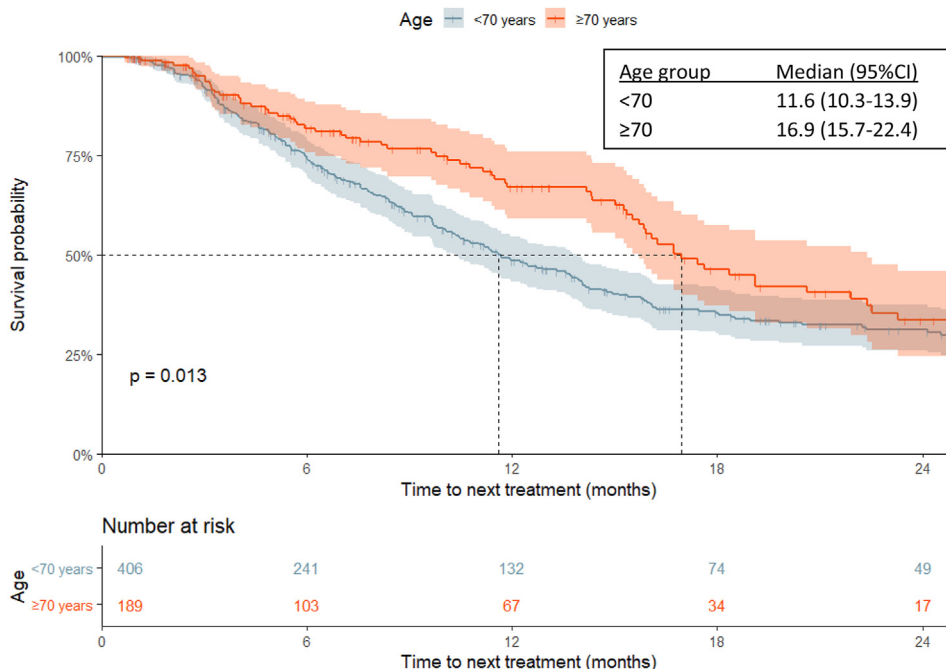
b) Overall survival of BC patients treated with palbociclib with and without a dose reduction.

**Fig. 3.** Kaplan-Meier estimate of time to next treatment (a) and overall survival (b) in patients treated with palbociclib; with or without dose reduction.

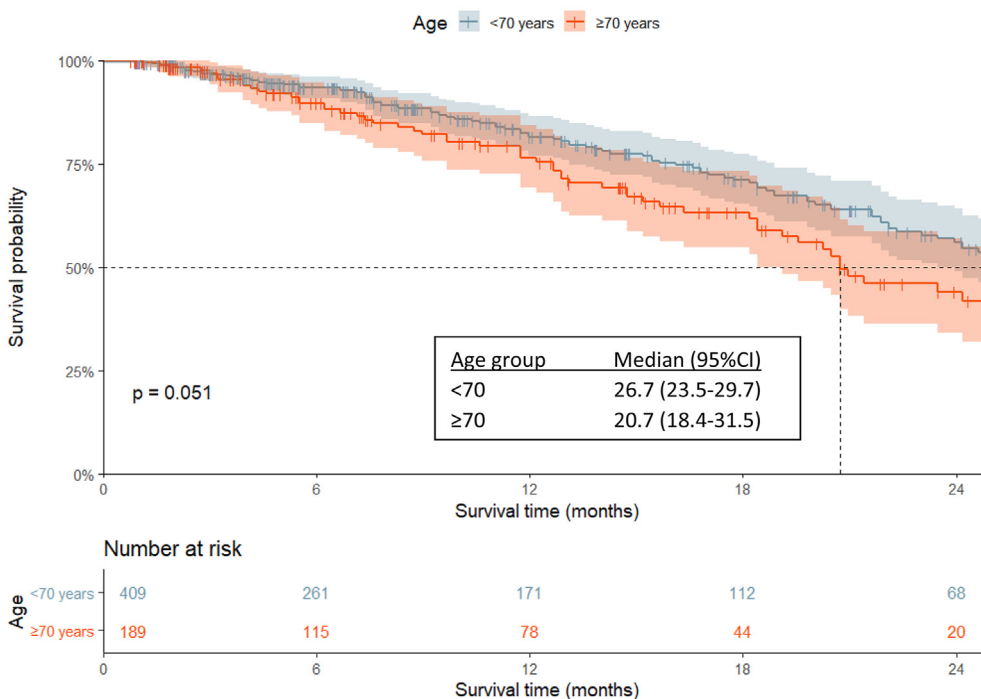
of real-world patients. Palbociclib became available in the Netherlands in 2017, but we did not observe significant differences in patient characteristics or outcomes since its introduction (supplement 7 and 8).

#### 4.4. Limitations and strengths

The use of RWD has limitations. First, RWD includes no pre-defined progression evaluation, no standardized toxicity



a) Time to next treatment of older (≥70 years) and younger (<70 years) BC patients treated with palbociclib.



b) Overall survival of older (≥70 years) and younger (<70 years) BC patients treated with palbociclib.

Fig. 4. Kaplan-Meier estimate of (a) time to next treatment and (b) overall survival in older (≥70 years) BC patients treated with palbociclib versus younger patients (<70 years).

registration, and the history of the disease and treatment information can be incomplete. Secondly, additional information on receptor status, menopausal status, specific stage of disease, previous treatments, adverse events, response status, and the reason for dose reduction or palbociclib discontinuation were missing and

would have improved the data. If the reason for dose reduction or discontinuation had been available, we could further limit the bias by distinguishing patients discontinuing early because of early unacceptable toxicity from patients with early progressive disease. In addition, frailty information, which is important in the

comparison between older and younger patients, was missing. This information could have explained which selected group of older patients was treated. The CCI did not differ between the old and young patients, suggesting the older patients treated were relatively fit patients. A third limitation is that data from 2020 were incomplete in the databases, which led to lower numbers of patients. Finally, as mentioned before, comparing patients requiring a dose reduction to those who did not could be biased since patients who progress early cannot get to dose reductions. Their shorter prognosis could lower the estimated survival in the group without dose reductions. We, therefore, cannot conclude that dose reductions lead to improved survival. However, these results indicate that dose reductions can be performed safely, without affecting TTNT and OS.

#### 4.5. Future research

High-quality data on medicine use can improve the effective use of medicines and eventually lead to changes in practice guidelines. We suggest that this study has to be repeated when more hospitals participate in the DICA medicines program, eventually leading to population-based data on palbociclib usage.

Since only 33 (6%) patients initially started with a lower dose of palbociclib in our study, we could not compare patients starting with a lower-dose palbociclib to patients who needed a dose reduction. Starting lower-dose palbociclib could benefit patients by preventing adverse events. This would hardly affect dose intensity as most dose reductions were performed within three months. Our study demonstrated that dose reductions did not affect the effectiveness of palbociclib treatment, but this should be investigated prospectively. Older or frail patients can experience more adverse events. Starting a lower dose of palbociclib can be even more critical for this group to reduce the probability of adverse events and facilitate extended treatment on palbociclib.

## 5. Conclusion

Palbociclib dose reductions occurred in real-world practice similarly to the phase-III clinical trials (PALOMA-2 and -3). Patients with dose reductions had no poorer outcomes compared to patients not requiring a dose reduction. Older patients treated with palbociclib had more frequent dose reductions, but this did not appear to affect OS.

### Ethics approval and consent to participate

In compliance with Dutch regulations, the DICA medicines program is not considered subject to the Medical Research Involving Human Subjects Act.

### Consent for publication

Data from the DICA medicines program were used, containing real-world data of patients treated in clinical practice. Patients are offered opt-out in the hospital.

### Availability of data and material

The data that support the findings of this study are available from DICA but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of DICA and the participating hospitals.

## Funding

Dutch health insurer VGZ has funded the DICA medicines program from which the data were retrieved.

## Authors' contributions

RI contributed to the concept and design of this study, performed the statistical analyses and interpreted the data, and wrote the manuscript with the help of the co-authors. JvB contributed substantially with the statistical analyses and interpretation of the data and revised the manuscript carefully. MW substantively revised the work. MvD made substantial contributions to the conception and design of the research and revised the manuscript. SvDF substantively revised the work. AR made substantial contributions to the conception and design of the research and revised the manuscript. PG made substantial contributions to the conception and design of the research and revised the manuscript, MP substantively revised the work, AdB substantively revised the work, EB made substantial contributions to the conception and design of the research and revised the manuscript, and DH made substantial contributions to the conception and design of the research and revised the manuscript.

All authors read and approved the final manuscript before submission.

## Declaration of competing interest

The authors declare that they have no competing interests.

## Acknowledgement

The DICA medicines program was financially supported by Dutch health insurance company, VGZ Coöperatie VGZ U.A. Their support was used for the initial costs of developing the dashboards.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2021.11.013>.

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