



## Real-world palbociclib effectiveness in patients with metastatic breast cancer: Focus on neutropenia-related treatment modification strategies and clinical outcomes

Mariska Q.N. Hackert<sup>a</sup>, Cornelia F. van Uden-Kraan<sup>a</sup>, Mariette J. Agterof<sup>b</sup>, Annette W.G. van der Velden<sup>c</sup>, Birgit E.P.J. Vriens<sup>d</sup>, Johan J.B. Janssen<sup>e</sup>, Maud Geenen<sup>f</sup>, Annemieke van der Padt-Pruijsten<sup>g</sup>, Ewoudt M.W. van de Garde<sup>h,i,\*</sup>

<sup>a</sup> Santeon hospital group, Utrecht, The Netherlands

<sup>b</sup> Department of Internal Medicine, St. Antonius Hospital, Utrecht/Nieuwegein, The Netherlands

<sup>c</sup> Department of Internal Medicine, Martini Hospital, Groningen, The Netherlands

<sup>d</sup> Department of Medical Oncology, Catharina Hospital, Eindhoven, The Netherlands

<sup>e</sup> Department of Medical Oncology, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands

<sup>f</sup> Department of Medical Oncology, OLVG, Amsterdam, The Netherlands

<sup>g</sup> Department of Internal Medicine, Maastad Hospital, Rotterdam, The Netherlands

<sup>h</sup> Department of Clinical Pharmacy, St. Antonius Hospital, Utrecht/Nieuwegein, The Netherlands

<sup>i</sup> Division of Pharmacoepidemiology and Clinical Pharmacology, Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

### ARTICLE INFO

#### Keywords:

Palbociclib  
Real-world  
Clinical practice  
Treatment modification strategies  
Efficacy-effectiveness gap  
Metastatic breast cancer

### ABSTRACT

**Introduction:** In addition to clinical trials, real-world data is needed to verify the effectiveness of the CDK 4/6 inhibitor palbociclib. The primary aim was to examine real-world variation in treatment modification strategies for neutropenia and its relation to progression-free survival (PFS). The secondary aim was to assess if there is a gap between real-world and clinical trial outcomes.

**Materials and Methods:** In this multicenter, retrospective observational cohort study 229 patients were analyzed who started palbociclib and fulvestrant as second- or later-line therapy for HR-positive, HER2-negative metastatic breast cancer in the Santeon hospital group in the Netherlands between September 2016 and December 2019. Data were manually retrieved from patients' electronic medical records. PFS was examined using the Kaplan-Meier method to compare neutropenia-related treatment modification strategies within the first three months after neutropenia grade 3 – 4 occurred, as well as patients' eligibility to have participated in the PALOMA-3 clinical trial or not.

**Results:** Even though treatment modification strategies differed from those in PALOMA-3 (dose interruptions: 26 vs 54%, cycle delays: 54 vs 36%, and dose reductions: 39 vs 34%), these did not influence PFS. Patients who were PALOMA-3 ineligible experienced a shorter median PFS than those who were eligible (10.2 vs. 14.1 months; HR 1.52; 95% CI 1.12 – 2.07). An overall longer median PFS was found compared to PALOMA-3 (11.6 vs. 9.5 months; HR 0.70; 95% CI 0.54 – 0.90).

**Conclusion:** This study suggests no impact of neutropenia-related treatment modifications on PFS and confirms inferior outcomes outside clinical trial eligibility.

### 1. Introduction

Oncology patients are often informed on their drug's effectiveness

using the results of clinical trials. Clinical trials provide fundamental evidence on a drug's performance by matching study groups and controlling for key sources of bias. However, due to trial selection and

**Abbreviations:** CDK 4/6, cyclin-dependent kinases 4 and 6; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PFS, progression-free survival.

\* Corresponding author at: Department of Clinical Pharmacy, St. Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands.

E-mail address: [e.van.de.garde@antoniusziekenhuis.nl](mailto:e.van.de.garde@antoniusziekenhuis.nl) (E.M.W. van de Garde).

<https://doi.org/10.1016/j.ctarc.2023.100691>

Available online 14 February 2023

2468-2942/© 2023 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

restrictive enrolment criteria, this evidence, needed for regulatory approval, may not hold for the population at large that will be using the drug. Additional real-world evidence is needed to completely judge the drug's impact [3,13,14].

Since November 2016, palbociclib, a first-in-class cyclin-dependent kinases 4 and 6 (CDK 4/6) inhibitor, is available in the Netherlands for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer [6]. In the phase-2 and -3 clinical trials (PALOMA-2 and -3) [5,7], the combination of palbociclib with either letrozole or fulvestrant significantly improved progression-free survival (PFS) for women compared to those using letrozole or fulvestrant alone. Neutropenia was found to be the most common toxicity [7,19]. Regardless of these episodes of neutropenia, patients reported consistently good quality of life and overall health throughout the first six months of treatment [16].

Generally, data from real-world experiences have confirmed palbociclib's effectiveness and tolerability in various unselected populations [10]. Frequencies of toxicity seem comparable, however, there seems to be a difference between the clinical trials and real-world setting in how episodes of neutropenia are managed [2,8,22]. For instance, a study in the Netherlands showed that more cycle delays, less dose reductions, and less dose interruptions occurred in clinical practice compared with PALOMA-3 [2]. From a pharmacokinetic perspective the exposure to palbociclib over time differs between aforementioned treatment modification strategies and, although evidence is inconclusive [8,12,15,22], it is not inconceivable that this might impact effectiveness.

The primary aim of the present study was to examine real-world variation in treatment modification strategies for neutropenia and its relation to PFS in patients who started using palbociclib and fulvestrant in second- or later-line therapy of HR-positive, HER2-negative metastatic breast cancer. The secondary aim was to assess if there is an efficacy-effectiveness gap between the real-world and clinical trial setting.

## 2. Materials and methods

Six large teaching hospitals of the Santeon hospital group, the Netherlands, participated in this study: the St. Antonius Hospital (Utrecht / Nieuwegein), Martini Hospital (Groningen), Canisius-Wilhelmina Hospital (Nijmegen), Catharina Hospital (Eindhoven), OLVG (Amsterdam) and Maasstad Hospital (Rotterdam). Five hospitals provided a list of patients that received at least one dose of palbociclib for the treatment of HR-positive, HER2-negative metastatic breast cancer between September 2016 and December 2019 through the Santeon Farmadatabase [18], and one hospital provided a patient list from their own data. In total, 320 female patients aged 18 years and older were identified.

For this study, 229 out of 320 patients who used palbociclib (125 mg) and fulvestrant (500 mg) in second- or later-line therapy were selected: 75 patients with other medication combinations (mainly with letrozole as first-line therapy), 6 patients with a different or unknown start dose, 9 patients with unknown start or end of treatment dates, and 1 patient in the neoadjuvant setting were excluded. For every patient, start date of treatment, reason for ending treatment and related dates were manually retrieved from their electronic medical records, together with all records of reported side effects, toxicities and treatment modifications, and their timing relative to treatment start date. Side effects and toxicities were graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0). Data were collected between 30 November 2020 and 22 March 2022 and stored in a de-identified fashion in REDCap [11], hosted at the St. Antonius Hospital (Utrecht / Nieuwegein).

The analyses were conducted using IBM SPSS Statistics 26. Descriptive statistics were used to report data on patient characteristics, and the frequency and timing of all side effects and toxicities, and the frequency of all treatment modification strategies. In line with PALOMA-

3 [5], the primary outcome was PFS, defined as the time from the start of treatment to either disease progression or death, whichever occurred first. Patients with end of treatment due to side effects, toxicities or other reasons (e.g., an operation) were censored. PFS was examined in R using the Kaplan-Meier method combined with the log-rank test.

For the primary aim, survival curves were compared based on patients' exposure to treatment modification strategies in response to neutropenia. First, for each patient it was checked whether neutropenia grade 3 – 4 occurred in the first half year after the start of treatment. Then, it was examined which treatment modification strategies were used for these patients in the first three months after neutropenia occurred. Patients were grouped into frequent scenarios, including those who experienced: no treatment modification ('no'), at least one dose interruption and / or cycle delay ('interruption'), and at least one dose reduction and one dose interruption and / or cycle delay ('reduction and interruption'). PFS was based on the date neutropenia grade 3 – 4 occurred instead of the treatment start date.

In line with the secondary aim, the real-world PFS was compared with the clinical trial PFS using external reference data [5]. Hazard ratios were assessed by first digitizing the clinical trial Kaplan-Meier curve with the R-package 'digitize'. The extracted date points for survival probability were used for reconstructing the Kaplan-Meier curve with the algorithm as described by Guyot et al. [9]. The coordinates of the Kaplan-Meier curve from the published graph were read with the R-coding script by Guyot et al. [9], together with the information on numbers at risk and total number of events, to reconstruct the Kaplan-Meier data. With this reconstructed individual patient data, Kaplan-Meier curves and Cox hazard ratios were estimated using the R routines 'survfit' and 'coxph'. Next, real-world survival curves were compared based on patients' compliance to the PALOMA-3 inclusion criteria: an Eastern Cooperative Oncology Group (ECOG) performance status 0 – 1, and a disease measurable by RECIST (version 1.1) or bone disease only. Disease relapse or progression had to occur after prior endocrine therapy (with an aromatase inhibitor for postmenopausal patients or with tamoxifen for pre- or perimenopausal patients) in the advanced setting or during treatment or within 12 months of completion of the adjuvant therapy. One prior line of chemotherapy was allowed. Patients were not eligible if they had previously received any CDK inhibitor, fulvestrant, everolimus, or PI3K/mTOR pathway inhibitor; or had extensive metastatic, symptomatic, visceral spread who were at the risk of life-threatening complications in the short-term, or had uncontrolled central nervous system metastases.

## 3. Ethics

Bureau Onderzoek & Innovatie of Santeon, the Netherlands, approved this study (reference number 2020-011). Informed consent was waived due to the retrospective nature of the study in the metastatic breast cancer setting.

## 4. Results

In this study, 229 patients were studied with a median follow-up of 34.8 months. Median age was 65 years (range 38 – 87) compared with 57 years in PALOMA-3 (range 30 – 88) (see Table 1), with 10% having an ECOG performance status  $\geq 2$ . Patients had more previous lines of endocrine treatment (45% had  $\geq 3$  lines compared with 14% in PALOMA-3), and patients more often received chemotherapy for the treatment of their metastatic breast cancer (37% vs. 33%).

Most hematological toxicities (Table 2) and non-hematological side effects (Table 3) from palbociclib occurred similarly in the real-world compared to the PALOMA-3 clinical trial. In general, real-world patients more often reported side effects, especially related to fatigue and decreased appetite. During treatment, neutropenia grade 3 – 4 was experienced by 60% of the patients, compared to 65% in PALOMA-3. Side effects and toxicities most often started during the first half year

**Table 1**  
Baseline characteristics of patients in the PALOMA-3 and real-world population.

	PALOMA-3 (N = 347)	Real-world (N = 229)	Missing
Median age, years (range)	57 (30 – 88)	65 (38 – 87)	
ECOG performance status			
0 – 1	347 (100%)	201 (90%)	5
≥ 2	0	23 (10%)	
Number of previous lines of endocrine treatment			
1	160 (46%)	17 (7%)	
2	140 (40%)	108 (47%)	
≥ 3	47 (14%)	104 (45%)	
Previous chemotherapy	113 (33%)	84 (37%)	

**Table 2**  
Hematological toxicities of patients in the PALOMA-3 and real-world population.

	PALOMA-3 (N = 345)	Real-world (N = 229)	Real-world (N = 229)	Time between start treatment and occurrence of toxicity <sup>1</sup>		
	Grade 3 – 4	Grade 3 – 4		≤ 6 months	> 6 – 12 months	> 12 months
Neutropenia	224 (65%)	137 (60%)	123 (90%)	9 (7%)	5 (4%)	
Leukopenia	147 (43%)	69 (30%)	57 (83%)	5 (7%)	7 (10%)	
Thrombocytopenia	10 (3%)	10 (4%)	6 (60%)	1 (10%)	3 (30%)	
Anemia	10 (3%)	14 (6%)	9 (64%)	1 (7%)	4 (29%)	

<sup>1</sup> Neutropenia categorized based on first event; others based on timing lowest cell counts during follow-up.

of treatment. Treatment modification strategies were mostly used to treat neutropenia. In total, 26% of the 229 patients experienced at least one dose interruption, 54% had at least one cycle delay, and 39% had at least one dose reduction during treatment, compared with respectively 54%, 36%, and 34%, in PALOMA-3. Also, 5% of the 229 patients had other treatment modification strategies (e.g. taking palbociclib every other day or for 2 weeks instead of 3, or having a 2-week break instead of 1 each treatment cycle).

In total, 24 (11%) patients were still on treatment when data collection ended; 178 (78%) and 4 (2%) patients discontinued treatment respectively due to disease progression and disease-related death. Also, 19 (8%) and 4 (2%) patients discontinued treatment respectively due to side effects or toxicities, and other reasons (e.g. an operation). The overall real-world median PFS was 11.6 months compared with 9.5 months in PALOMA-3 (HR 0.70; 95% CI 0.54 – 0.90) (see Fig. 1).

Neutropenia grade 3 or higher was experienced by 123 patients in the first half year of treatment. Grouped towards frequent scenarios, 39 patients (32%) had no medication alterations, 39 patients (32%) had an interruption and 38 patients (31%) had a reduction and interruption. Patients did not significantly differ in their median PFS according to the treatment modification strategy (see Fig. 2).

In total, 93 patients (41%) met the eligibility criteria for the PALOMA-3 clinical trial. In this study, patients would have mainly been excluded from participation in PALOMA-3 due to prior treatment with fulvestrant, everolimus and / or multiple lines of chemotherapy, and tamoxifen (for postmenopausal patients). Patients who did not meet the PALOMA-3 eligibility criteria showed a significantly shorter median PFS compared with patients that did meet the PALOMA-3 eligibility criteria (10.2 vs. 14.1 months; HR 1.52; 95% CI 1.12 – 2.07) (see Fig. 3).

**Table 3**  
Non-hematological side effects of patients in the PALOMA-3 and real-world population.

	PALOMA-3 (N = 345)	Real-world (N = 229)	Real-world (N = 229)		
	Any grade	Any grade	Time between start treatment and first occurrence of side effect		
			≤ 6 months	> 6 – 12 months	> 12 months
Infections	144 (42%)	76 (33%)	49 (65%)	11 (14%)	16 (21%)
Fatigue	135 (39%)	166 (72%)	144 (87%)	15 (9%)	7 (4%)
Decreased appetite	52 (15%)	83 (36%)	63 (76%)	11 (13%)	9 (11%)
Stomatitis	43 (12%)	Grouped together: 150 (66%)	131 (87%)	10 (7%)	9 (6%)
Nausea	112 (33%)				
vomiting	58 (17%)				
Diarrhoea	74 (21%)				
Rash	52 (15%)	31 (14%)	21 (68%)	5 (16%)	5 (16%)
Alopecia	58 (17%)	52 (23%)	37 (71%)	11 (21%)	4 (8%)
Asthenia	24 (7%)	26 (11%)	14 (54%)	9 (35%)	3 (12%)
Pyrexia	38 (11%)	32 (14%)	24 (75%)	3 (9%)	5 (16%)
Dry skin	20 (6%)	19 (8%)	12 (63%)	5 (26%)	2 (11%)
Vision blurred	20 (6%)	Grouped together: 66 (29%)	47 (71%)	10 (15%)	9 (14%)
Lacrimation increased	20 (6%)				
Dry eye	11 (3%)				
Dysgeusia	23 (7%)	49 (21%)	39 (80%)	7 (14%)	3 (5%)
Epistaxis	22 (6%)	30 (13%)	27 (90%)	1 (3%)	2 (7%)
Febrile neutropenia	3 (1%)	1 (0%)	1 (100%)		

## 5. Discussion

The primary aim of the present study was to examine real-world variation in treatment modification strategies for neutropenia and its relation to PFS in patients who started using palbociclib and fulvestrant in second- or later-line therapy of HR-positive, HER2-negative metastatic breast cancer. The secondary aim was to assess if there is an efficacy-effectiveness gap between the real-world and clinical trial setting.

Most hematological toxicities and non-hematological side effects from palbociclib occurred similarly in the real-world compared to the PALOMA-3 clinical trial. In response, treatment modification strategies varied widely in the real-world setting. Although dose reductions occurred more or less as often (39 vs 34%), patients experienced less dose interruptions (26 vs 54%), more cycle delays (54 vs 36%) and alternative treatment modification strategies (5%) than patients participating in PALOMA-3. These findings are comparable with Bui et al. [2], except for dose reductions that occurred less often in that study. More importantly, the variety in treatment modification strategies that were used in the first three months after neutropenia grade 3 – 4 occurred did not seem to affect PFS. Even though hospitals may not follow the guidelines regarding neutropenia [6], this study suggests that this does not impact the effectiveness of palbociclib and fulvestrant.

Remarkably, this study demonstrated median PFS to be longer in the real-world than in the clinical trial setting (11.6 vs 9.5 months). This difference in median PFS was even longer within patients that did meet the PALOMA-3 eligibility criteria (14.1 vs 9.5 months). As in PALOMA-3 the date of randomization was used to calculate PFS instead of the

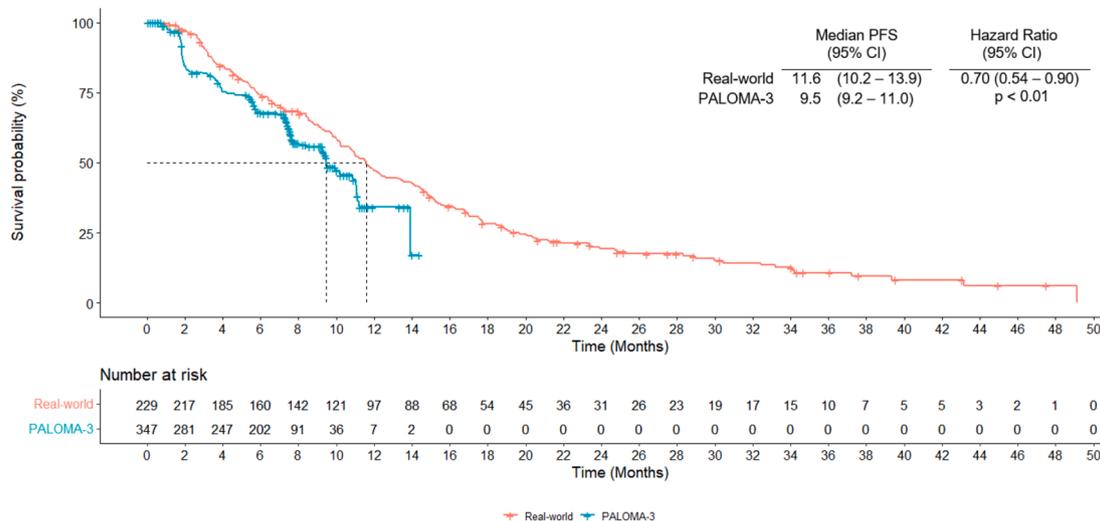


Fig. 1. Kaplan-Meier curve of PFS in the PALOMA-3 (N = 347) and real-world (N = 229) population.

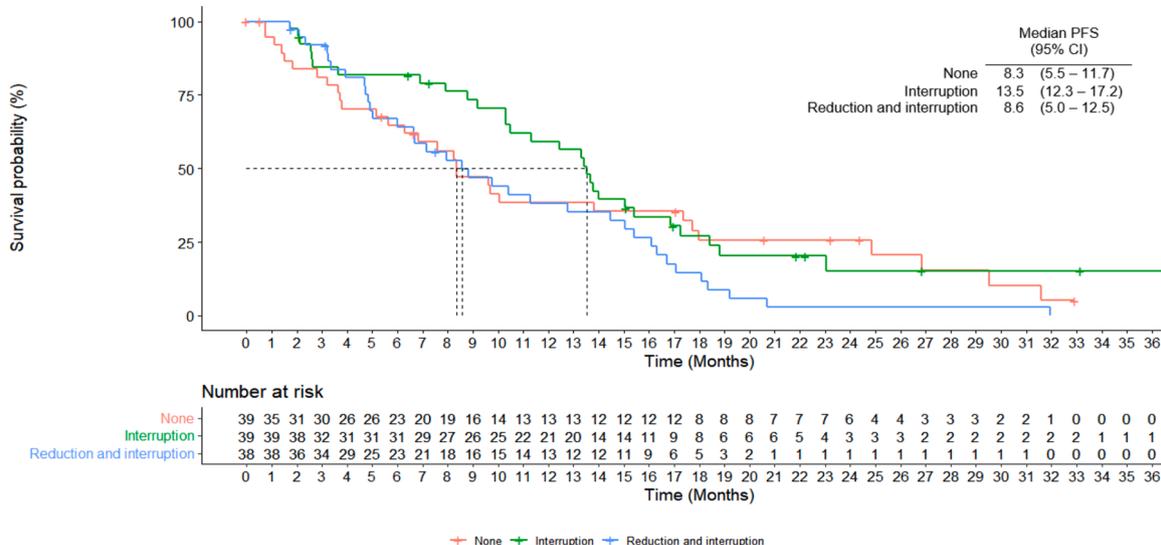


Fig. 2. Kaplan-Meier curves of PFS based on patients' exposure to treatment modification strategies in response to neutropenia (N = 116).

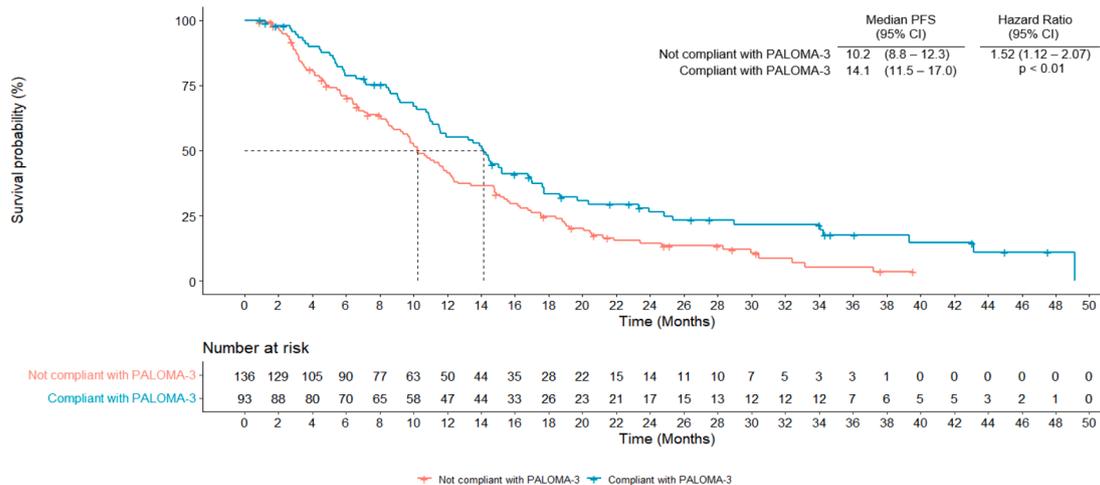


Fig. 3. Kaplan-Meier curves of PFS among patients who did and did not meet the PALOMA-3 eligibility criteria (N = 229).

treatment start date as in the present study, this may cause even an underestimated PFS in the real-world setting. The longer real-world PFS seems counterintuitive, as patients in clinical practice overall had a poorer performance status and were more heavily pre-treated. More thorough clinical and radiological assessments in the PALOMA-3 clinical trial may explain this finding. First, tumor assessment took place every eight weeks compared to less frequent assessments up to every 12 weeks in routine care [2]. Second, in PALOMA-3, disease progression was based on a uniform interpretation of computed tomography (CT) and / or magnetic resonance imaging (MRI), while in clinical practice, the oncologist's interpretation of imaging scans and / or the patient's clinical status were leading [22]. In clinical practice, physicians may have a higher threshold to stop or change therapy in response to minor imaging changes, and perhaps associated clinical deterioration. Physicians may await the results of the next tumor assessment, twelve weeks later, before concluding progression and changing therapy. This approach, however, could also lead to a possible delay in starting effective consecutive therapies and consequently a suboptimal overall survival. A logical next step to explore this further will be to compare overall survival from this cohort with the long-term follow-up data from PALOMA-3. Now, this is not possible yet because the majority of the patients in the present cohort are still alive. If future research supports our assumption that assessment bias influences real-world PFS, then we may need to rethink patient' assessment strategies to decrease the efficacy-effectiveness gap.

This study used high quality real-world data to complement clinical trial results, by thoroughly reviewing patients' medical records in a multicenter, unselected real-world cohort with a relatively long follow-up time. However, some study limitations need to be considered when interpreting the findings. The SONIA study [17] was carried out at the same time as this study. The aim of the SONIA study is to evaluate whether the sequence of an aromatase inhibitor plus CDK 4/6 in the first-line followed by fulvestrant in second-line is superior to the sequence of an aromatase inhibitor in first-line followed by fulvestrant plus CDK 4/6 in second-line. Consequently, the guidelines regarding neutropenia [6] may more often have been adopted in this study, causing less diversity in treatment modification strategies. Moreover, laboratory diagnostics, including neutropenia, may have been taken at different frequencies and time points in the treatment cycle of patients. Also, patients may have experienced treatment modifications due to other side effects in the three months period after neutropenia grade 3 – 4 occurred, that were not taken into account, effecting aforementioned findings. The manual collection of patient data from electronic medical records may have left room for human error. Disease and treatment information may have been incomplete or overlooked, as standardized registration of side effects and treatment modifications does not take place in all patients' electronic medical records. Patients self-reporting of side effects through open-ended questioning by health care providers during monthly clinic visits may have introduced unintended under-reporting of the number and type of side effects patients experience. However, this is likely less the case for (observable) side effects and laboratory diagnostics, such as neutropenia [1].

In addition to clinical trial results, data from real-world settings could offer patients an overview of what can be expected from a treatment. Therefore, an effort should be made to provide patients with personalized, up-to-date information on the outcomes of care delivery within the hospital in which they are being treated. It may help them to consider their options from a personal view (e.g. how important the drugs' possible benefits and harms may be to them) [4]. In the case of palbociclib and fulvestrant, informing patients that treatment modification strategies do not seem to impact the drugs' effectiveness may help reduce patients' anxiety for worse outcomes when faced with a dose alteration. This will result in patients being more involved in care decisions together with their health care providers (e.g. do we start or continue treatment) and a better understanding of the course of the treatment process. Even in cases of 'effective' health services, where

there is no equally good alternative as usual in shared decision-making, it can still be of value to better inform patients during the care process leading to higher patient satisfaction and compliance [20,21].

## 6. Conclusions

This study showed no impact of neutropenia-related treatment modifications on PFS and confirms inferior outcomes outside clinical trial eligibility in patients who started using palbociclib and fulvestrant in second- or later-line therapy of HR-positive, HER2-negative metastatic breast cancer.

## Funding

This work was supported by Pfizer (grant number 62,785,943) and ZonMw as part of the 'Experiment Uitkomstindicatoren Santeon'. The funders were not involved in collection, management, analysis, and interpretation of the data; writing this manuscript or the decision to submit the article for publication.

## Data availability statement

Data are available on reasonable request. The (intellectual) property rights about the generated data will reside at Santeon, Utrecht, The Netherlands.

## Declaration of Competing Interest

None declared.

## CRedit authorship contribution statement

**Mariska Q.N. Hackert:** Funding acquisition, Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Cornelia F. van Uden-Kraan:** Funding acquisition, Conceptualization, Methodology, Writing – review & editing, Supervision. **Mariette J. Agterof:** Validation, Writing – review & editing. **Annette W.G. van der Velden:** Validation, Writing – review & editing. **Birgit E.P.J. Vriens:** Validation, Writing – review & editing. **Johan J.B. Janssen:** Validation, Writing – review & editing. **Maud Geenen:** Validation, Writing – review & editing. **Annemieke van der Padt-Pruijsten:** Validation, Writing – review & editing. **Ewoudt M.W. van de Garde:** Funding acquisition, Conceptualization, Methodology, Writing – review & editing, Supervision.

## Acknowledgements

We thank Stefan Russel, Iris de Haan, Coen van Leijen and Dimitri Sprokkereef for their contribution to the data collection. We thank Marjon Verschuieren for extracting data from the survival curves in the PALOMA-3 clinical trial study publication.

## References

- [1] E. Basch, A. Lasonos, T. McDonough, A. Barz, A. Culkin, M.G. Kris, et al., Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for adverse events: results of a questionnaire-based study, *Lancet Oncol.* 7 (2006) 903–909, [https://doi.org/10.1016/S1470-2045\(06\)70910-X](https://doi.org/10.1016/S1470-2045(06)70910-X).
- [2] T.B.V. Bui, D.M.T. Burgers, M.J. Agterof, E.M.W. van de Garde, Real-world effectiveness of palbociclib versus clinical trial results in patients with advanced /metastatic breast cancer that progressed on previous endocrine therapy, *Breast Cancer: Basic Clin. Res.* 13 (2019) 1–6, <https://doi.org/10.1177/1178223418823238>.
- [3] J. Corrigan-Curay, L. Sacks, J. Woodcock, Real-world evidence and real-world data for evaluating drug safety and effectiveness, *JAMA* 320 (9) (2018) 867–868, <https://doi.org/10.1001/jama.2018.10136>.
- [4] C.M. Cramer-van der Welle, E.A. Kastelij, B.C. Plouvier, C.F. van Uden-Kraan, F. M.N.H. Schramel, H.J.M. Groen, et al., Development and evaluation of a real-world

- outcomes-based tool to support informed clinical decision making in the palliative treatment of patients with metastatic NSCLC, *Clin. Cancer Inform.* 5 (2021) 570–578, <https://doi.org/10.1200/CCI.20.00160>.
- [5] M. Cristofanilli, N.C. Turner, I. Bondarenko, J. Ro, S.A. Im, N. Masuda, et al., Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial, *Lancet Oncol.* 17 (2016) 425–439, [https://doi.org/10.1016/S1470-2045\(15\)00613-0](https://doi.org/10.1016/S1470-2045(15)00613-0).
- [6] European Medicines Agency. Ibrance, INN-palbociclib – WC500217196. Samenvatting van de productkenmerken. [http://www.ema.europa.eu/docs/nl\\_NL/document\\_library/EPAR\\_-\\_Product\\_Information/human/003853/WC500217196.pdf](http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/003853/WC500217196.pdf). Published 2016. Accessed June 24, 2020.
- [7] R.S. Finn, M. Martin, H.S. Rugo, S. Jones, S.A. Im, K. Gelmon, et al., Palbociclib and letrozole in advanced breast cancer, *N. Engl. J. Med.* 375 (20) (2016) 1925–1936, <https://doi.org/10.1056/nejmoa1607303>.
- [8] F. Fu, J. Kano, J. Ma, M Guindy, The impact of real-world alternative dosing strategies of palbociclib on progression-free survival in patients with metastatic breast cancer, *Current Oncol.* 29 (2022) 1761–1772, <https://doi.org/10.3390/curroncol29030145>.
- [9] P. Guyot, A.E. Ades, M.J. Ouwens, N.J. Welton, Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves, *BMC Med. Res. Methodol.* 12 (9) (2012), <https://doi.org/10.1186/1471-2288-12-9>.
- [10] N. Harbeck, M. Bartlett, D. Spurdin, B. Hooper, L. Zhan, E. Rosta, et al., CDK 4/6 inhibitor in HR+/HER2- advanced/metastatic breast cancer: a systematic review of real-world evidence studies, *Future Oncol.* 17 (16) (2021) 2107–2123, <https://doi.org/10.2217/fon-2020-1264>.
- [11] P.A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, J.G. Conde, Research electronic data capture (REDCap): a metadata-driven methodology and workflow process for providing translational research informatics support, *J. Biomed. Inform.* 42 (2) (2009) 377–381, <https://doi.org/10.1016/j.jbi.2008.08.010>.
- [12] R.K. Ismail, J. van Breeschoten, M.W.J.M. Wouters, M. van Dartel, S. van der Flier, A.K.L. Reyners, et al., Palbociclib dose reductions and the effect on clinical outcomes in patients with advanced breast cancer, *Breast* 60 (2021) 263–271, <https://doi.org/10.1016/j.breast.2021.11.013>.
- [13] S. Jin, R. Pazdur, R. Sridhara, Re-evaluating eligibility criteria for oncology clinical trials: analysis of investigational new drug applications in 2015, *J. Clin. Oncol.* 35 (33) (2017) 3745–3752, <https://doi.org/10.1200/JCO.2017.73>.
- [14] S. Khozin, G.M. Blumenthal, R. Pazdur, Real-world data for clinical evidence generation in oncology, *J. Natl. Cancer Inst.* 109 (11) (2017) djx187, <https://doi.org/10.1093/jnci/djx187>.
- [15] B. Moftakhar, M. Lekkala, M. Strawderman, T.C. Smith, P. Meacham, B. Fitzgerald, et al., Impact of early dose intensity reduction of palbociclib on clinical outcomes in patients with hormone-receptor-positive metastatic breast cancer, *Breast Cancer Res. Treat.* 183 (2020) 411–418, <https://doi.org/10.1007/s10549-020-05793-1>.
- [16] D. Richardson, L. Zhan, R. Mahtani, L. McRoy, D. Mitra, M. Reynolds, et al., A prospective observational study of patient-reported functioning and quality of life in advanced and metastatic breast cancer utilizing a novel mobile application, *Breast Cancer Res. Treat.* 187 (2021) 113–124, <https://doi.org/10.1007/s10549-020-06082-7>.
- [17] SONIA study. [www.sonia-studie.nl](http://www.sonia-studie.nl). Accessed November 23, 2022.
- [18] E.M.W. Van de Garde, B.C. Plouvier, H.W.H.A. Fleuren, E.A.F. Haak, K.L.L. Movig, M.J. Deenen, et al., Pharmacotherapy within a learning healthcare system: rationale for the Dutch Santeon Farmadatabase, *Eur. J. Hosp. Pharm.* 26 (1) (2019) 46–50, <https://doi.org/10.1136/ejpharm-2017-001329>.
- [19] S. Verma, C.H. Bartlett, P. Schnell, A.M. DeMichele, S. Loi, J. Ro, et al., Palbociclib in combination with fulvestrant in women with hormone receptor-positive /HER2-negative advanced metastatic breast cancer: detailed safety analysis from a multicenter, randomized, placebo-controlled, phase III study (PALOMA-3), *Oncologist* 21 (2016) 1165–1175, <https://doi.org/10.1634/theoncologist.2016-0097>.
- [20] J.E. Wennberg, *Tracking medicine: A Researchers' Quest to Understand Health Care*, Oxford University Press, New York, 2010.
- [21] J.E. Wennberg, E.S. Fisher, J.S. Skinner, Geography and the debate over Medicare reform, *Health Aff.* 21 (1) (2002), <https://doi.org/10.1377/hlthaff.w2.96>.
- [22] J. Wilkie, M.A. Schickli, M.J. Berger, M. Lustberg, R. Reinbolt, A. Noonan, et al., Progression-free survival for real-world use of palbociclib in hormone receptor-positive metastatic breast cancer, *Clin. Breast Cancer* 20 (1) (2020) 33–40, <https://doi.org/10.1016/j.clbc.2019.06.010>.