Differences in health-related quality of life in patients with or without progression on palbociclib therapy. Preliminary results from the non-interventional study PERFORM

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DISCUSSION AND CONCLUSIONS

The analysis of PRO data 4 years after the enrollment of the first PERFORM patient provides important insights into QoL during first-line palbociclib treatment. Notably, unlike most RCTs and many other real-word studies, the PERFORM study continues to collect data, inclusive of QoL after completion of first-line treatment and beyond disease progression. Here, we focus on QoL data during first-line treatment. Our analyses describes an association of the progression event with a lower score in QoL: mean change from baseline in FACT-B total score, FACT-G total score, breast cancer subscale, and TOI showed a more pronounced and, for some timepoints (i.e. 3–6 months, 6–9 months), clinically relevant decline[8] for patients with PD in respective 3-month intervals when compared to those without PD throughout. Interestingly, these observations seem to be predominantly based on respective changes in the subscale scores physical, emotional and functional well-being. The deterioration in QoL may be related to tumor progression, which is noticeable to the patient in the form of worsening of tumor symptoms or general well-being but also could result from noticeable side effects of subsequent therapy, as well as information about (imperceptible) tumor growth.

These data of interim analysis 4 of the PERFORM study complement previous data from the pivotal trial PALOMA-2, which demonstrated decreased time to permanent deterioration in QoL in patients with PD versus non-PD[6,8]. Furthermore, Marschner N. et al reported findings from mixed-model analyses, of more than 8,000 questionnaires from 2,314 patients with metastatic breast, pancreatic, lung, and colorectal cancer showed that disease progression was accompanied by statistically significant and clinically relevant deterioration in many health-related QoL scales.[13] In ABC, each PD was associated with a statistically significant worsening in physical and functional well-being, depression, and global QoL. Interestingly, while the magnitude of deterioration was moderate and generally not clinically meaningful after the first progression, it became more pronounced after subsequent progressions.[13]

PERFORM provides real-world findings supporting these results and expands existing knowledge by providing important insights into QoL for palbociclib-treated patients from initiation of treatment through disease progression and beyond, regardless of later-line treatments. Here, we analyzed change from baseline in the FACT-B total score and corresponding subscales in patients with and without disease progression. The observed more pronounced and for some timepoints clinically relevant mean decline from baseline appears to signal disease progression as patient-relevant endpoint.

BACKGROUND

CDK4/6 inhibitors combined with endocrine therapy (ET) is the standard of care first-line treatment for HR+/HER2- advanced breast cancer (ABC) patients based upon demonstrated efficacy, safety and tolerability in pivotal trials.[1-5] Several trials have presented that quality of life (QoL) is maintained/prolonged in patients treated with ET-based palbociclib therapy compared to ET monotherapy.[6-8] Real-world evidence (RWE) for effectiveness and QoL is important and complementary to clinical trial data as patients in trials do not comprehensively represent the totality of cancer patient populations seen in clinical practice.[9] A highly relevant question, rarely addressed in randomized clinical trials (RCT) and RWE is the impact of disease progression (PD) on patients' QoL. As maintaining patients' QoL is a major objective in the treatment of an incurable disease, it is crucial to understand whether PD is associated with changes in QoL outcomes, especially as progression-free survival (PFS) is frequently not recognized as a patient-relevant endpoint among health technology assessments (HTA).[10] Here, we present the results of interim analysis 4 of the PERFORM study focused on QoL, which includes an examination of the FACT-B questionnaires as well as FACT-B total score, FACT-G total score, trial outcome index (TOI) and the breast cancer subscale in patients with and without PD.

METHODS

The PERFORM study (NCT04767594) is an observational, prospective, international cohort study designed to generate real-world evidence on effectiveness, safety, tolerability, and patient-reported outcomes (PRO) in patients with HR+/HER2- ABC treated in the first-line setting with palbociclib plus ET in Germany and Austria. Here, we present the results of interim analysis 4. The primary study endpoint is first-line PFS, defined as start of first-line treatment to progression or death, whichever comes first. Patients without tumor progression or death at the time of analysis were censored at their date of last contact or at start of second-line, whichever came first. QoL data were collected using the FACT-B questionnaire.[11] The questionnaire was administered by the site at baseline, and at end of treatment with palbociclib only (EOT questionnaire), irrespective of ongoing ET. In addition, questionnaires were provided to patients via postal service every 3 months throughout study participation across all treatment lines. QoL data were analyzed for patients with ≥ 1 evaluable baseline FACT-B subscale score and ≥ 1 corresponding evaluable post baseline FACT-B subscale score after start of palbociclib treatment. We analyzed change from baseline over time in FACT-B total scores, subscale scores, and the trial outcome index (TOI)[12] for first-line patients with and without PD in consecutive 3-month intervals, provided that the subgroup size was ≥ 20. Questionnaire scores collected immediately after first progression were compared to scores collected from patients without prior progression in the same timeframe. If the end of palbociclib treatment (EOT) questionnaire was completed between the first progression and a subsequent 3-monthly questionnaire, the respective 3-monthly questionnaire was replaced by the EOT assessment. Documentation, including data cleaning, is currently ongoing for this study; enrollment was ongoing at time of data cut.

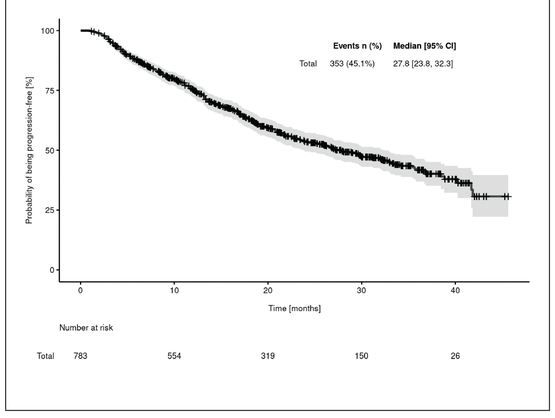
RESULTS

From October 27th, 2020 (first patient enrolled) until data cutoff (DC) on September 30th, 2024, 1,412 patients were enrolled across 188 study sites in Germany and Austria. Of these, 1,321 qualified for interim analysis 4, meaning they had signed informed consent at least 6 months prior to the DC allowing for sufficient observation time. 783 patients were evaluable for the FACT-B analysis and were hence included in the PRO analysis set. Median age of patients included in this analysis was 67.5 years (range 33.0–96.1 years), with 57.5 % of patients ≥ 65 years. Most patients were female (99.4 %) and postmenopausal (91.6 %). Patient characteristics for the PRO analysis set are summarized in **Table 1**. Median follow-up time and median PFS in the PRO analysis set were 27.5 months (95 % CI 26.2; 28.6) and 27.8 months [95 % CI 23.8; 32.3], respectively **(Figure 1)**. Mean change from baseline in FACT-B total score **(Figure 2A)**, FACT-G total score **(Figure 2B)**, TOI **(Figure 2H)** and the breast cancer subscale **(Figure 2G)**, showed a more pronounced and, for some time intervals, clinically relevant decline for patients with PD versus those without PD (i.e., for 3–6 months, and 6–9 months). Mean change from baseline in social/family well-being was similar for patients with PD versus those without PD **(Figure 2D)**. In contrast, differences in change from baseline for patients with versus those without PD were observed for the physical, functional, and emotional well-being subdomains, favoring the patient group without PD **(Figures 2C, 2F, and 2E)**.

Table 1: Patient characteristics at baseline of first-line treatment, PRO analysis set

	Total (N=783)
Median age at start of 1st-line treatment (range) [years]	**67.5 (33.0–96.1)**
<65 years [n (%)]	333 (42.5%)
65–74 years [n (%)]	242 (30.9%)
75–79 years [n (%)]	110 (14.0%)
≥80 years [n (%)]	98 (12.5%)
Sex [n (%)]	
Female	778 (99.4%)
Male	5 (0.6%)
Menopausal status [n (%)]	
Pre-/Perimenopausal	61 (7.8%)
Postmenopausal	717 (91.6%)
Not derivable	5 (0.6%)
ECOG Performance Status [n (%)]	
0	358 (45.7%)
1	330 (42.1%)
2–4	73 (9.3%)
Not assessed	22 (2.8%)

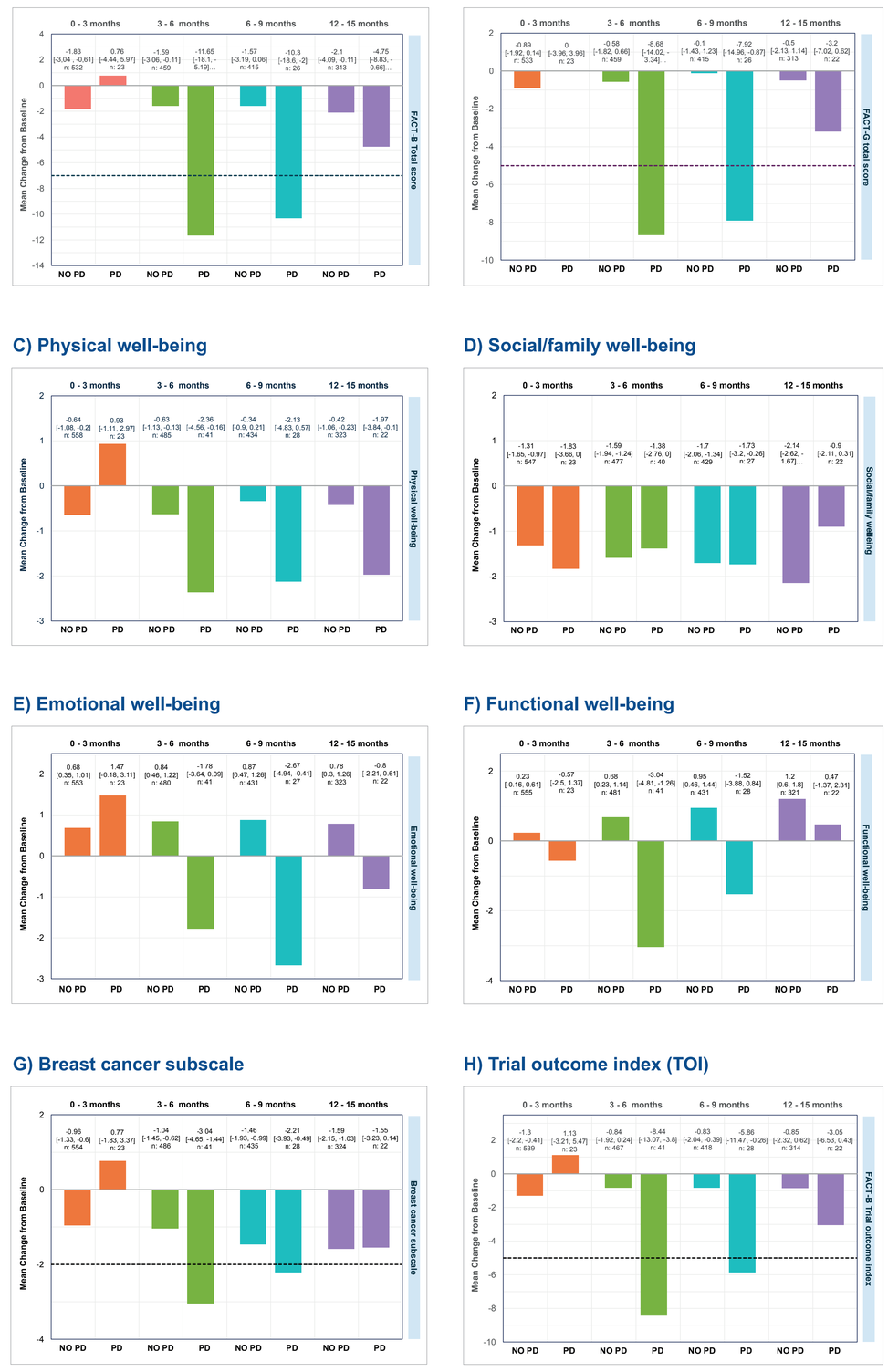
Figure 1: Progression-free survival of first-line treatment, PRO analysis set



LIMITATIONS

Non-interventional studies have general limitations such as selection and observer bias. In addition, missing data especially on potentially relevant confounders can affect conclusions. Furthermore, timing of assessments can influence results: in contrast to many RCTs, there was no obligatory assessment of QoL directly related to the progressive event (i.e., if palbociclib treatment discontinued prior to progression). Results of tumor assessments may impact QoL, especially emotional well-being. Compared to clinical trials, monitoring was less stringent, which may lead to less consistent data collection and reporting, and loss to follow-up can introduce additional bias. The data has been generated in a German/Austrian cohort of patients and may thus not be generalizable to other populations. Finally, the data are of descriptive, unadjusted nature and therefore purely hypothesis generating, and additional follow-up and analysis is needed.

Figure 2: Mean changes from baseline over time for patients with and without first progressive disease (PD) in respective intervals in FACT-B total score (A), FACT-G total score (B), physical well-being (C), social/family well-being (D), emotional well-being (E), functional well-being (F), breast cancer subscale (G), and trial outcome index (H)



m is the mean change from baseline, the confidence interval is shown in square brackets, and n is the number of evaluable scores at that time. The dotted line shows the minimum important difference MID.
PD – progressive disease
The whole PRO-group had a follow-up of minimum 6 month. Follow-up in subgroups with later time intervals might be limited.

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Conflicts of Interest: Vesna Bjelic-Radisic: Speaker's Bureau, Responsible Investigator Study Site, Travel/Accomodation Expenses; Matthias Korell: Responsible Investigator Study Site; Georg Pfeiler: Honoraria, Consulting or Advisory Role, Speaker's Bureau, Responsible Investigator Study Site, Travel/Accomodation Expenses; Thomas Gabrysiak: Responsible Investigator Study Site; Volker Petersen: Responsible Investigator Study Site; Mustafa Deryal: Responsible Investigator Study Site; Thomas Fietz: Consulting or Advisory Role, Responsible Investigator Study Site; Julia Caroline Radosa: Honoraria, Consulting or Advisory Role, Expert Testimony, Responsible Investigator Study Site, Travel/Accomodation Expenses; Thomas Decker: Honoraria, Consulting or Advisory Role, Speaker's Bureau, Responsible Investigator Study Site; Björn Schöttker: Responsible Investigator Study Site; Jan Knoblich: Responsible Investigator Study Site; Uwe Rhein: Responsible Investigator Study Site; Alexander Wegenast: Full/Part-time employment, Leadership, Stocks/Shares, Honoraria; Esther Glastetter: Full/Part-time employment, Leadership, Stocks/Shares; Miguel Cordova: Full/Part-time employment, Stocks/Shares; Emanuele Zanucco: Full/Part-time employment, Leadership, Stocks/Shares, Honoraria; Martin Glasstetter: Full/Part-time employment; Ursula Oppermann: Full/Part-time employment; Rupert Bartsch: Honoraria, Consulting or Advisory Role, Responsible Investigator Study Site, Travel/Accomodation Expenses; Michael Patrick Lux: Honoraria, Consulting or Advisory Role, Speaker's Bureau, Responsible Investigator Study Site, Travel/Accomodation Expenses

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Abbreviations: ABC: Advanced Breast Cancer | DBC: Data Base Cut | EOT: End Of Treatment | ECOG: Eastern Cooperative Oncology Group Performance Status | ET: Endocrine Therapy | HER2: Human-Epidermal-Growth-Factor-Receptor 2 | HR: Hormone Receptor | HTA: Health Technology Assessments | n: Number | NA: Not Applicable | PD: Progressive Disease | PFS: Progression-Free Survival | PRO: Patient Reported Outcome | Q: Quartile | QoL: Quality of Life | RWE: Real-World Evidence | TOI: Trial Outcome Index