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Real-world effectiveness of 1L line palbociclib + endocrine therapy and subsequent treatments in patients with HR+/HER2- Advanced Breast Cancer: Interim results from the PERFORM Study

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Background

Combination of a CDK4/6 inhibitor (CDK4/6i) with endocrine therapy (ET) is standard of care 1L treatment for HR+/HER2- advanced breast cancer (ABC) patients based upon results of the pivotal trials[1–5]. Real-world evidence complements data from clinical trials, as some patient subgroups accrued to clinical trials may not represent a real-world cancer patient population. In a rapidly evolving therapeutic landscape, with new treatment options after failure of 1L CDK4/6i + ET, optimal treatment sequence is a matter of ongoing discussion and consequently real-world data on therapy sequence is relevant in the absence of prospective clinical trial results. Here we present data from the pre-planned interim analysis (IA) 4 of the prospective non-interventional PERFORM study four years after inclusion of the first patient.

Methods

The PERFORM non-interventional study (NCT04767594) is an observational, prospective, international cohort study designed to generate real-world evidence on effectiveness, safety, tolerability, and patient-reported outcomes (PRO) during and beyond 1L treatment with palbociclib + ET in patients with HR+/HER2- ABC in Germany and Austria. The primary endpoint is 1L progression-free survival (PFS), defined as start of 1L treatment to first progression or death, whichever occurs first. Secondary effectiveness endpoints include PFS of 2L treatment, defined as start of 2L treatment to first progression after start of 2L therapy or death, time to first subsequent therapy (TFST), time to first subsequent chemotherapy (TFSC), defined as time from start date of 1L treatment to start date of any systemic 2L treatment (TFST) or chemotherapy (TFSC), and overall survival (OS), defined as time from the start date of 1L treatment to death from any cause. The Kaplan-Meier method was used for time-to-event analyses, except for TFST and TFSC. Instead, cumulative incidence functions were used for modelling of TFST and TFSC, where the start of first subsequent therapy and chemotherapy respectively, serves as event of interest and death serves as competing event, respectively. For the PFS analysis, patients without tumor progression or death at the time of analysis will be censored e.g. at date of last contact or at the start date of a next-line therapy, whichever comes first. Observation period was estimated using reverse Kaplan-Meier method with date of death as censoring date[7]. Tumor assessments were recorded and evaluated according to local medical routine standards. Overall response rate was defined as proportion of patients with best overall response of complete response (CR) or partial response (PR) in the respective treatment line. Based on data from IA 4, we describe real-world patient and disease characteristics, treatment patterns, and provide outcome data for more than 1,000 patients overall and for more than 400 patients undergoing 2L treatment.

Limitations

Limitations of the study include its descriptive, exploratory, and hypothesis-generating nature. Documentation, including data cleaning, is still ongoing in this study and enrollment was still ongoing at time of data-base cut. TFST, TFSC and OS with 54.7 %, 68.2 %, 76.8 % respectively, of patients censored at time of data-base cut are still immature and need further follow-up.

Results

PATIENT POPULATION

From 27th of October 2020 until database cut on September 30th 2024, 1,412 patients were enrolled at 188 study sites across Germany and Austria. Of these, 1,321 qualified for IA 4 (enrolled), with at least 6 months of follow-up to provide sufficient observation time for this analysis. 107 patients were excluded from the analysis set (n = 1,171), as either off-label use (n = 48) or violation of in- or exclusion criteria (n = 57) has been identified after treatment start or either palbociclib or ET was not started (n = 2). Median observation time from start of 1L treatment was 27.0 months (95 %CI; 25.8, 28.2) for the total cohort and 13.9 months (95 % CI; 12.3, 15.2) from start of 2L treatment for patients with documented start of 2L therapy.

PATIENT AND TUMOR CHARACTERISTICS

Median age was 69.3 years, 1,076 patients (91.9 %) were postmenopausal, 369 (31.5%) were 75 years or older and 151 patients (12.9 %) presented with ECOG ≥2 at start of 1L treatment **(Table 1)**. 460 patients (39.3 %) presented with *de novo* advanced disease at initial diagnosis, 711 (60.7 %) were initially diagnosed with early breast cancer with median time since diagnosis to start of 1L treatment of 8.4 years. 95 patients (8.1 %) had a treatment-free interval (TFI) of ≤ 12 months, and 350 patients (29.9 %) had a TFI of > 12 months. 545 patients (46.5 %) presented with visceral disease at inclusion, 397 patients (33.9 %) with bone-only disease **(Table 1)**.

Letrozole was most commonly administered with 1L palbociclib as endocrine combination partner in 747 patients (63.8 %), followed by fulvestrant in 251 patients (21.4 %), anastrozole in 113 patients (9.6 %), and exemestane in 60 patients (5.1 %) **(Table 1)**.

EFFECTIVENESS OF 1L TREATMENT

At database cut-off, 488 patients were still under 1L treatment, and 683 patients had discontinued 1L treatment: 428 (36.5 %) due to disease progression, 110 (9.4 %) due to (serious) adverse events, 56 (4.8 %) were lost to follow-up, 34 (2.9 %) had withdrawn informed consent, and 55 (4.7 %) had discontinued for other reasons **(Table 2)**. The estimated median PFS of 1L treatment with palbociclib + ET was 25.7 months **(Table 2, Figure 1A)**.

Overall response rate (ORR) was 35.2 %, clinical benefit rate (CBR) 66.9 % and disease control rate (DCR) was 76.3 %. For 156 patients (13.3 %) no tumor response was documented at time of database cut **(Table 2)**.

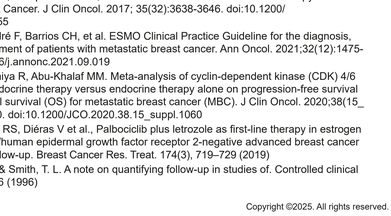
Median overall survival (OS) is immature as, at the time of database cut-off, only 272 patients (23.2 %) had experienced an event. The 12-month OS rate was 90.3 % and the 24-month rate was 78.4 % **(Table 2, Figure 1B)**. Accounting for the fact that some patients may have died before starting further treatment 18.5 % (95 % CI; 16.4, 21.0) and 35.9 % (95 % CI; 33.0, 39.1) had started their first subsequent therapy at 12 and 24 months, respectively, while 10,6 % (95 % CI; 8.9, 12.6) and 22.5 % (95 % CI; 20.0, 25.4) had started their first subsequent chemotherapy **(Table 2)**.

2L TREATMENTS AND EFFECTIVENESS

At the time of database cut, 402 patients had started 2L treatment. A chemotherapy-containing treatment was used in 182 patients (45.3 %). A total of 78 patients (19.4 %) received a CDK4/6i-based 2L therapy, 69 patients (17.2 %) other ET-containing combination therapies and 52 patients (12.9 %) ET monotherapy. For 21 patients, other treatment options were documented as 2L therapy including antibody-drug conjugates. With regard to the individual therapies, the combination of everolimus and exemestane was most widely used and was documented for 51 patients (12.7 %), followed by capecitabine in 42 patients (10.4 %), and fulvestrant in 31 patients (7.7 %).
2L therapies and the regiments applicable for more than 20 patients are depicted in **Figure 2**.

Median PFS of 2L therapy was 6.3 months [95 % CI; 5.3, 8.1] **(Table 2 and Figure 3)**.

Figure 2: Overview 2L treatment patterns



*3 patients switched to another CDK4/6i with no (S)AE and no PD, but were classified as 2L treatment in the PERFORM

Conclusions

The PERFORM study confirms that 1L palbociclib +ET is effective and feasible for a broad patient population, with real-world results consistent with PALOMA-2.[6] Importantly, PERFORM provides valuable prospective data on 2L treatments, showing diverse therapy choices after progression, and will continue to monitor outcomes and quality of life in future analyses.

Discussion

The IA4 of the PERFORM non-interventional study offers deeper insights into patient characteristics and the effectiveness of 1L treatment with palbociclib + ET, as well as subsequent treatments in a real-world setting. The effectiveness data on 1L palbociclib + ET from PERFORM are consistent with and complement data of the PALOMA-2 trial[6]. Median PFS was 25.7 months in the overall population (median overall survival is immature).

PERFORM also captures data on treatments applied after 1L treatment failure, providing rare prospective insights into the rapidly evolving 2L treatment landscape. In the ongoing observation, 36.6 % of the patients received an endocrine-based therapy as 2L treatment (including CDK4/6i-based and other ET combination therapies), while 45.3 % received chemotherapy. Notably, a median progression-free survival (PFS) of 6.3 months was achieved in the 2L setting. With more than 17 %, therapy with a CDK4/6 inhibitor beyond progression appears to be a fairly common option, although the guidelines recommend it as a case-by-case decision. Endocrine monotherapy (12.9 %) appears to play a subordinate role. However, these distributions may be influenced by selection/time bias at the time of the database cutoff for patients already receiving a 2L treatment. Further follow-up will be needed to observe how this evolves over time.

PERFORM will continue follow-up over the next two and a half years. Future PERFORM analyses will not only assess the overall effectiveness of 2L treatments but will also examine effectiveness and quality of life of individual 2L treatment cohorts in detail.

Figure 1A: Progression-free survival of 1L treatment (Palbociclib + ET, n = 1171)

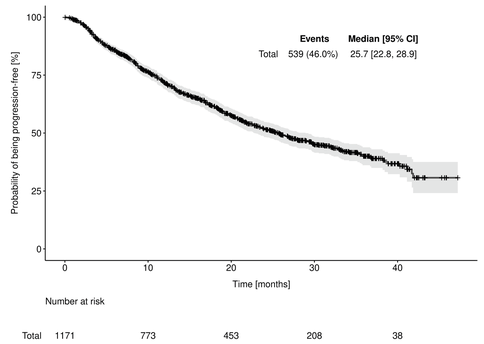


Figure 1B: Overall survival from start of 1L treatment (Palbociclib + ET, n = 1171)

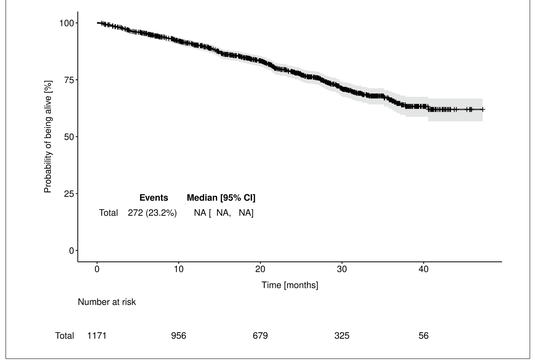


Table 1: Patient and tumor characteristics

	Full analysis set (n = 1171)	Patients who started 2L (n = 402)
Age at start of 1L treatment [years]		
Median (25%/75% quantiles)	69.3 (59.8 - 77.3)	65.3 (58.1 – 74.1)
<65 years [n (%)]	447 (38.2)	198 (49.3)
65–74 years [n (%)]	355 (30.3)	114 (28.4)
75–79 years [n (%)]	185 (15.8)	49 (12.2)
≥80 years [n (%)]	184 (15.7)	41 (10.2)
Sex [n (%)]		
Female	1161 (99.1)	397 (98.8)
Male	10 (0.9)	5 (1.2)
Menopausal status [n (%)]		
Pre-/Perimenopausal	85 (7.3)	31 (7.7)
Postmenopausal	1076 (91.9)	366 (91.0)
Not derivable	10 (0.9)	5 (1.2)
ECOG Performance Status [n (%)]		
0	507 (43.3)	187 (46.5)
1	481 (41.1)	167 (41.5)
2–4	151 (12.9)	39 (9.7)
Not assessed / missing	32 (2.7)	9 (2.2)
***De novo* advanced disease [n (%)]**		
Yes	460 (39.3)	127 (31.6)
No	711 (60.7)	275 (68.4)
Time since initial diagnosis [years]		
Median (25%/75% quantiles) for patients with non- de novo advanced disease	8.4 (4.0 - 13.7)	6.4 (3.3 - 12.5)
Treatment-free interval* [n (%)]		
TFI > 12 months	350 (29.9)	127 (31.6)
TFI ≤ 12 months	95 (8.1)	46 (11.4)
De novo advanced disease	460 (39.3)	127 (31.6)
Missing	266 (22.7)	102 (25.4)
Disease site present at baseline of 1L treatment [n (%)]		
Visceral	545 (46.5)	184 (45.8)
Non-visceral only (excl. bone only)	134 (11.4)	57 (14.2)
Bone only	397 (33.9)	134 (33.3)
No metastases present at inclusion**	95 (8.1)	27 (6.7)
Endocrine combination partner [n (%)]		
Anastrozole	113 (9.6)	27 (6.7)
Exemestane	60 (5.1)	19 (4.7)
Fulvestrant	251 (21.4)	108 (26.9)
Letrozole	747 (63.8)	248 (61.7)

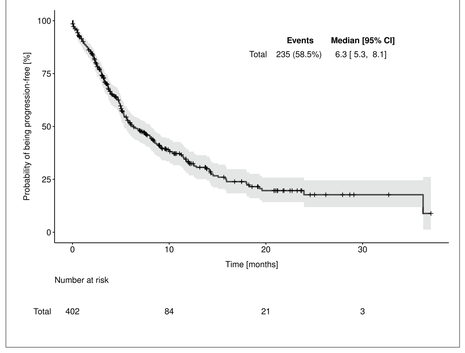
* Treatment-free interval is defined as time from last (neo)adjuvant treatment to date of recurrence (either metastatic relapse or locally advanced, inoperable/not complete resectable relapse, whichever occurs first). Missings in treatment-free interval apply to patients without (neo)adjuvant treatment and in case of input errors (i.e. date of first recurrence before last (neo)adjuvant treatment or date of first recurrence after inclusion).
** Subgroup without metastases present at inclusion includes patients with locally advanced breast cancer and patients with removed metastases (surgery, radiation) after initial diagnosis.

Table 2: Effectiveness of treatment

	Total (n = 1171)
Best response [n (%)] in 1L	
CR	71 (6.1)
PR	341 (29.1)
SD ≥24 weeks	371 (31.7)
SD <24 weeks	111 (9.5)
Non-CR/Non-PD	5 (0.4)
Non-PD (acc. to PI)	6 (0.5)
PD	110 (9.4)
Missing	156 (13.3)
ORR (%)	**35.2**
CBR (%)	**66.9**
DCR (%)	**76.3**
Overall survival	
Median [month (95% CI)]	NA (NA, NA)
12-month rate [% (95% CI)]	90.3 (88.4, 91.9)
24-month rate [% (95% CI)]	78.4 (75.6, 80.9)
Reason for end of 1L treatment [n (%)]	
Progressive disease	428 (36.5)
(Serious) Adverse Event	110 (9.4)
Lost to follow-up	56 (4.8)
Withdrawal of informed consent by subject	34 (2.9)
No (S)AE and no PD but switch in same substance class	3 (0.3)
Other	52 (4.4)
Still under treatment	488 (41.7)
Time to first subsequent treatment[#]	
Events [n (%)]	402 (34.3)
Competing Events [n (%)]	129 (11.0)
Censored [n (%)]	640 (54.7)
% of pts with first subsequent treatment	
12-month rate [% (95 % CI)]	18.5 (16.4, 21.0)
24-month rate [% (95 % CI)]	35.9 (33.0, 39.1)
36-month rate [% (95 % CI)]	43.4 (39.9, 47.1)
Time to first subsequent chemotherapy[^]	
Events [n (%)]	264 (22.5)
Competing Events [n (%)]	163 (13.9)
Censored [n (%)]	744 (63.5)
% of pts with first subsequent chemotherapy	
12-month rate [% (95 % CI)]	10.6 (8.9, 12.6)
24-month rate [% (95 % CI)]	22.5 (20.0, 25.4)
36-month rate [% (95 % CI)]	29.8 (26.6, 33.4)

[#] The event is first subsequent treatment and the competing event is death.
[^] The event is first subsequent chemotherapy and the competing event is death.

Figure 3: Progression-free survival of 2L treatment (n = 402).



Conflicts of Interest:
Rupert Bartsch: Honoraria, Consulting or Advisory Role, 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
Natalja Deuerling: Responsible Investigator Study Site
Martin Glasstetter: Full/Part-time employment
Katja Gratzke: Full/Part-time employment
Alexander Wegenast: Full/Part-time employment, Leadership, Stocks/Shares, Honoraria
Esther Glastetter: Full/Part-time employment, Leadership, Stocks/Shares
Seray Sener: Full/Part-time employment, Leadership, Stocks/Shares, Sponsor/Funding, Travel/Accommodation/Expenses, Other relationship
Johanna Dzieran: Full/Part-time employment, Stocks/Shares
Michael Patrick Lux: Honoraria, Consulting or Advisory Role, Speaker's Bureau, Responsible Investigator Study Site, Travel/Accomodation Expenses

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Abbreviations:
1L: First-line / First line | 2L: Second-line / Second line | ABC: Advanced Breast Cancer | Acc. to PI: According to Principal Investigator | CDK4/6i: Cyclin-Dependent-Kinase 4/6 inhibitor | CBR: Clinical Benefit Rate | CI: Confidence Interval | CR: Complete Response | DCR: Disease Control Rate | ECOG: Eastern Cooperative Oncology Group Performance Status | ET: Endocrine Therapy | HER2: Human-Epidermal-Growth-Factor-Receptor 2 | HR: Hormone Receptor | IA: Interim Analysis | n: Number | NA: Not Applicable | ORR: Overall Response Rate | PD: Progressive Disease | PFS: Progression-Free Survival | PR: Partial Response | Q: Quartile | (S)AE: (Serious) Adverse Event | SD: Stable Disease | SE: Standard Error

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