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# Patterns of treatment and outcome of palbociclib plus endocrine therapy in hormone receptor-positive/HER2 receptor-negative metastatic breast cancer: a real-world multicentre Italian study

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***Abstract***

**Background:** The CDK4/6 inhibitor palbociclib combined with endocrine therapy (ET) has proven to prolong progression-free survival (PFS) in women with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2–) metastatic breast cancer (MBC). Few data are available regarding the efficacy of such a regimen outside the clinical trials.

**Patients and methods:** This is a multicentre prospective real-world experience aimed at verifying the outcome of palbociclib plus ET in an unselected population of MBC patients. The primary aim was the clinical benefit rate (CBR); secondary aims were the median PFS, overall survival (OS) and safety. Patients received palbociclib plus letrozole 2.5 mg (cohort A) or fulvestrant 500 mg (cohort B).

**Results:** In total, 191 patients (92 in cohort A, 99 in cohort B) were enrolled and treated, and 182 were evaluable for the analysis. Median age was 62 years (range 47–79); 54% had visceral involvement; 28% of patients had previously performed one treatment line (including chemotherapy and ET), 22.6% two lines and 15.9% three. An overall response rate of 34.6% was observed with 11 (6.0%) complete responses and 52 (28.6%) partial responses. Stable disease was achieved by 78 patients (42.9%) with an overall CBR of 59.8%. At a median follow-up of 24 months (range 6–32), median PFS was 13 months without significant differences between the cohorts. When analysed according to treatment line, PFS values were significantly prolonged when palbociclib-based therapy was administered as first-line treatment (14.0 months), to decrease progressively in second and subsequent lines (11.7 and 6.7 months, respectively). Median OS was 25 months, ranging from 28.0 months in 1st line to 18.0 and 13.0 months in 2nd and subsequent lines, respectively.

**Conclusions:** Our data indicate that palbociclib plus ET is active and safe in HR+/HER2– MBC, also suggesting a better performance of the combinations in earlier treatment lines.

***Keywords:*** endocrine therapy, metastatic breast cancer, palbociclib, real world, visceral involvement

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## Introduction

Hormone receptor (HR)-positive(HR+)/human epidermal growth factor receptor 2-negative (HER2) breast cancers represent up to 75% of invasive breast tumours.[1] Endocrine therapy (ET) remains the therapeutic backbone for the treatment of women with HR+/HER2− advanced and/or metastatic disease.[2–4] However, the effectiveness of ET is limited by pre-existing endocrine resistance and by resistance acquired during treatment, and up to 50% of HR+ patients with metastatic breast cancer (MBC) develop mechanisms of therapeutic resistance to the ET they receive.[5]

In order to modify the development of resistance to ET thereby enabling patients to receive effective HR-directed treatments, additional strategies and new classes of agents targeting other patterns of growth have been developed. The role of cell-cycle signalling in both breast cancer oncogenesis and antioestrogen resistance has emerged as a promising area of research. Dysregulated mechanisms governing the cell cycle are considered a hallmark of cancer and result in uncontrolled cellular proliferation.[6,7]

Cyclin-dependent kinases (CDK) 4 and 6 are cell-cycle regulators that complex with cyclin D to hyperphosphorylate retinoblastoma (Rb), inactivating and uncoupling G1- to S-phase cell-cycle progression. Uncontrolled formation of cyclin D1 and CDK 4/6 complexes plays an integral role in both the initiation and progression of breast cancer and may be associated with endocrine resistance.[8,9]

Potent and selective inhibitors of CDK 4/6 have become available as cancer therapeutics in the last decade and have recently shown a clinically meaningful efficacy with a good tolerability profile in patients with MBC.[10] Palbociclib, a first-in class, orally bioavailable CDK4/6 inhibitor, has been shown to cause cell-cycle arrest in endocrine-resistant breast cancer cell lines, and synergistic effects have been observed when the agent was combined with ET.[11,12] These findings led to the design and implementation of the PALOMA trials, combining palbociclib with ET, and ultimately led to its approval as a novel therapeutic agent in HR+ MBC. The history of the drug development started with PALOMA-1 trial, a phase II study which enrolled 165 postmenopausal patients with HR+/HER2− MBC randomised 1:1 to receive palbociclib plus letrozole *versus* letrozole alone.[13] Ninety-eight percent of patients had a stage IV disease; in the palbociclib-letrozole group 52% ($n=44$) women had de novo metastatic disease. Only 15 and 14 patients in each arm had primary endocrine resistance; visceral disease was present in 44% and 53% of patients in experimental and control arm, respectively. All patients had not received any systemic treatment for advanced disease. The primary objective of the trial was progression-free survival (PFS), which was 20.2 months in the experimental arm *versus* 10.2 months in the letrozole alone arm (HR = 0.49; 95% CI 0.32–0.75; $p=0.0004$) in the intention to treat (ITT) population. With regard to secondary objectives, a greater clinical benefit rate (CBR, 81% *versus* 58%) and higher response rates (RR, 43% *versus* 33%) were observed in the letrozole–palbociclib arm. The median duration of response was 20.3 and 11.1 months for the palbociclib plus letrozole and the letrozole alone group, respectively. The combination treatment resulted in a statistically non-significant prolongation of overall survival (OS): 37.5 *versus* 33.3 months for the experimental and the control arm, respectively (HR = 0.813; 95% CI 0.492–1.345; $p=0.42$). The most frequent grade 3–4 adverse events (AEs) were neutropenia, leukopenia and fatigue (54%, 19% and 4% in the combination group, respectively). No cases of febrile neutropenia or neutropenia-related infections were reported.

The promising results of PALOMA-1 granted further research to test the efficacy of palbociclib in phase III trials in different clinical settings. In PALOMA-2 study, 666 postmenopausal women with HR+/HER2− MBC were randomised 2:1 to receive palbociclib plus letrozole *versus* letrozole plus placebo.[14] Thirty-one percent and 32.4% of patients in each arm had *de novo* stage IV disease; in the total population, half had already received (neo)adjuvant chemotherapy, and 56% in each arm adjuvant ET. About 20% of patients in both arms had relapsed $\leqslant$12 months from diagnosis, half had visceral involvement and 23.2% and 21.6%, respectively, had bone-only disease. The study met its primary objective, with a statistically significant improvement of PFS in the experimental arm (24.8 *versus* 14.5 months, HR = 0.58; 95% CI 0.46–0.72; $p<0.001$). The RR was found to be 42.1% and 34.7% and the CBR 84.9% and 70.3%, in the experimental and placebo arm, respectively. Most common grade 3–4 toxicities in the combination arm were neutropenia (66.4%), leukopenia (24.8%), anaemia

(5.4%), fatigue (1.8%) and febrile neutropenia (1.8%). The analysis of patient-reported outcomes showed an improvement in pain scores in treatment-naïve patients favouring the combination arm, with no negative effects on quality of life (QoL) of patients receiving palbociclib for a prolonged period.[15] In the randomised, double-blind, phase III PALOMA-3 trial, 521 women with HR+ MBC progressing during or shortly after prior ET (⩽12 months in the adjuvant and ⩽1 month in the metastatic setting) were randomised 2:1 to palbociclib plus fulvestrant *versus* placebo plus fulvestrant, with premenopausal women receiving also a gonadotropin-releasing hormone (GnRH) agonist.[16] Seventy-nine percent of patients had acquired ET and 21% had primary resistance. Median PFS was 9.5 months in the palbociclib arm *versus* 4.6 months in the placebo one (HR = 0.46, 95% CI 0.36–0.59; $p < 0.0001$). The RR, time to response, and CBR were also significantly improved.[17] The benefit observed was independent from the degree of endocrine sensitivity, the menopausal status, the presence of visceral metastases and PIK3CA/ESR1 status (mutated *versus* wild-type).[18–20] AEs were more frequent with the combined treatment, particularly leukopenia or neutropenia, but toxicity was globally manageable with QoL improvements in the palbociclib arm.[21,22] An updated analysis of the OS data has recently been reported: while in the entire population the improvement in OS was not statistical significant (34.9 *versus* 28.0 months in the experimental and control arm, respectively, HR = 0.81; 95% CI 0.64–1.03), among 410 patients with sensitivity to previous ET the median OS was 39.7 months (95% CI, 34.8 to 45.7) in the palbociclib–fulvestrant group and 29.7 months (95% CI, 23.8 to 37.9) in the placebo–fulvestrant group (HR = 0.72; 95% CI 0.55–0.94; absolute difference, 10.0 months).[23] Results from the PALOMA trials have led to the approval of palbociclib in women with HR+/HER2− MBC in combination with an aromatase inhibitor (AI) (as initial ET-based therapy in postmenopausal women) or in combination with fulvestrant in women with disease progression, previously treated with ET (plus a GnRH agonist in premenopausal status).

Beside randomised clinical trials, treatment patterns and clinical effectiveness of palbociclib in patients with advanced MBC have not been extensively assessed in the real-world setting so far. The aim of this observational, prospective, longitudinal cohort study was to describe the performance of palbociclib combined with ET in a large population of unselected MBC women, with a focus on potential prognostic and/or predictive factors for disease outcome and treatment response.

## Patients and methods

### *Study design*

This is a prospective, longitudinal multicentre cohort study conducted from December 2016 to April 2019 at four oncology Institutions in Northern Italy (three university hospitals, one community hospital). All of them usually treat more than 150 new cases of breast cancer per year and are well representative of the geographical area. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of the coordinating Institution (ICS Maugeri IRCCS Pavia Ethic Committee, approval number 2295) and adopted by the satellite Centres. All patients provided written informed consent for the analysis and anonymised publication of clinical data.

### *Study population*

Eligible patients were pre- and postmenopausal women with a histologically proven HR+ MBC, candidate to receive palbociclib plus ET as first or subsequent line of therapy according to their contingent clinical situation. Additional inclusion criteria were HER2− disease [immunohistochemistry (IHC) 0–1+ or IHC 2+, confirmed as fluorescence *in situ* hybridisation (FISH) negative], presence of measurable or evaluable lesions and life expectancy of at least 4 months. They were also required to have adequate bone marrow, hepatic and renal function, according to clinical practice guidelines for antineoplastic drug administration. Previous chemotherapy or ET for metastatic disease was allowed. Data collection started from the administration of the first dose of palbociclib and included patients' performance status and age at the study entry, disease characteristics, HR and HER2 status, sites and number of metastases and tumour biology, as well as previous therapies received in the neoadjuvant, adjuvant and metastatic setting.

### *Treatment plan*

Patients received palbociclib 125 mg daily, 3 weeks on/1 week off in a 28-day cycle, combined

with letrozole 2.5 mg administered orally on a continuous daily dosing schedule (cohort A) or fulvestrant at the dose of 500 mg intramuscular on days 1, 14, 28, then every 4 weeks thereafter (cohort B). Premenopausal women received a GnRH analogue in combination with ET and palbociclib. Treatment was administered until documented disease progression (PD), unacceptable toxicity or patient refusal and was given in an outpatient setting, according to the officially approved national guidelines. The tumour assessment was performed approximately every 4 months, unless clinical signs of PD, according to clinical practice and physician's approach, as well as to the sites of metastatic disease. Treatment efficacy was evaluated by Response Evaluation Criteria In Solid Tumors (RECIST version 1.1).[24] A complete blood count and organ function test was performed before each cycle; no prespecified treatment modifications were planned to have the closest situation to clinical practice; dose reductions, delay or discontinuations of palbociclib were performed according to observed side effects. AEs were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 5.0).[25]

## Statistical analysis

The primary aim of the study was to analyse the activity of palbociclib plus ET in terms of CBR that was defined as the percentage of patients experiencing complete response (CR), partial response (PR), or stable disease (SD) lasting 6 months or more. According to RECIST criteria, CR was defined as the disappearance of all target lesions; PR as a decrease of at least 30% in the sum of diameters of target lesions, taking as reference the baseline sum diameters; PD as an increase of at least 20% in the sum of diameters of target lesions or the appearance of new lesions; SD was defined as a neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Secondary aims included the evaluation of the safety of the treatments, PFS and OS. PFS was defined as the time interval from the start of therapy with palbociclib plus ET to the date of PD; OS was calculated as the interval from therapy start to the date of death or of last follow-up evaluation. A subgroup analysis was performed to identify potential prognostic and/or predictive factors for disease outcome and treatment response. As for subgroup analysis, the variables investigated were: ECOG performance status (0 *versus* 1–2); age ($\leqslant$65 *versus* >65 years); disease-free interval (DFI) from adjuvant treatment ($\leqslant$24 months *versus* >24 months); number of metastatic sites (>2 *versus* $\leqslant$2); visceral involvement (yes *versus* no); line of treatment (1st–2nd line *versus* 3rd line, including both chemotherapy and ET); previous treatment with everolimus/exemestane or fulvestrant in the metastatic setting; the menopausal status. Visceral involvement was defined as the presence of metastasis to visceral organs, including lung, liver, peritoneum or pleura. Data were collected in a dedicated database program by the research team.

Continuous variables' distribution was expressed in terms of median and interquartile range (25th–75th percentiles) since most of the variables deviated significantly from the normal distribution, and categorical variables' distribution was described by absolute and relative frequency (%). The presence of a statistically significant difference in terms of variables distribution by outcomes' values was assessed by the non-parametric Wilcoxon Rank Sum test (for numeric explanatory variables) or by the Pearson's or Fisher's Exact tests for categorical explanatory variables. The Fisher's Exact test was preferred over the Pearson chi-square test when the minimum number of observations by contingency table was <5. PFS and OS were calculated using the Kaplan–Meier method and the log-rank test was applied to compare survival profiles between the groups. Cox regression was applied to estimate the time-dependent risk of the outcomes of interest in univariate and multivariate analysis. The statistical significance threshold was set to $p < 0.05$ for all analyses. All statistical procedures were performed by the R statistical software tool (www.r-project.org).

## Results

### *Patient characteristics*

Over the study period, 191 patients with HR+/HER2− MBC were enrolled and treated and 182 were considered for data analysis. Nine patients were excluded for incomplete or missing data (two in cohort A and seven in cohort B) as described in the CONSORT diagram (Figure 1). Clinical and demographic characteristics are reported in Table 1.

The median age in the whole population was 62 years (range 47–79); 51.6% of the patients

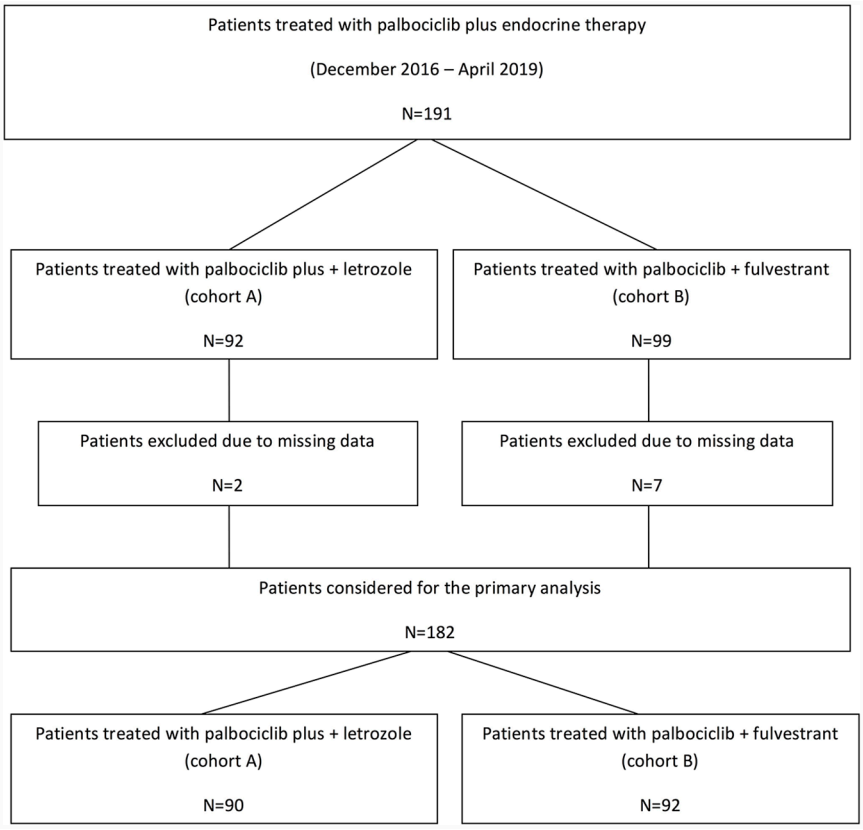


**Figure 1.** The figure shows the CONSORT flow chart.

were aged 65 years or less. The majority of the patients (133, 73%) were postmenopausal with an ECOG performance status of 0–1 (90.6%). Visceral metastases were present in more than half of cases (53.8%), whereas 24.7% of patients had bone-exclusive disease. The majority of women had metastases involving two or more organs (35.7% and 25.8%, respectively). Median DFI was ⩽12 months in 47.8% of patients, while 44 of them had a metastatic disease *ab initio* (24.2% of the overall population).

As for early stage of disease, 23% and 42.3% of patients had received prior (neo)adjuvant chemotherapy, respectively, and 75.7% had been treated with ET in the adjuvant setting. Forty-four patients (24.3%) entered the study affected by *de novo* MBC. Sixty-one patients (33.5%) received palbociclib-based therapy as first-line treatment for metastatic disease, and 121 (66.4%) as second or later lines; the median number of prior lines was two in cohort A (range 0–3) and three in cohort B (range 1–5), including ET (median 3) and chemotherapy (median 2). The majority of patients had received an AI for the metastatic disease, while 20.3% and 24.8% had previously received everolimus/exemestane and fulvestrant 500, respectively.

### *Treatment activity and efficacy*

All patients received a minimum of six cycles of palbociclib-based therapy; the median number of administered courses was 15 in cohort A (range 7–24) and 13 in cohort B (range 6–23). Table 2 shows treatment activity according to therapy line. An overall RR of 34.6% (95% CI 28.1–41.8) was observed, with 11 (6.0%) CR and 52 (28.6%) PR. SD was achieved by 78 patients (42.9%), lasting more than 24 weeks in 46 of them (25.2%), for an overall CBR of 59.8% (95% CI 52.6–66.7). Median time to response was 6 months (range 4–8). Forty-one patients (22.5%) experienced PD during treatment. Within the population receiving palbociclib combined with letrozole (cohort A), the overall RR was 28.9% (95% CI 20.5–39.0), with 4.4% CRs, while patients treated with palbociclib plus fulvestrant (cohort B) achieved an overall RR of 40.2% (95% CI 30.8–50.4), with 7.6% CRs. On the other hand, a

**Table 1.** Main baseline characteristics of the study population (N = 182).

| | Cohort A (P + L) | Cohort B (P + F) | Overall |
|---|---|---|---|
| | *N* = 90 | *N* = 92 | *N* = 182 |
| Enrolled/evaluable no (%) | 92/90 (97.8) | 99/92 (92.9) | 191/182 (95.2) |
| Median age, years (range) | 59 (47–71) | 64 (51–79) | 62 (47–79) |
| ⩽65 years | 51 (56.6) | 43 (46.8) | 94 (51.6) |
| >65 years | 39 (43.4) | 49 (53.2) | 88 (48.4) |
| ECOG performance status | | | |
| 0 | 52 (51.7) | 52 (56.5) | 104 (57.1) |
| 1 | 25 (27.8) | 36 (39.1) | 61 (33.5) |
| 2 | 13 (14.5) | 4 (4.4) | 17 (9.4) |
| Menopausal status | | | |
| Pre | 29 (32.3) | 20 (21.8) | 49 (26.9) |
| Post | 61 (67.7) | 72 (78.2) | 133 (73.1) |
| Histology no (%) | | | |
| Ductal | 71 (78.8) | 69 (75.0) | 140 (76.9) |
| Lobular | 14 (15.5) | 18 (19.5) | 32 (17.5) |
| Other | 5 (5.7) | 5 (5.5) | 10 (5.6) |
| Receptor status | | | |
| ER+/PgR+ | 66 (73.3) | 72 (78.6) | 138 (75.8) |
| ER+/PgR– | 20 (22.2) | 14 (15.1) | 34 (18.7) |
| ER–/PgR+ | 4 (4.5) | 6 (6.3) | 10 (5.5) |
| Median DFI, months | | | |
| 0—*de novo* MBC | 18 (20.0) | 26 (28.8) | 44 (24.2) |
| ⩽12 months | 45 (50.0) | 42 (45.6) | 87 (48.0) |
| >12 months | 27 (30.0) | 24 (26.0) | 51 (28.0) |
| (Neo)adjuvant CHT | | | |
| Yes | 49 (54.0) | 47 (51.0) | 96 (53.0) |
| No | 41 (46.0) | 45 (49.0) | 86 (47.0) |
| Adjuvant HT | | | |
| Tamoxifen | 15 (16.6) | 12 (13.0) | 27 (14.8) |
| Letrozole | 11 (12.2) | 10 (10.8) | 21 (11.5) |
| Anastrazole | 10 (11.2) | 12 (13.0) | 22 (12.0) |

*(Continued)*

**Table 1.** (Continued)

| | Cohort A (P + L) | Cohort B (P + F) | Overall |
|---|---|---|---|
| | ***N*** **= 90** | ***N*** **= 92** | ***N*** **= 182** |
| Exemestane | 14 (15.6) | 15 (16.3) | 29 (15.9) |
| Tamoxifen -> aromatase inhibitors | 22 (24.4) | 17 (18.3) | 39 (21.5) |
| Prior HT and/or CHT lines for MBC | | | |
| None | 32 (35.5) | 29 (31.5) | 61 (33.5) |
| 1 | 28 (31.1) | 23 (25.0) | 51 (28.0) |
| 2 | 19 (21.1) | 22 (23.9) | 41 (22.6) |
| ⩾3 | 11 (12.3) | 18 (19.6) | 29 (15.9) |
| Prior HT for MBC | | | |
| None | 32 (35.6) | 29 (31.5) | 61 (33.5) |
| Aromatase inhibitors | 25 (27.7) | 14 (15.2) | 39 (21.4) |
| Everolimus | 18 (20.0) | 19 (20.6) | 37 (20.3) |
| Fulvestrant 500 | 15 (16.7) | 30 (32.7) | 45 (24.8) |
| Prior CHT for MBC | | | |
| None | 32 (35.7) | 29 (31.5) | 61 (33.5) |
| Taxane | 20 (22.0) | 25 (27.0) | 45 (25.0) |
| Capecitabine | 14 (15.6) | 23 (25.0) | 37 (20.3) |
| Vinorelbine | 12 (13.4) | 5 (5.6) | 17 (9.2) |
| Eribuline | 5 (5.6) | 4 (4.4) | 9 (4.9) |
| Other | 7 (7.7) | 6 (6.5) | 13 (7.1) |
| *De novo* MBC | 18 (20.0) | 26 (28.6) | 44 (24.3) |
| Dominant metastatic sites | | | |
| Visceral | 46 (51.1) | 52 (56.5) | 98 (53.8) |
| Non visceral | 11 (12.2) | 28 (30.5) | 39 (21.5) |
| Bone only | 33 (36.7) | 12 (13.0) | 45 (24.7) |
| Number of metastatic sites | | | |
| 1 | 39 (43.3) | 31 (33.6) | 70 (38.5) |
| 2 | 31 (34.4) | 34 (36.9) | 65 (35.7) |
| ⩾3 | 20 (22.2) | 27 (29.3) | 47 (25.8) |
| Median follow-up, months (range) | 25 (9–32) | 22.5 (6–30) | 24 (6–32) |

CHT, chemotherapy; DFI, disease-free interval; HT, hormonal therapy; L, letrozole; MBC, metastatic breast cancer; P, palbociclib.

**Table 2.** Treatment activity.

| | Whole population | | | Cohort A (palbociclib + letrozole) | | | Cohort B (palbociclib + fulvestrant) | | |
|---|---|---|---|---|---|---|---|---|---|
| | *n* = 182 | | | *n* = 90 | | | *n* = 92 | | |
| | *N* | % | 95% CI | *N* | % | 95% CI | *N* | % | 95% CI |
| Overall response rate | 63 | 34.6 | 28.1–41.8 | 26 | 28.9 | 20.5–39.0 | 37 | 40.2 | 30.8–50.4 |
| Complete response | 11 | 6.0 | | 4 | 4.4 | | 7 | 7.6 | |
| Partial response | 52 | 28.6 | | 22 | 24.4 | | 30 | 32.6 | |
| Stable disease | 78 | 42.9 | | 38 | 42.2 | | 40 | 43.5 | |
| Disease progression | 41 | 22.5 | | 26 | 28.9 | | 15 | 16.3 | |
| Clinical benefit rate | 109 | 59.8 | 52.6–66.7 | 56 | 62.2 | 51.9–71.5 | 53 | 57.6 | 47.4–67.2 |
| mPFS, months (range) | 13 (3.2–25) | | | 15.8 (8.5–25.0) | | | 12.2 (3.0–19.0) | | |
| **First line** | *n* = 61 | | | *n* = 32 | | | *n* = 29 | | |
| | *N* | % | 95% CI | *N* | % | 95% CI | *N* | % | 95% CI |
| Overall response rate | 29 | 47.5 | 35.5–59.8 | 14 | 43.8 | 28.2–60.7 | 15 | 51.7 | 34.4–68.6 |
| Complete response | 8 | 13.1 | | 3 | 9.4 | | 5 | 17.2 | |
| Partial response | 21 | 34.4 | | 11 | 34.4 | | 10 | 34.5 | |
| Stable disease | 25 | 41.0 | | 14 | 43.8 | | 11 | 37.9 | |
| Disease progression | 7 | 11.5 | | 4 | 12.5 | | 3 | 10.3 | |
| Clinical benefit rate | 48 | 78.7 | 66.9–87.1 | 23 | 71.8 | 54.6–84.4 | 25 | 86.2 | 69.4–94.5 |
| mPFS, months (range) | 14 (9.5–25.0) | | | 15.1 (7.2–25) | | | 13.5 (6.5–18) | | |
| **Second line** | *n* = 51 | | | *n* = 28 | | | *n* = 23 | | |
| | *N* | % | 95% CI | *N* | % | 95% CI | *N* | % | 95% CI |
| Overall response rate | 16 | 31.3 | 20.3–45.0 | 5 | 17.9 | 7.9–35.6 | 11 | 47.8 | 29.2–67.0 |
| Complete response | 3 | 5.9 | | – | – | | 3 | 13.0 | |
| Partial response | 13 | 25.5 | | 5 | 17.9 | | 8 | 34.8 | |
| Stable disease | 23 | 45.1 | | 16 | 57.1 | | 7 | 30.4 | |
| Disease progression | 12 | 23.5 | | 7 | 25.0 | | 5 | 21.7 | |
| Clinical benefit rate | 33 | 64.7 | 51.0–76.4 | 15 | 53.6 | 35.8–70.5 | 18 | 78.3 | 58.1–90.3 |
| mPFS, months (range) | 11.7 (6.8–17.5) | | | 13 (6.5–17.5) | | | 11.5 (5.8–17) | | |
| **⩾Third line** | *n* = 70 | | | *n* = 30 | | | *n* = 40 | | |
| | *N* | % | 95% CI | *N* | % | 95% CI | *N* | % | 95% CI |
| Overall response rate | 18 | 25.7 | 16.9–37.0 | 3 | 10.0 | 3.5–25.6 | 15 | 37.5 | 24.2–53.0 |
| Complete response | – | – | – | – | – | – | – | – | – |
| Partial response | 18 | 25.7 | | 3 | 10.0 | | 15 | 37.5 | |
| Stable disease | 30 | 42.9 | | 11 | 36.7 | | 19 | 47.5 | |
| Disease progression | 22 | 31.4 | | 16 | 53.3 | | 6 | 15.0 | |
| Clinical benefit rate | 27 | 38.6 | 28.0–50.3 | 5 | 16.7 | 7.3–33.6 | 22 | 55.0 | 39.8–69.3 |
| mPFS, months (range) | 6.7 (4.2–15.0) | | | 7.5 (5.2–15) | | | 6.0 (4.2–11) | | |

CI, confidence interval; mPFS, median progression-free survival; *n*, number.

higher CBR was observed in cohort A (62.2%, 95% CI 51.9–71.5) compared with cohort B (57.6%, 95% CI 47.4–67.2, $p=0.004$). As concerns the line of treatment, an overall RR of 47.5% (95% CI 35.3–59.8) and a CBR of 78.7% (95% CI 66.8–87.1) were observed in the whole population treated as first line, with an apparent higher activity in patients in cohort B (51.7% overall RR with CBR of 86.2%, $p=0.034$). Among the 44 patients treated for *de novo* metastatic disease at diagnosis, 23 (52.2%) achieved an objective response, with CBR of 72.7%. In patients receiving palbociclib plus ET as second-line treatment, we observed three (5.9%) CRs and 13 (25.5%) PRs, for an overall RR of 31.3% (95% CI 20.3–45.0), with CBR of 64.7%. Again, both overall RR and CBR were higher in patients treated with palbociclib plus fulvestrant. Finally, no CRs were recorded in the population treated as third or subsequent line of treatment in both cohorts, and PR as best response was achieved in 25.7% of patients (95% CI 16.9–37.0), with CBR of 38.6%. As for previous hormonal treatment for metastatic disease, 12/37 (32.4%) patients pretreated with everolimus/exemestane and 16/45 (35.5%) patients previously given fulvestrant obtained an objective response.

After disease progression on palbociclib plus ET, 70.7% of patients had visceral involvement, 21.9% had non-visceral disease (nodal and/or skin and/or bone metastases) and 7.3% had bone-only disease. Overall, 28 patients (68.2%) received chemotherapy as further treatment, 21/29 in the palbociclib-letrozole group and 7/12 in the palbociclib–fulvestrant group: taxane-based therapy in 12 and four patients, capecitabine ± vinorelbine in five and two patients, anthracycline-based in four and one, in the two cohorts, respectively. Thirteen patients (31.7%) received subsequent ET which consisted of fulvestrant in nine patients (five in cohort A and four in cohort B) and everolimus plus exemestane in two patients in each group.

At a median follow-up of 24 months (range 6–32), median PFS was 13 months (range 3.2–25), without significant differences between the two cohorts (Table 2). When analysed according to treatment line, median PFS values were significantly prolonged when palbociclib-based therapy was administered in early treatment lines. Figure 2 shows PFS survival according to line of treatment (1–2 *versus* ⩾3) for cohort A and B patients calculated using the Kaplan–Meier method. In cohort A, median PFS was

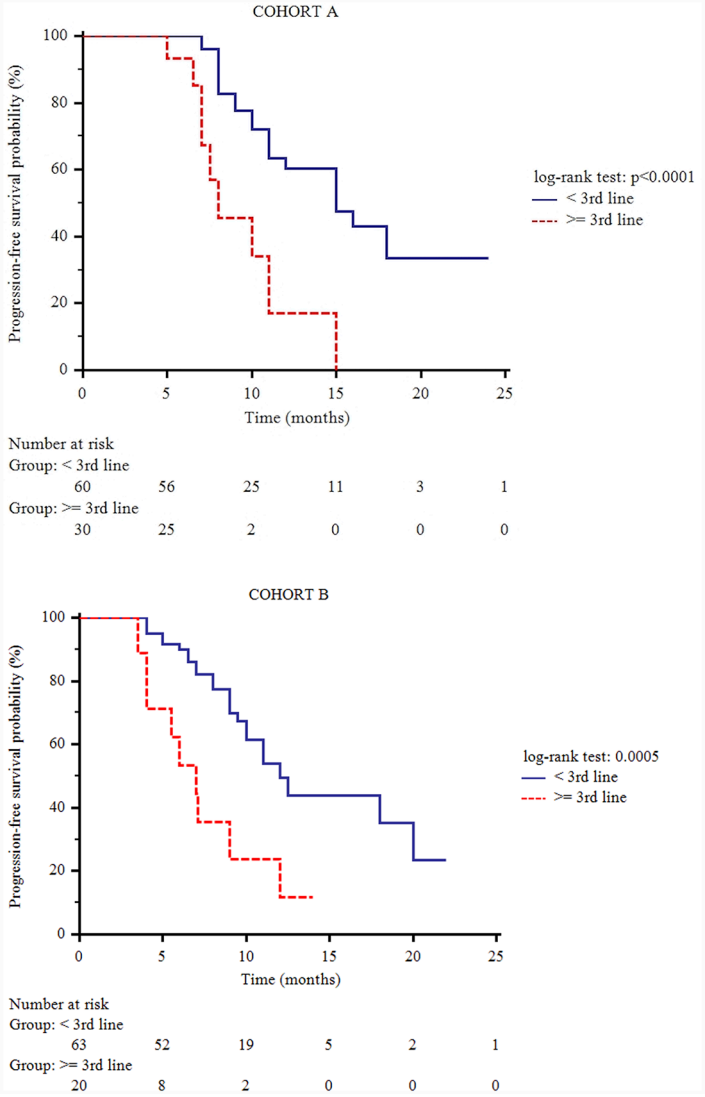


**Figure 2.** The figure shows progression-free survival according to line of treatment (1–2 *versus* ⩾3) for cohort A and B patients calculated using the Kaplan–Meier method.

14.9 months in patients treated with palbociclib as first or second line of treatment and 7.5 months for patients receiving palbociclib as third or further line of treatment (HR = 0.39, 95% CI, 0.12–0.69, $p<0.0001$). In cohort B, median PFS was 13.5 months in patients treated with palbociclib as first or second line of treatment and 6.0 months for patients receiving palbociclib as third or further line of treatment (HR = 0.41, 95% CI 0.24–0.85, $p=0.0005$).

Median OS in the whole population was 25 months (range 12.5–32.4+), ranging from 28.0 months in 1st line to 18.0 and 13.0 months in 2nd and subsequent lines, respectively.

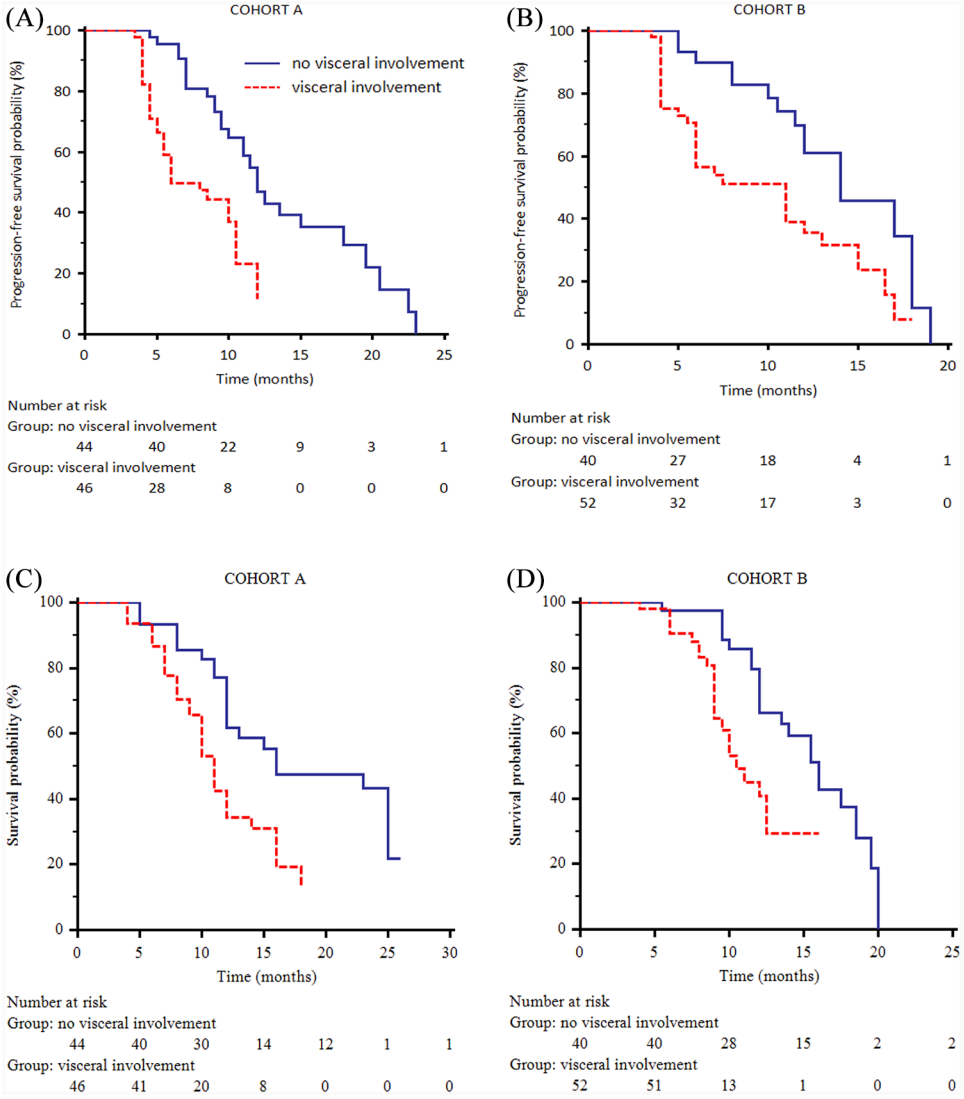


**Figure 3.** Progression-free survival and overall survival according to visceral involvement for cohort A and B calculated using the Kaplan–Meier method. (A) Progression-free survival for cohort A; (B) progression-free survival for cohort B; (C) overall survival for cohort A; and (D) overall survival for cohort B.

Figure 3 shows PFS and OS according to visceral involvement for cohort A and B. In cohort A, median PFS in patients with and without visceral involvement was 8.4 and 13.7 months (Figure 3A), respectively (HR = 2.73, 95% CI 1–55–4.81, $p < 0.0001$), and median OS in patients with and without visceral involvement was 12 and 18 months, respectively (HR = 2.35, 95%CI 1.23–4.56, p = 0.004) (Figure 3C). In cohort B, median PFS in patients with and without visceral involvement was 7.2 and 14.5 months, respectively (HR = 2.15, 95% CI 1.22–3.79, $p = 0056$) (Figure 3B), and median OS in patients with and without visceral involvement was 10 and 16 months, respectively (HR = 2.1, 95% CI 1.16–4.02, $p = 0.0030$) (Figure 3D).

A subgroup analysis was performed in order to identify variables of potential predictive and/or prognostic value. At univariate analysis, the DFI from adjuvant treatment (⩽24 months *versus* >24 months), the treatment line (1–2 *versus* ⩾3) and visceral involvement were significantly associated to a worse PFS (HR = 1.34, 95% CI 1.14–2.34, $p = 0.005$; HR = 3.12, 95% CI 1.95–5.01, $p < 0.001$ and HR = 2.47, 95% CI 1.56–3.98, $p = 0.004$, respectively), and the difference was maintained in multivariate analysis for the treatment line and the visceral involvement (HR = 2.18, 95% CI 1.74–3.34, $p < 0.001$ and HR = 1.23, 95% CI 1.15–2.93, $p = 0.003$, respectively). As regarding OS, at univariate analysis, the treatment line and visceral involvement were significantly

**Table 3.** Univariate and multivariate analysis for progression-free survival and overall survival.

| Variables | Progression-free survival | | | | Overall survival | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value |
| EGOG PS (0 *versus* 1–2) | 0.88 (0.67–1.23) | 0.455 | na | na | 0.94 (0.87–1.45) | 0.335 | na | na |
| Age (>65 *versus* ⩽65) | 0.83 (0.62–1.15) | 0.389 | na | na | 0.90 (0.73–2.34) | 0.229 | na | na |
| DFI from adjuvant treatment (>24 mo *versus* ⩽24 mo) | 1.34 (1.14–2.34) | 0.005* | 1.26 (0.91–2.97) | 0.256 | 1.84 (0.58–3.83) | 0.532 | na | na |
| No of metastatic sites (>2 *versus* ⩽2) | 1.29 (0.95–1.76) | 0.067 | na | na | 1.93 (0.88–3.34) | 0.421 | na | na |
| Visceral involvement (yes *versus* no) | 3.12 (1.95–5.01) | <0.001* | 2.18 (1.74–3.34) | <0.001* | 3.60 (2.67–6.34) | <0.001* | 3.68 (2.25–5.18) | <0.001* |
| Line of treatment (1–2 *versus* ⩾3) | 2.47 (1.56–3.98) | 0.004* | 1.23 (1.15–2.93) | 0.003* | 1.56 (1.07–2.47) | 0.004* | 1.86 (0.97–3.57) | 0.072 |
| Previous F500 treatment (yes *versus* no) | 0.93 (0.86–1.93) | 0.116 | na | na | 0.89 (0.83–2.08) | 0.341 | na | na |
| Previous EVE treatment (yes *versus* no) | 0.78 (0.54–1.39) | 0.505 | na | na | 0.95 (0.81–1.86) | 0.478 | na | na |
| Previous AI treatment (yes *versus* no) | 0.84 (0.45–1.34) | 0.876 | na | na | 0.92 (0.78–1.23) | 0.879 | na | na |
| Menopausal status (pre *versus* post) | 0.97 (0.75–2.45) | 0.372 | na | na | 0.94 (0.71–3.04) | 0.457 | na | na |

AI, aromatase inhibitor; CI, confidence interval; DFI, disease-free interval; EVE, everolimus; F500, fulvestrant 500 mg; mo, months; na, not applicable.
* indicates statistically significant differences ($p < 0.05$).

associated to a worse survival (HR = 3.60, 95% CI 2.67–6.34, $p < 0.001$ and HR = 1.56, 95% CI 1.07–2.47, $p = 0.004$) but only the presence of liver metastasis maintained its negative predictive role also in multivariate analysis (HR = 3.68, 95% CI 2.25–5.18, $p < 0.001$) (Table 3).

### *Treatment safety*

The median drug exposure time in the whole population was 14.4 months (range 6–24). Overall, treatment was well tolerated with good adherence in the outpatient setting. In particular, in cohort A, 52.1% of patients (47/90) delayed the treatment due to grade3–4 haematological toxicities while in cohort B palbociclib was delayed in 45 cases (44.5%); dose reductions were required in 14.5% (13 patients) and 19.5% (18 patients) in cohort A and B, respectively. In no cases treatment was interrupted due to severe drug-related AEs and no deaths occurred because of toxicity. As expected, the main toxicity observed was haematological, with neutropenia of any grade occurring in 151 patients (82.9%), being of grade 3–4 in 92 patients (50.5%); only 4.3% of patients experienced febrile neutropenia. Non-haematological toxicity was manageable with low-mild nausea/vomiting in 16.4% of patients, grade 1–2 alopecia in 12.7%; grade 3 fatigue was recorded in 12.2% and 8.6% of treated patients in cohort A and B, respectively. No substantial difference in incidence and severity of AEs was seen between the two groups of women receiving palbociclib combined with letrozole or fulvestrant

**Table 4.** Treatment toxicity in the whole population (182 evaluable patients).

| Toxicity | Cohort A (palbociclib + letrozole) | | | | Cohort B (palbociclib + fulvestrant) | | | | Overall | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* = 90 | | | | *n* = 92 | | | | *n* = 182 | | | |
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) |
| Haematological | | | | | | | | | | | | |
| Leukopenia | 4 (4.4) | 10 (11.1) | 12 (13.3) | – | 7 (7.6) | 8 (8.6) | 4 (4.3) | – | 11 (6.0) | 18 (9.8) | 16 (8.7) | – |
| Neutropenia* | 11 (12.2) | 14 (15.5) | 39 (43.3) | 8 (8.8) | 13 (14.1) | 21 (22.8) | 39 (38.0) | 6 (6.5) | 24 (13.1) | 35 (19.2) | 78 (42.8) | 14 (7.6) |
| Thrombocytopenia | 14 (15.5) | 2 (2.2) | 4 (4.4) | – | 8 (8.6) | 6 (6.5) | 1 (1.0) | – | 22 (12.0) | 8 (4.3) | 5 (2.7) | – |
| Anaemia | 15 (16.6) | 7 ( 7.7) | 3 (3.3) | – | 24 (26.0) | 5 (5.4) | – | – | 39 (21.4) | 12 (6.5) | 3 (1.6) | – |
| Non haematological | | | | | | | | | | | | |
| Nausea/vomiting | 10 (11.1) | 1 (1.1) | – | – | 16 (17.3) | 3 (3.2) | | | 26 (14.2) | 4 (2.1) | – | – |
| Mucositis | 9 (10) | 3 (3.3) | – | – | 5 (5.4) | 2 (2.1) | – | – | 14 (7.6) | 5 (2.7) | – | – |
| Diarrhoea | 6 (6.6) | 3 (3.3) | | – | 3 (3.2) | 1 (1.0) | – | – | 9 (4.9) | 4 (2.1) | – | |
| Constipation | 5 (5.5) | – | – | – | 11 (11.9) | – | – | – | 16 (8.7) | – | – | – |
| Abdominal pain | 3 (3.3) | – | – | – | 8 (8.6) | – | – | – | 11 (6.0) | – | – | – |
| Fatigue | 16 (17.7) | 12 (13.3) | 11 (12.2) | – | 22 (23.9) | 14 (15.2) | 8 (8.6) | – | 38 (20.8) | 26 (14.2) | 19 (10.4) | – |
| Anorexia | 13 (14.4) | – | – | – | 6 (6.5) | – | – | – | 19 (10.4) | – | – | – |
| Cutaneous toxicity | 5 (5.5) | – | – | – | 5 (5.4) | – | – | – | 10 (5.4) | – | – | – |
| Headache | 19 (21.1) | 1 (1.1) | – | – | 9 (9.7) | 4 (4.3) | – | – | 28 (15.3) | 5 (2.7) | – | – |
| Arthralgia | 9 (10.0) | 1 (1.1) | – | – | 25 (27.1) | 2 (2.1) | – | – | 34 (18.6) | 3 (1.6) | – | – |
| Alopecia | 11 (12.2) | 4 (4.4) | – | – | 5 (5.4) | 3 (3.2) | – | – | 16 (8.7) | 7 (3.8) | – | – |
| Hypertransaminasemia | 9 (10.0) | 2 (2.2) | 3 (3.3) | – | 5 (5.4) | 4 (4.3) | – | – | 14 (7.6) | 6 (3.2) | 3 (1.6) | – |

*n*, number.
*Febrile neutropenia in 8/182 patients (4.3%).

(Table 4). In addition, toxicities did not significantly differ when evaluated depending on line of treatment, age or predominant site of metastatic disease (data available upon request).

## Discussion

The combination of ET with CDK4/6 selective inhibitors, palbociclib, ribociclib and abemaciclib, has become the new standard of care for women affected with HR+/HER2− MBC on the basis of prolonged PFS and improved RR in both the first- and second-line setting shown in randomised phase III trials.[2–4,10] There is agreement among guideline recommendations that such an approach is the most effective treatment option in these patients, and the recently reported benefit in OS further reinforced the main role of CDK 4/6 inhibitors plus ET in the current treatment strategy.[23,26,27]

Palbociclib has been the first selective CDK4/6 inhibitor to be approved by the FDA and EMA for this setting of patients, and an increasing body of data from real-life studies has become available in recent years.[28] As known, the strength of real-world experiences is based on the possibility to verify the reproducibility of evidence-based data outside controlled randomised trials, providing support to physicians in the daily clinical practice.

In the reported study we could confirm the good performance of palbociclib combined with letrozole or fulvestrant in a large population of unselected patients with HR+/HER2− MBC. As expected, the median PFS and OS values in both cohorts were significantly prolonged when palbociclib-based therapy was administered as first-line treatment and confirmed the results of the reported clinical trials.[14–16] However, the median OS in the overall population was 25 months, that is lower than what expected from the recent update of PALOMA-3 trial, where a median OS value of 34.9 months was reported.[23] To explain this discrepancy, we must consider that our study has enrolled a considerable proportion of patients (64.5%) who had previously received one or two lines of ET and/or chemotherapy in a metastatic setting. On the other hand, it is interesting to note that women who received palbociclib plus ET in further lines still benefited from the combination, with a CBR of 64.7% and 38.6% as second- or third-line treatment, respectively. These findings, in line with other published real-life experiences in heavily pretreated patients, are in contrast with a subgroup analysis of the PALOMA-3 trial in which patients who received ⩾3 previous lines did not derive any benefit from the addition of palbociclib to ET.[16,29–33]

According to current guidelines, visceral crisis, defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease, is the only exception in which chemotherapy should be preferred to ET as first-line treatment in HR+/HER2− MBC.[2] Therefore, we wanted to analyse how PFS and OS correlated with visceral involvement both in cohort A and cohort B: at univariate and multivariate analysis, visceral involvement was significantly associated with a worse prognosis (HR = 2.18 $p < 0.001$ for PFS, HR = 3.68 $p < 0.001$ for OS), especially in case of liver metastases, confirming the negative prognostic role of such a disease presentation in HR-positive advanced breast cancer.[34,35] Similarly, ORR and CBR were significantly lower in women with visceral disease in a recently reported large retrospective analysis on 423 women treated with palbociclib plus ET; as in our experience, long-term outcomes were significantly more favourable in patients without visceral involvement.[36] These findings contrast with the evidence from pivotal trials showing that palbociclib had similar efficacy in nearly all pre-specified subgroups.[14,16]

On the other hand, we know from a recent update of the MONARCH-2 trial that abemaciclib combined with fulvestrant significantly improves OS in patients affected by HR-positive advanced disease with predominantly visceral involvement. In this randomised phase III trial, patients with visceral disease at baseline and primary resistance to prior ET experienced a numerically more pronounced OS effect relative to patients with non-visceral disease, bone-only or other metastatic sites.[27] Since a clinical trial that directly compares all the available CDK4/6 inhibitors (palbociclib *versus* ribociclib *versus* abemaciclib) in this difficult-to-treat subset of patients is unlikely to be designed, a meta-analysis would be helpful to provide indirect evidence supporting physicians' treatment choice in specific clinical presentations.

While the PALOMA-2 trial included only postmenopausal women, in the PALOMA-3 trial the menopausal status at study entry was considered a stratification factor. Overall, 79% of patients

were postmenopausal while 21% premenopausal or perimenopausal receiving goserelin. Median PFS for premenopausal women in the palbociclib arm was consistent with the significant PFS improvement in the same arm for postmenopausal women without statistical significant differences between the two groups. Also in our analysis, the menopausal status did not influence the clinical outcomes.

Additional recently published works assessed the real-world patterns of treatment and clinical outcomes among patients with ER+/HER2− MBC receiving palbociclib-based therapy in different settings.[37–42] Three of them are retrospective analyses which included patients who were treated with palbociclib plus letrozole as first-line ET or with palbociclib plus fulvestrant for disease progression after ET. In the IRIS trial the 12-month PFS rate was 85% at 18 months in the letrozole group, and 85% of patients remained progression free; the 12- and 18-month survival rates were 93% and 89%, respectively. In the fulvestrant group, the 6-month PFS rate was 95% and the 6-month OS rate was 98%.[37] In the FLATIRON study a median PFS of 21.9 months and an OS rate of 91.9% were reported.[38] Similar results have been reported in a single-centre cohort study on 70 patients treated upfront with palbociclib plus letrozole, with a median PFS of 26.4 months, without significant differences in women reducing palboclib dose due to toxicity.[39] In the RENATA study, a prospective analysis in the Latin American population, palbociclib was associated with AIs in 63.9% of patients, and with fulvestrant in the remaining. Results showed a mPFS of 36.7 months in first line and of 24.2 months in second line; the median OS in the entire population was not reached.[40] The MARIA study is an ongoing prospective, multicentre study that includes women treated in Italy and Germany initiating their first or second-line therapy with palbociclib in combination with an AIs or fulvestrant. The results of the interim analysis showed that the 6-, 12-, and 18-month PFS rate was 96%, 78%, and 64% in patients receiving palbociclib plus AI as first-line therapy, respectively. Among patients receiving palbociclib plus fulvestrant as first-line therapy, the 6-, 12-, and 18-month PFS rate was 91%, 64%, and 39%, respectively. For second-line therapy, the 6-, 12-, and 18-month PFS rate was 75%, 38%, 38% among palbociclib plus AI and 71%, 54%, and 45% for palbociclib plus fulvestrant.[41] Another a prospective multicentre real-world analysis in the USA and Canada population is ongoing (the POLARIS study) and the results are not available yet.[42]

As for treatment safety, our study confirms the tolerability of both the combinations in clinical practice, with data globally in line with the results in PALOMA-3 trial and in the available real-world experiences. No substantial differences in incidence and severity of AEs were seen between the two groups of women receiving palbociclib combined with letrozole or fulvestrant, and no increased toxicity was observed in patients >65 years compared with a younger population, in line with the recently reported data on a large geriatric population receiving palpociclib in a non-trial setting.[43] Nevertheless, we experienced fewer dose reductions (17% of patients in the whole population, most frequently due to neutropenia), compared with randomised phase III trials (36% and 34% of patients in PALOMA-2 and PALOMA-3, respectively) even if we had more cycle delays, as often happens in clinical practice. As previously reported, this did not seem to affect treatment effectiveness.[14–16,36,43,44]

The strength of the present experience is the prospective evaluation in a large cohort of unselected breast cancer patients of palbociclib plus ET combinations in a real-world setting with a long follow-up time. Our data also provide information concerning the prior treatment with fulvestrant and/or everolimus, confirming no detrimental effect of both the agents on palbociclib-treated patients. As known from the literature, inherent data are hardly available from randomised trials in this setting, while some suggestions have emerged from real-world studies, with mixed results. In two previous compassionate use programmes, no differences in median PFS were observed in patients receiving palbociclib following fulvestrant and/or everolimus.[45,46] This is consistent with our results: in the subgroup analysis, 32.4% of patients pretreated with everolimus/exemestane and 35.5% of patients previously treated with fulvestrant obtained an objective response, reinforcing recent suggestions that palbociclib could reverse the acquired resistance to ET.[9,47,48] A more recent trial on 60 everolimus-pretreated patients reported a median PFS of 5.8 months in the whole population and 6.4 months in 48% of patients also receiving fulvestrant as previous treatment line.[49] Conversely, a small experience in 29 patients pretreated with everolimus showed a CBR of 17.4% without overall RR, and a median PFS of only 2.9 months.[32]

These observations have been confirmed by the results of a multicentre retrospective analysis showing a statistically significant difference in terms of overall RR in women pretreated with everolimus/exemestane compared with those previously given fulvestrant.[36] Taken together, the available data suggest no detrimental effect of fulvestrant pretreatment on palbociclib-based therapy outcome and a less favourable impact in everolimus-pretreated patients. However, the observed differences across patient subgroups remain largely unexplained.

The long follow-up time of this study allowed us to evaluate treatment outcomes after disease progression on palbociclib plus ET: while 68% of patients were given chemotherapy as next-line treatment, 32% received subsequent ET, which consisted of fulvestrant or everolimus plus exemestane. Notwithstanding the restricted number of women experiencing disease progression over the study period, these observations are in line with recently reported data on a subgroup of patients enrolled in the TREnd trial, suggesting an ongoing benefit from a subsequent ET line after progression to CDK4–6-based regimens.[50]

Some limitations of our study should be acknowledged. First of all, a consistent percentage of enrolled patients received chemotherapy and/or ET before palbociclib-based combination with letrozole or fulvestrant so that the reported data may not be fully representative of current clinical practice, in which clinicians aim at prescribing these combinations earlier in the process. However, recent results from many clinical trials have substantially changed treatment algorithms, supporting the recommendation to adopt a sequence of all the available endocrine-based treatments and delay chemotherapy until occurrence of certain forms of endocrine resistance or visceral crisis.[48]

As an additional limitation, QoL was not prospectively evaluated in our population, thus we were not able to confirm the reported data and the more recent follow-up updates on such a relevant issue.[15,51–53]

Despite these limitations, the current study provides much needed insight into the real-world use of palbociclib plus ET in women with HR+/HER2-negative MBC, capturing detailed clinical, treatment and outcome data through a median follow-up period of 24 months which is, to our knowledge, the longest reported to date outside of clinical trials.

## Conclusion

Our findings confirm the results of randomised clinical trials and available real-world experiences published in the literature, further highlighting the benefit of palbociclib-based combinations in both early and later treatment lines, with a favourable safety profile. Treatment algorithms suggested by the official oncology guidelines currently support the use of new combinations of hormone therapies plus targeted agents in the first- or second-line setting in patients with HR+/HER2− disease without visceral crisis. Nevertheless, the optimal sequence strategy and its impact on disease outcome still remains a major debate, and several putative predictive biomarkers have so far failed the expectation for personalised treatment.[54] As new evidence accumulates, progressive changes in guideline recommendations are expected in the near future. Meanwhile, all patient-, disease and treatment-related factors (response to previous treatments, disease status and symptoms, safety and compliance issues, patient preference and attitudes) will have to be taken into account for an optimal personalised sequential strategy in daily clinical practice.

## Conflict of interest statement

The authors declare that there is no conflict of interest.

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