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REVIEW

Palbociclib in metastatic breast cancer: current evidence and real-life data

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Abstract

The purpose of this review is to summarize the background and latest evidence for the use of palbociclib, an oral, first-in-class, highly selective cyclin-dependent kinase 4/6 inhibitor, in advanced breast cancer, with a focus on some of the unanswered questions about the performance of this agent in clinical practice. The available clinical data from both controlled clinical trials and real-life experiences concerning palbociclib-based combinations in patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2–) metastatic disease, including patient-reported outcomes and subgroup analyses, have been reviewed and discussed. Palbociclib significantly improved progression-free survival and clinical benefit rates when added to letrozole in postmenopausal women as initial endocrine-based therapy, and it prolonged progression-free survival and overall survival when added to fulvestrant in women who progressed on previous endocrine therapy in randomized clinical trials. Tolerability profile was manageable, with neutropenia occurring most commonly, without detrimental impact on quality of life. Available data from real-life experiences confirm the good performance of palbociclib in unselected, heavily pretreated populations. Palbociclib in combination with endocrine therapy is a valuable emerging option for patients with HR+/HER2– advanced or metastatic breast cancer. Further investigation is needed to provide solutions for palbociclib resistance and to identify the best sequence to use for the best patient benefit with a minimal toxicity.

Keywords: metastatic breast cancer, palbociclib, real-life studies.

Citation

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Introduction

Breast cancer (BC) is the second most common cancer overall and the most common cancer in women. Although treatable, metastatic breast cancer (MBC) remains virtually an incurable disease with a median overall survival (OS) of 3 years and a 5-year OS of only 25%.[1] Approximately 70% of BC cases are hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2–). Sequential endocrine therapy (ET) is considered the mainstay treatment for premenopausal and postmenopausal women with HR+/HER2– MBC without extensive visceral involvement, according to all international guidelines.[2–4] However, the effectiveness of ET is limited by pre-existing endocrine resistance and by resistance acquired during treatment.[5] From a clinical point of view, primary endocrine resistance is defined as a relapse while on the first 2 years of adjuvant ET or disease progression (PD) within the first 6 months of first line ET for MBC. Secondary resistance occurs when a relapse happens after 2 years of adjuvant ET or a PD is evident after 6 months of ET for MBC.[2] These concepts have prompted the development of additional strategies and new classes of agents targeting other patterns of growth, to reverse or postpone ET resistance. Two different strategies are being pursued to improve the efficacy of ET, namely intensification of endocrine manipulations and cotargeting of ER with other molecular components of oncogenic signaling pathways mediating endocrine resistance.

Palbociclib, ribociclib,[6] and abemaciclib[7] have been approved in recent years for the treatment of endocrine-resistant MBC in combination with ET considering their efficacy in prolonging progression-free survival (PFS), increasing clinical benefit rate (CBR) and response rate (RR) in different clinical context and treatment lines.

These agents are orally available, highly selective inhibitors of CDK4 and CDK6, serine-threonine kinases that regulate the

cell cycle progression. In fact, when they are activated by the expression of D-type cyclins, they initiate the phosphorylation of retinoblastoma tumor suppressor protein (pRb) with subsequent release of transcription factors from the E2F family. These factors coordinate a gene expression program that is required for determining cell cycle progression, DNA replication, and mitosis.[8] CDK 4/6 inhibitors hamper the phosphorylation of CDK 4/6, leading to hypophosphorylation of pRb and hindering the activation of the transcription factors necessary for S-phase entry. They also determine an arrest of the progression of the cell cycle at the G1 phase, preventing DNA synthesis required for cellular replication.[9,10] The mechanisms of resistance to these molecules can derive from p16 hyperexpression (mediating intrinsic resistance), activation of alternative proliferative pathways such as mTOR and PI3K (acquired resistance), or deregulation of cyclin expression.[11]

This article aims to review the available clinical data from both controlled clinical trials and real-life experience with the use of palbociclib in MBC, because this drug was the first approved in Europe and many data regarding daily practice use are available in the literature. It is also the only CDK4/6 inhibitor for which recent data demonstrated an improvement on OS.[12–14]

Methods

In this narrative review, we describe and discuss the evidence from the phase III trials regarding palbociclib use in MBC, providing critical analysis of the specific settings of clinical interest. We also analyze the real-life studies available in the literature, focusing on data regarding the same populations addressed in the perspective trials. Our analysis also concentrates on the toxicity profile of the drug in unselected patients.

Pivotal clinical trials of palbociclib

In 2015, the randomized phase II PALOMA-1 trial defined for the first time the efficacy and activity of palbociclib. It enrolled 165 postmenopausal, treatment-naive patients with HR+/HER2– MBC to receive palbociclib plus letrozole *versus* letrozole alone. Half of the population had *de novo* metastatic disease, with visceral involvement in 44% of patients in the combination arm and 53% in the control arm. Only 15 and 14 patients in each arm had primary endocrine resistance according to the definition mentioned previously. Randomization was performed depending on disease site (visceral *versus* bone-only) and disease-free interval (DFI) from the end of adjuvant or neoadjuvant treatment to disease recurrence. The study met its primary endpoint with a PFS of 20.2 *versus* 10.2 months in the combination arm *versus* letrozole alone arm (hazard ratio [HR]=0.49; p=0.0004). Secondary endpoints also favored the letrozole-palbociclib arm with a greater CBR (81 *versus* 58%; p=0.0009), and higher RR (43 *versus* 33%; p=0.13). The median duration of response (DOR) was 20.3 months for the palbociclib plus letrozole group, and 11.1 months for the letrozole alone group. The combination treatment resulted in a statistically nonsignificant prolongation of OS *versus* control arm (37.5 *versus* 33.3 months; p=0.42). The most frequent G3-4 adverse events (AEs) in the combination arm were neutropenia (54%), leucopenia (19%), and fatigue (4%). No cases of febrile neutropenia or neutropenia-related infections were reported.[15] The promising results of PALOMA-1 led to further research to test the efficacy of palbociclib in phase III trials in different clinical settings (Table 1).

In 2016, the phase III PALOMA-2 study enrolled 666 postmenopausal, treatment-naïve women with HR+/HER2– MBC to receive palbociclib plus letrozole *versus* letrozole plus placebo. About 30% of patients had *de novo* stage IV disease, with visceral involvement in 50% and bone-only disease in about 20% of the cases. Half of them had already received adjuvant/neoadjuvant chemotherapy (CT) and 56% had received adjuvant ET (47 and 44% with tamoxifen, and 6.8 and 5.9% with letrozole in the combination and control arm, respectively). About 20% of patients in both arms had relapse ≤12 months from diagnosis. A randomization 2:1 was performed according to the site of disease (visceral *versus* nonvisceral) and DFI. The study met its primary endpoint, with an improvement of PFS in the combination arm (24.8 *versus* 14.5 months; p<0.001). Secondary endpoints also favored the palbociclib arm with a higher RR (42.1 *versus* 34.7%, p=0.06) and a greater CBR (84.9 *versus* 70.3%, p<0.001). Most common grade 3–4 AEs in the combination arm were neutropenia (66.4%), leucopenia (24.8%), anemia (5.4%), fatigue (1.8%), and febrile neutropenia (1.8%).[12] The study also evaluated patient-reported outcomes (PROs) using the Functional Assessment of Cancer Therapy (FACT)-Breast and EuroQOL 5 dimensions (EQ-5D) questionnaires. These results, published in a different paper, did not show clinically significant differences from baseline in the questionnaire scores, but significantly greater improvement in pain scores was observed in the palbociclib plus letrozole arm (–0.256 *versus* –0.098; p=0.0183). In both arms, patients who obtained a CBR to palbociclib had significantly reduced deterioration of FACT-Breast Total score *versus* patients with PD. No significant differences in FACT-Breast and EQ-5D index scores were observed in patients who developed neutropenia (Table 1).[16]

In the same year, the results of PALOMA-3, a phase III trial, were published.[13] The study randomized 521 women with HR+/HER2– MBC progressing to ET to receive fulvestrant plus palbociclib *versus* fulvestrant plus placebo. In the overall population, about 80% of patients were endocrine-sensitive to prior ET; 80% were postmenopausal and had a DFI>24 months; 25% had not received previous treatment for metastatic disease. Eighty-five percent had a metastatic disease with visceral involvement in 206 (59.4%) of cases in the experimental arm *versus* 105 (60.3%) in the control arm. A randomization 2:1 was performed depending on sensitivity to previous ET, menopausal status, and presence of visceral metastases. An analysis of PIK3CA mutation and oestrogen-receptor expression as possible biomarkers of response was

Table 1. Randomized trials with palbociclib in metastatic breast cancer (MBC) patients.

	PALOMA-1[15] N=165	PALOMA-2[16] N=666	PALOMA-3[13] N=521	TREND[18] N=115
Study design	Phase II Open label Randomized 1:1	Phase III Placebo controlled Double blind Randomized 2:1	Phase III Placebo controlled Double blind Randomized 2:1	Phase II Open label Randomized 1:1
Treatment line	First line	First line	Progressed on previous ET	Progressed on previous ET
Study arms	PAL+LET *versus* LET alone	PAL+LET *versus* LET+PBO	PAL+F500 *versus* F500+PBO	PAL alone *versus* PAL+prior ET
Primary endpoint	PFS 20.2 *versus* 10.2 mo (HR 0.49)	PFS 24.8 *versus* 14.5 mo (HR 0.58)	PFS 9.5 *versus* 4.6 mo (HR 0.46)	CBR 60 *versus* 54% (*p* 0.52)
Secondary endpoints	OS 37.5 *versus* 33.3 mo (HR 0.81)	OS NA	OS 34.9 *versus* 28.0 mo (HR 0.81)	PFS 6.5 *versus* 10.8 mo (HR 0.69)
Visceral metastases	N=80 mPFS 12.8 *versus* 7.4 mo (HR 0.55)	N=324 mPFS 19.3 *versus* 12.9 mo (HR 0.63)	N=311 mPFS 8.0 *versus* 3.5 mo (HR 0.47)	NA
Bone-only disease	N=29 mPFS NA *versus* 13.3 mo (HR 0.29)	N=151 mPFS NA *versus* 11.2 mo (HR 0.36)	N=124 mPFS 14.3 *versus* 9.2 mo (HR 0.63)	NA
Liver metastases	NA	N=121 mPFS 13.7 *versus* 8.4 mo (HR 0.62)	N=208 mPFS 7.5 *versus* 2.4 mo (HR 0.49)	NA
Pre/ perimenopausal status	None	None	N=108 mPFS 9.5 *versus* 5.6 mo (HR 0.50)	None
Postmenopausal status	100%	100%	N=413 mPFS 9.9 *versus* 3.9 mo (HR 0.45)	100%
Age <65 years	N=493* PAL+LET (N=310) *versus* LET alone (N=183) mPFS 22.0 *versus* 12.3 mo (HR 0.50)		N=392 F500+PAL (N=26) *versus* F500+PBO (N=131) mPFS 10.9 *versus* 5.4 mo (HR 0.59) §	NA
Age ≥65 years	N=338* PAL+LET (N=218) *versus* LET alone (N=120) mPFS 27.5 *versus* 16.4 mo (HR 0.49)		N=129 F500+PAL (N=86) *versus* F500+PBO (N=43) mPFS 14.9 *versus* 5.6 mo (HR 0.43) §	NA

*, joint analysis; §, approximate data; ABC, advanced breast cancer; CBR, clinical benefit rate; CI, confidence interval; F500, fulvestrant 500 mg; HR, hazard ratio; LET, letrozole; mo, months; mPFS, median progression-free survival; N, number; NA, not available; OS, overall survival; PAL, palbociclib; PBO, placebo.

performed in the overall population. The trial met its primary endpoint with an improvement in PFS for the fulvestrant plus palbociclib arm *versus* fulvestrant plus placebo arm (9.5 *versus* 4.6 months, $p<0.0001$, respectively). Secondary endpoints favored the combination arm with a higher RR (25.0 *versus* 11.1%, $p=0.0012$) and a greater CBR (64 *versus* 36%, $p<0.0001$) than the control arm. PIK3CA mutations and oestrogen-receptor expression did not affect the benefit of palbociclib treatment. The most common grade 3–4 AEs in the combination arm were neutropenia (62.0%), leukopenia

(25.2%), anemia (2.6%), thrombocytopenia (2.3%), and fatigue (2.0%). Febrile neutropenia was reported in 0.6% of patients in the experimental arm. Recently, an updated analysis showed a nonstatistically significant improvement in OS in the entire population (34.9 *versus* 28.0 months in the experimental arm *versus* the control arm, p=0.09). However, patients with a sensitivity to previous ET had a longer OS with palbociclib plus fulvestrant than with fulvestrant alone (39.7 *versus* 29.7 months, p=0.44).[14] The trial evaluated also PROs using the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30 version 3.0) and its breast cancer module (QLQ-BR23). The results from this analysis showed that patients receiving palbociclib had a significant improvement of pain and time to deterioration questionnaire scores (Table 1).[17]

In 2018, the results of the phase II of the TREND trial were released. In this study, 115 women with HR+/HER– MBC progressing on prior ET were randomized to receive palbociclib alone or in combination with the ongoing ET. The last ET was an aromatase inhibitor (AI) in 60 and 50% of patients in the combination arm and monotherapy arm, respectively, and fulvestrant in 38 and 50%, respectively. About 75% of patients had visceral metastasis, and 7% of patients had a bone-only disease. A randomization 1:1 was performed with the following prespecified stratification factors: number of previous ET lines (1 *versus* 2), duration of prior-line ET (≤6 *versus* >6 months), metastatic disease site (visceral *versus* nonvisceral), and treating center. The trial results were negative for its primary endpoint of CBR (54 *versus* 60%, p=0.52, for the combination arm *versus* the palbociclib alone arm, respectively). As for the secondary endpoints, median PFS was not statistically significant for the palbociclib arm (10.8 *versus* 6.5 months, p=0.12); however, a greater duration of CBR was obtained in the palbociclib arm (11.5 *versus* 6 months, p=0.0021). The most common grade 3–4 AEs in the combination arm were neutropenia (72%), leukopenia (38%), and mucositis (5%); those in the palbociclib monotherapy arm were neutropenia (70%) and leukopenia (33%) (Table 1).[18]

Subgroup analysis of pivotal clinical trials

Visceral and liver metastasis

Visceral metastases were highly prevalent in patients enrolled in the PALOMA studies (PALOMA-1: 48%, PALOMA-2: 48.6%; PALOMA-3: 58.3%) and in the TREND trial (76%). The most common site for visceral metastases was the liver (PALOMA-1: not specified; PALOMA-2: 37%; PALOMA-3: 67%; TREND: not specified), followed by the lung (PALOMA-3: 28%; PALOMA-1, PALOMA-2, and TREND: not specified).[19] Regarding the primary endpoint of the PALOMA trials, patients with visceral metastasis had a greater PFS with palbociclib than in the control arms (PALOMA-2: 19.3 *versus* 12.9 months, p<0.005; PALOMA-3: 8.0 *versus* 3.5 months, p=0.82). As for the secondary endpoints, RR favored the combination arms (PALOMA-2: 55.1 *versus* 40.0%, p=not reported; PALOMA-3: 28.6 *versus* 6.7%, p=not reported). Similarly, time to deterioration of quality of life (QoL) was delayed in the combination arms.[20] Response rate favored patients with lung metastases treated with palbociclib (PALOMA-3: 25 *versus* 11.6%, p=not reported). Patients with liver metastasis and treated with palbociclib had a greater PFS (PALOMA-2: 13.7 *versus* 8.4 months, p=not reported; PALOMA-3: 7.5 *versus* 2.4 months, p=not reported), RR (PALOMA-2: 41.3 *versus* 37.0%, p=not reported; PALOMA-3: 27.2 *versus* 3.8%, p=not reported), and time to treatment response (TTR) (PALOMA-3: 3.8 *versus* 5.6 months, p=not reported).

Bone-only disease

Patients with bone-only disease represented 18% of patients in the PALOMA-1 trial, 23% in PALOMA-2, 21% in PALOMA-3, and 8% in the TREND trial. A greater improvement in PFS was observed in the palbociclib arm (in PALOMA-1, HR=0.294, p=0.44; in the PALOMA-2 trial, 36.2 *versus* 11.2 months, p<0.0001; in PALOMA-3, 14.3 *versus* 9.2 months, p=0.0394; in TREND, not reported). No data are reported in each study regarding secondary endpoint results or QoL.

Menopausal status

In all trials, pre- and perimenopausal patients were made functionally menopausal by using goserelin for ovarian suppression before randomization. This hampers the drawing of conclusions regarding the primary and secondary endpoints. Besides, the PALOMA-3 trial is the only trial that clearly reported separate results for pre-/perimenopausal and postmenopausal patients. However, no differences were seen in PFS in the pre- or peri–menopausal patients (9.5 *versus* 5.6 months in the experimental and control arms, respectively, p=not reported) and in the postmenopausal group (9.9 *versus* 3.9 months, in the experimental and control arms, p=not reported).

Elderly

Elderly patients, defined as patients aging ≥65 years, represented about 46% of patients in the PALOMA-1 trial, 39% in PALOMA-2, and 25% in PALOMA-3. In the TREND trial, these data were not reported. A recent pooled analysis by Rugo and colleagues on elderly patients showed that, also in this subgroup, PFS was significantly improved in patients receiving palbociclib (in PALOMA 1–2, age 65–74: 27.5 *versus* 21.8 months, p=0.016; in PALOMA 1–2, age ≥75: not reached *versus* 10.9 months, p<0.001; in PALOMA-3, age 65–74: 16.1 *versus* 3.7 months, p<0.001; in PALOMA-3, age ≥75: 13.6 *versus* 7.4 months, p<0.18). Regarding AEs, older patients had higher incidence of anemia (age ≥75%: 43.4%; age 65–74: 29.9%; <65 age: 24.6%), thrombocytopenia (age ≥75%: 25.3%; age 65–74: 21.3%; <65 age: 17.6%), leukopenia (age ≥75%: 55.4%; age 65–74: 43.0%; <65 age: 47.9%), and neutropenia (age ≥75%: 90.4%; age 65–74: 76.9%; <65 age: 80.8%). However, the incidence of febrile

neutropenia was similar across all age groups (age ≥75%: 2.4%; age 65–74: 0.9%; <65 age: 1.2%).

In both PALOMA-2 and PALOMA-3 trials, elderly patients had a similar baseline health-related QoL scores (HRQoL) to younger ones. Palbociclib in addition to either fulvestrant or letrozole did not result in significant deterioration in well-being scale or total FACT-B scores. In the PALOMA-3 trial, in the 65–74 year-old group, the combination arm resulted in a statistically significant delay in deterioration in pain scores.[21]

Endocrine resistance

In the PALOMA-3 trial, sensitivity to previous ET was a prespecified stratifications factor. In the TREND trial, number of previous ET lines (1 *versus* 2) and duration of prior-line ET (≤6 *versus* >6 months) were prespecified stratifications factor.

In PALOMA-3, endocrine-sensitive patients were about 78% of the total population. In the TREND trial, about 70% of patients had received one ET line, and 30% had received more than two ET lines; 26% of patients had a duration of prior ET ≤6 months and 74% a duration >6 months.

According to primary endpoint, in PALOMA-3, patients with endocrine-sensitive disease had a greater PFS if treated with palbociclib (12.0 *versus* 4.2 months, $p<0.000001$) than endocrine-resistant patients (7.4 *versus* 5.1 months, $p=0.0537$); in the TREND trial, patients with a prior duration of ET line >6 months had similar CBR when treated with palbociclib (59 *versus* 63%, $p=0.68$) than patients with a duration of prior ET line ≤6 months (30 *versus* 55%, $p=0.19$). Regarding secondary endpoints, in the TREND trial, patients with a prior duration of ET line >6 months had a greater PFS than patients with a duration of prior ET line ≤6 months (HR 0.53, $p=0.02$). Similar AEs were reported in the two groups.

Oligometastatic disease versus widely metastatic disease

Patients with limited number and sites of metastasis account for 30% of PALOMA-2 and PALOMA-3. According to primary endpoints, in the PALOMA-2 trial, patients with oligometastatic disease had a similar PFS to plurimetastatic ones (HR 0.51 *versus* 0.61, *p*=not reported); the same results were reported in PALOMA-3 patients (*p* interaction=0.43). However, in the update analysis of PALOMA-3, a greater benefit in PFS was observed for patients with only one or two disease sites who were treated with palbociclib (13.4 *versus* 5.6 months, *p*=not reported).[20] No subgroup analysis regarding safety and QoL evaluation was performed.

Real-life studies

Among 21 real-life experiences with palbociclib-based combinations that are available in the literature (Table 2),[22–42] only 5 comprised a prospective design. Enrolled population, therapeutic line, and companion drug are highly heterogeneous. More than 6000 patients have been included in these studies.

Palbociclib in combination with letrozole or fulvestrant

Two trials[22,23] evaluated the combination of palbociclib with letrozole and one with fulvestrant.[24] In the remaining studies, palbociclib was administered in combination with different ETs that could be an AI, fulvestrant, tamoxifene, or others (megestrol).

The trial by Masuda and colleagues, which enrolled 42 Japanese patients, had 1-year PFS probability as the primary endpoint; among secondary endpoints were efficacy, activity, safety, and tolerability. In a subset of patients, an analysis of the pharmacokinetic (PK) profile and of the possible biomarkers of tumor sensitivity and/or resistance in tumor tissue samples (such as the Ki-67 index) was performed. Regarding the primary endpoint, the 1-year PFS probability was 75%, similar to the results of PALOMA-1 and PALOMA-2 trials; among secondary endpoints, mPFS and mOS were not reached, 40.5% had an ORR, 85.7% a disease control, and the 1-year survival probability was 92.2%. Health-related QoL data were not reported. From the subgroup analysis, great insight on the effect of patients' baseline characteristics can be noticed because patients with higher PFS had nonvisceral metastasis and *de novo* metastatic disease. In fact, patients with nonvisceral *versus* visceral metastasis evidenced a higher 1-year PFS (95.2 *versus* 51.8%, *p*=not reported, respectively) and a greater mPFS (not reached *versus* 16.7 months, *p*=not reported). A different probability of 1-year PFS was evident according to patient's DFI from the primary diagnosis: 60% if DFI ≤12 months, 79.3% if DFI >12 months, and 78.9% if *de novo* metastatic disease. Moreover, patients with a Ki-67 ≤20% had a higher PFS (not reached *versus* 16.7 months). In total, 59.5% of patients required at least a dose reduction; in these patients, mPSF was not reached *versus* 16.7 months in patients who did not have a dose reduction. Most of the toxicities were manageable by dose modifications and/or therapy support. Only three serious AEs were described (subarachnoid hemorrhage, febrile neutropenia, and cerebral hemorrhage). The PK analysis provided data similar to the non-Japanese population of PALOMA-1.[22]

In the trial by Stearns, 334 patients with MBC in an expanded-access study program (EAP) were analyzed. The primary endpoint was safety; secondary endpoints were efficacy and activity in the Canadian cohort of patients. For the first time, PROs and pain were evaluated using the EuroQol-5D (EQ-5D) questionnaire and the visual analogue scale (VAS). Toxicity was consistent with PALOMA-1 and PALOMA-2 trials. The general health status, QoL, and pain control were maintained during the treatment with minimal changes from baseline.[23]

A third trial by Du Rusquec and colleagues included 60 patients treated with fulvestrant plus palbociclib. Patients were

Table 2. Real-life studies with palbociclib in advanced breast cancer (ABC).

Author (Ref)	Pts N/ mean age	Postmenopausal status	Prior F500/ EVE	Treatment line	Combined drug	Metastatic sites	Outcome	Toxicity (any grade)	Toxicity (G3–G4)
Li et al.[33]*	1242/62.7	100%	12.4%/NA	1st: 37% 2nd: 32% 3rd: 19% 4th: 12%	NA	Liver 15.8% Lung 15.5% Bone and bone marrow 72.1%	Dose reduction rate: 6.3–9.6% at 1 mo 23.1–25.3% at 3 mo 29.1–31.5% at 6 mo 31.9–33.7% at 12 mo	NA	NA
Ban et al.[27]*	24/52.7	71%	70.8%/4.1%	>4	AI	Visceral and bone 58.3% Bone-only 29.1% Visceral 12.5%	SD 58.3% ORR 0% mPFS 4.8 mo mOS 11 mo	Neutropenia 75% Anemia 50% Thrombocytopenia 41.6% Nausea 12.5% Stomatitis 8.3% Epistaxis 4.1%	Neutropenia 66.6% Thrombocytopenia G3 12.5%
Bui et al.[36]*	46/67	85%	17%/12.5%	≥3 ET line 28%	F500 AI	Visceral 61% Lung 94% Liver 43% Brain or pleural 9%	mPFS 10 mo	NA	NA
Darden et al.[38§]	604/41	NA	NA	NA	AI 41.4% F500 58.6%	Visceral 51.3% No visceral 48.7%	Treatment satisfaction according to CTSQ	NA	NA
Dhakal et al.[28]*	23/68	95%	NA/100%	NA	NA	Visceral 83%	ORR 0% CRB 17.4% mPFS 2.9 mo mOS 19.8 mo	NA	NA
Du Rusquec et al.[24§]	60/61	NA	46.7%/100%	NA	F500 100%	Visceral 83.3% Bone-only 16.7%	PR 26.7% SD 45% PD 28.3%	Neutropenia 93.3% Anemia 65% Thrombocytopenia 55%	Neutropenia 73.4% Anemia G3 5.0% Thromocytopenia 11.6% Febrile neutropenia G4 1.7%

Table 2. (*Continued*)

Author (Ref)	Pts N/ mean age	Postmenopausal status	Prior F500/ EVE	Treatment line	Combined drug	Metastatic sites	Outcome	Toxicity (any grade)	Toxicity (G3–G4)
							mPFS 5.8 mo mOS NR	Febrile neutropenia 3.3% Fatigue 16.7% Nausea 3.3% Stomatitis 3.3% Hypertransaminasemia 1.7%	Fatigue 3.3% Stomatitis 1.7%
Gong et al.[34*]	100/ 61	86%	17%/ NA	1st–2nd:29% 3rd–4th: 52% ≥5th: 19%	LET 69% F500 17% Other 14%	NA	Dose modification 38% Dose changes 18.4%	Neutropenia 59.6% Anemia NA Thrombocytopenia 11.8% Fatigue 4.8% Mucositis 9.5% Acute kidney injury 2.4%	Neutropenia 54.8% Anemia G3 2.4% Thrombocytopenia G3 2.4% Fatigue G3 2.4% Mucositis G3 2.4% Pneumonitis G3 2.4% Septic shock 2.4%
Hoste et al.[25*]	82/ 67.1	100%	NA	≥4	LET 89% F500 3.7% TAM 2.4% Other AI 2.4% Megestrol 2.4%	Bone-only 37.8%	CBR 41.5% mPFS 3.17 mo	Neutropenia NR Anemia 2.8% Thrombocytopenia 8.3% Increased creatinine levels 2.8%	Neutropenia G3 66.7% Febrile neutropenia 2.8%
Kish et al.[32*]	763/ 64	NA	NA	1st: 39.5% 2nd: 15.7% 3th: 13.1% ≥4th: 31.7%	LET 80.2%	NA	NA	Neutropenia 74.6%	Neutropenia 48.1%

(Continued)

Table 2. (*Continued*)

Author (Ref)	Pts N/ mean age	Postmenopausal status	Prior F500/ EVE	Treatment line	Combined drug	Metastatic sites	Outcome	Toxicity (any grade)	Toxicity (G3–G4)
Masuda et al.[22§]	42/ 62.5	100%	0%	1st: 100%	LET 100%	Visceral 47.6% Nonvisceral 52.4% Bone-only 14.3%	1-year PFS 75% 1-year OS 92.9% mPFS and mOS NR ORR 40.5% Disease control 85.7%	Neutropenia 100% Leukopenia 71.4% Thrombocytopenia 26.2% Anemia 19% Stomatitis 73.8% Infections 23.8% Constipation 21.4% Rash 19% ALT/AST increase 19%/16.7%	Neutropenia 90.5% Leukopenia 50% Thrombocytopenia 2.4% Anemia 4.8% ALT/AST increase 9.5%/2.4%
Maurer et al.[30*]	34/ 59.2	100%	NA/ 82.3%	≥4	F500 23.5% TAM 3.0% AI 73.5%	Visceral 73.5% Bone-only 14.7% Other 11.8%	PR 9% SD 36.4% PD 52% CR 3% mPFS 3.1 mo mOS NR	Fatigue 55.9%	Fatigue G3/4 11.8% Neutropenia 76.5% Febrile neutropenia 2.9% Thrombocytopenia 11.8% Anemia G3 2.9%
Pizzuti et al.[37*]	423/ 60	79.7%	16.8%/ 19.8%	1st: 37.3% ≥2 (2–12): 62.7%	NA	Visceral 56.7% Bone-only 18.9%	ORR 31% CBR 52.7% CR 4.5% PR 26.5% SD 41.4% PD 27.6% mPFS 12 mo mOS 24 mo	Neutropenia 74.2% Anemia 28.9% Thrombocytopenia 22% Fatigue 43.5% Nausea/vomiting 14.2% Mucositis 7.1% Hypertransaminasemia 9.9%	Neutropenia 43.2% Anemia G3 2.4% Thrombocytopenia G3 2.8% Fatigue G3 2.1% Mucositis G3 0.2% Hypertransaminasemia 0.2%

Table 2. (*Continued*)

Author (Ref)	Pts N/ mean age	Postmenopausal status	Prior F500/ EVE	Treatment line	Combined drug	Metastatic sites	Outcome	Toxicity (any grade)	Toxicity (G3–G4)
Stearns et al.[23§]	334/ 61	100%	NA/ 36.1%	NA	LET 100%	Bone 78.1% Liver 35.9%	NA	Neutropenia 66.5% Leukopenia 19.8% Anemia 16.8% Thrombocytopenia 18% Fatigue 38% Nausea 22.5% Stomatitis 15.9% Arthralgia 12.3% Infection 25.4% Decreased appetite 11.1%	Neutropenia 54.5% Leukopenia 8.1% Anemia G3 3.9% Thrombocytopenia 3.6% Fatigue G3 4.2% Nausea G3 1.5% Arthralgia G3 0.6% Infection 3.3% Febrile neutropenia 2.1% Decreased appetite G3 0.6%
Watson et al.[35*]	64/ 62.5	80%	NA	1st: 56%	LET 62.5% F500 31% TAM 3% EXE 3%	Bone 72% Liver 39% Lung 36% Brain 6%	PR 17% SD 21% PD 33% mPFS 12 weeks	Neutropenia 95% Fatigue 43% Gastrointestinal 26% Infection 25% Anemia 11% Thromboembolic events 11.5%	Thromboembolic events G3 1.5% Febrile neutropenia 1.5% Thrombocytopenia G3 11%
Palumbo et al.[29§]	150/ 64	80%	Cohort A: 0/12% Cohort B: 43%/ 15%	1st: 26.6% 2nd: 28.6% 3rd: 17.3% ≥4th: 27.3%	LET: 43.3% (Cohort A) F500: 56.6% (Cohort B)	Visceral 46% (Cohort A) and 55% (Cohort B) Bone-only 17% (Cohort A) and 20% (Cohort B)	Cohort A: PR 32%, CBR 52%, mPFS 6.3 mo Cohort B: PR 25%, CBR 60%, mPFS 5.5 mo	Neutropenia 67% Anemia 52% Thrombocytopenia 34%	Neutropenia 35%

(*Continued*)

Table 2. (*Continued*)

Author (Ref)	Pts N/ mean age	Postmenopausal status	Prior F500/ EVE	Treatment line	Combined drug	Metastatic sites	Outcome	Toxicity (any grade)	Toxicity (G3–G4)
Taylor-Stokes et al.[31]*	652/ 65	87.4%	NA	1st: 57.7% 2nd: 34.8% ≥3rd: 7.5%	LET 55% F500 45%	Visceral 46.4% Nonvisceral 53.6% Bone-only 46.4%	LET group: PFS (12 mo=85%,24 mo=64%) OS (12 mo=95%,24 mo=90%) ORR 79.5% CBR 93.8% F500 group: PFS (12 mo=79.8%) OS (12 mo=87.9%) ORR 74% CBR 85.1%	NR	NR
Battisti et al.[26]*	118/ 59	82.2%	NA	≥4th: 96.6%	AI 48.3% F500 47.5% TAM 4.2%	Visceral 81.4% Bone-only 6.8%	CBR 47.5% ORR 15.8% CR 1% PR 14.8% SD 31.7% PD 52.7% mPFS 4.5 mo mOS 15.8 mo	Neutropenia 89.7% Anemia 66.9% Thrombocytopenia 50% Fatigue 53.4% Hypertransaminasemia 32.2% Diarrhea 7.6% Stomatitis 16.9% Skin rash 3.4% Nausea 19.5%	Neutropenia 56.8% Anemia 4.2% Thrombocytopenia 9.3% Fatigue 1.7% Hypertransaminasemia 5.1% Diarrhea 0.8% Stomatitis 0.8% Nausea 1.7% Febrile neutropenia 5.1%
Clifton et al.[39]*	605/57	100%	NA	1st: 46.8% 2nd: 20.7% ≥3rd: 32.6%	LET 58.2% F500 40% Other 1.8%	NA	PFS 344 days OS 882 days Dose reduction <65 yrs 35%;	NA	Neutropenic fever 2.1% Infection requiring antibiotic 19.3% Hospitalization 10.4%

Table 2. (*Continued*)

Author (Ref)	Pts N/ mean age	Postmenopausal status	Prior F500/ EVE	Treatment line	Combined drug	Metastatic sites	Outcome	Toxicity (any grade)	Toxicity (G3–G4)
							≥65 yrs 42.5% Dose delay <65 yrs 37.5%; ≥ 65 yrs 51.3%		
Xi j et al.[40]*	200/59.4	100%	NA	1st: 21% 2nd: 25% ≥3rd: 54%	LET 73.5% F500 25% ANA 1% TAM 0.5%	NA	PFS 1st line 20.7 m; 2nd line 12.8 mo; 3rd line 4.0 mo Dose reduction 29%	Neutropenia 47% Mucositis 4% Fatigue 3.5% Abscess 2% Nausea/vomiting 2% Diarrhea 1.5% Rash 1.5% Hypertransaminasemia 1.5% Neuropathy 1.5%	Neutropenia 41.5% Dose reductions 29%
Waller J et al.[41]*	162/60	91%	NA	1st: 65% 2nd: 31% ≥3rd: 4%	LET 65% F500 35%	Bone 79% Liver 19% Lung 22% Lymph nodes 21% Other 17%	CR 6% PR 60% SD≥24 weeks 21% SD<24 weeks 3% PD 3% 6 mo PFS 95% 6 mo OS 98% Dose reduction 77% Dose delay 15%	NA	NA
Varella L et al.[42]	411/53.5	NA	NA	1st: 35.8% 2nd: 26% 3rd: 12.9% ≥4th: 25.3%	LET 54.9% F500 38.4% Other 6.6%	Bone 52.8% Visceral 36.7% Lung 22% Lymph nodes 14.1% Other 4.6%	PFS 8.9 mo in LET group PFS 10.3 mo in F500 group OS not reached in LET group OS 24.5 mo in F500 group	Anemia Thrombocytopenia Pancytopenia Diarrhea Anorexia Dyspnea Mucositis Hypertransaminasemia Skin rash Nausea	Neutropenia 57.7%

*indicates retrospective trials; §indicates prospective trials; AEs, adverse events; AI, aromatase inhibitor; ANA, anastrozole; CBR, clinical benefit rate; CR, complete response; CTSQ, Cancer Therapy Satisfaction Questionnaire; ET, endocrine treatment; EVE, everolimus; F500, Fulvestrant 500 mg; LET, letrozole; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TAM, tamoxifen; yrs, years.

heavily pretreated with a median of 5 (range 1–14) previous treatment lines. All of them had already received everolimus, and 46.8% fulvestrant. As expected in advanced treatment lines, the median PFS was inferior to PALOMA-3 trial results (5.8 *versus* 9.5 months, respectively). However, in fulvestrant pretreated patients, this reduction was less pronounced (6.4 months). These data are in contrast with a subgroup analysis of the PALOMA-3 trial in which patients who received ≥3 lines of treatment did not derive any benefit from the addition of palbociclib to ET. Conversely, it is consistent with the TREND trial results, assuming that palbociclib could reverse the acquired resistance to ET. The median PFS was not influenced by the previous treatment with everolimus, and it was similar for patients with bone-only and visceral disease. Interestingly, it was possible to evaluate PFS in 40 patients receiving a subsequent treatment line (38 CT, 2 ET); the observed PFS of 3.3 months was similar to that described in the PALOMA-3 trial.[24]

Heavily pretreated patients

Six trials addressed palbociclib use in advance setting; in the first by Hoste and colleagues 82 MBC patients were enrolled within the compassionate-use program in Belgium (median number of prior systemic lines: 5.7, range 4–11). The primary endpoint was CBR for at least 6 months; the secondary endpoint was to evaluate all factors correlated with CBR including the following: prior everolumus/exemestane treatment; duration of prior ET; time between primary BC diagnosis and starting of palbociclib or time between first metastasis and starting palbociclib; age; use of CT before palbociclib; bone-only disease; dose reduction or delay of therapy; primary *versus* secondary metastasis. The study demonstrated a significant activity of palbociclib with a CBR of 41.5% and with 50% of patients being progression-free for more than 3.2 months. None of the investigated clinical variables could predict CBR. Safety data are consistent with the previous reported data with treatment delays or interruptions in 43.9% of patients.[25]

The second trial by Battisti and colleagues enrolled 118 patients treated in >4th line, representing the most extensive analysis in this setting of patients. The primary aim of the trial was to assess the efficacy and safety of palbociclib in combination with ET; secondary endpoints were ORR, PFS, and OS. Efficacy data were in agreement with the previously cited work, with a CBR of 47.5% and an ORR of 15.8%. About 14.8% of patients obtained a PR, 1% a CR, 31.7% a SD, and 52.7% a PD. Median PFS was 4.5 months in the whole population but patients who received palbociclib as earlier line (<3 prior CT lines) had higher PFS (5.9 *versus* 4.3 months, p=0.159). Moreover, patients with bone-only and endocrine-sensitive disease had a longer PFS (11 *versus* 4.4 months, p=0.024, and 5.9 *versus* 3.7 months, p=0.055, respectively). Median OS was 15.8 months, but it was longer in patients who received <3 prior CT lines (not reached *versus* 13.4 months, p=0.016), with bone-only disease (not reached *versus* 15.2 months, p=0.048) and with a progression-free interval on their previous ET greater than 6 months (18.1 *versus* 14.4 months, p=0.052). In 80.7% of patients, a dose reduction due to hematological toxicity was required, and the dose delay involved 49.1% of patients.[26]

The remaining studies have smaller sample sizes. Ban and colleagues enrolled 24 patients with a primary endpoint of activity and secondary endpoint of efficacy and safety. A SD was obtained in 58.3% of patients; No objective response was observed. Median PFS was 4.8 months and mOS was 11 months were favorable with the mPFS and mOS expected with single-agent CT in a similar cohort of patients. The toxicity profile was favorable, with hematological toxicities being the most commonly reported. The only difference from clinical trial was the incidence of grade 3 thrombocytopenia due to the great exposure to previous CT in the population.[27] The study by Dhakal and colleagues enrolled 23 everolimus pretreated patients to receive palbociclib in combination with fulvestrant or AI according to physician's choice. In this trial, a very reduced mPFS and CBR were observed in contrast with the PALOMA-3 trial (2.9 months and 17.4%, respectively), confirming a greater benefit of palbociclib in earlier lines of treatments. However, in the overall population, mOS was 19.8 months. No safety data were reported.[28]

A study performed by Palumbo and colleagues enrolled 150 postmenopausal patients divided into two cohorts: the cohort A (65 patients) received palbociclib plus letrozole, whereas the cohort B (85 patients) received palbociclib plus fulvestrant. The primary endpoint was CBR, secondary endpoints were PFS and safety. In cohort A, a CBR of 52% and a mPFS of 6.3 months were observed; whereas, in cohort B, the CBR was 60% and PFS 5.5 months. However, PFS was better in patients treated as ≤3rd *versus* >3rd line (p=0.003 in cohort A and p=0.002 in cohort B) suggesting a better outcome for earlier use of palbociclib. Safety profile was similar to the other real-life experiences with a prevalence of neutropenia (grade 1–2 in 67% and grade 3–4 in 35% of patients in both cohorts).[29] A smaller trial by Maurer and colleagues reported the activity and safety of palbociclib in combination with any ET administered in 34 heavily pretreated patients within a compassionate use program in Belgium. The objectives of the study were activity, in terms of ORR by RECIST and PERCIST criteria, and disease control rate (DCR) at 12 and 24 weeks, efficacy in terms of OS and PFS, and safety. Most patients had already been treated with ET (76.5%) or with mTOR inhibitors (82.4%). In the group of patients evaluable with RECIST (N=14), PR was 7.1%, SD was 64.3%, and PD was 28.6%. In the group evaluable by PERCIST (N=19), CR was 5.3%, PR 10.5%, SD 15.8%, and PD 68.4%. Irrespective of the type of response assessment, DCR was 52.9% at week 12 and 24.4% at week 24. Median PFS was 3.1 months in the overall cohort; no differences in PFS was observed between mTOR inhibitor-pretreated and naïve patients. Median OS was not reached. The most common AEs were neutropenia (76.5%); febrile neutropenia occurred only in one patient. Dose reductions and/or interruptions occurred in 29.4% of patients.[30]

Poor ECOG PS patients

A trial by Taylor–Stokes and colleagues analyzed 652 patients treated with palbociclib and F500 or letrozole, among which 17.4% had an ECOG PS >1. Such a population is usually underrepresented in clinical trials. The endpoints included ORR, CBR, and PFS rates at 6, 12, 18, and 24 months. The results were very similar to the PALOMA-3 trial. In particular, in the palbociclib plus AI group, the 12-month progression-free rate was 84.1%; 64.3% remained progression-free at 24 months. The survival rate at 12 months was 95 and 90% at 24 months; the ORR was 79.5%, and the CBR was 93.8%. In the palbociclib plus fulvestrant group, the 12-month progression-free rate was 79.8%, 89.6% for first-line patients, and 73.7% in second- or later-line patients. The survival rate was 87.9% overall, 91.1% for first-line patients, and 85.9% for second- or later-line patients; the ORR was 74%, and the CBR 93.2%. Dose reduction rates were lower than in PALOMA 2 and 3 trials, involving only 14.4% of patients, whereas 19.9% discontinued the treatment due to PD. No toxicity data were reported.[31]

Safety and dose modifications

In a recent retrospective study by Kish and colleagues, data from a US database of 763 patients treated with palbociclib and ET were included. This is the first trial in which patients' characteristics, dosing, and treatment patterns have been analyzed. Notably, 612 patients received letrozole. No efficacy data have been reported. Dose reductions were reported in 20.1%, mainly occurring within the first 6 months of treatment and about 69% within the first two cycles. Of note, five patients had an increase in their dose (three dose increases occurred in patients starting at 75 or 100 mg, and two dose increases in patients starting at 125 mg).[32]

Another trial by Li and colleagues evaluated the dosing patterns and their associated impacts on treatment cost in an US population. During the index period, across the first four lines of treatment, dose reduction rates were 31.9–33.7% and dose reductions/interruption rates were 63.5–80.9%. Those who experienced dose reduction or interruptions did so within the first cycles of treatment. Patients who experienced a dose interruption with an average length of 8.8 days (range 7.5–9.7) were older than patients who did not need dose interruptions (62.1 *versus* 60.7 years; $p<0.05$). Dose reductions were significantly lower with prior use of anastrozole. The authors concluded that the high proportion of dose changes may lead to drug wastage and incremental costs for payers.[33]

Another trial by Gong and colleagues evaluated the toxicities observed with palbociclib in combination with ET and the resulting dose modifications and prescriber's preferences in modifying the drug dose. A total of 100 patients were included: 38% of them required dose modifications, most of which occurred during the first two cycles of therapy (81.6%). A smaller proportion of patients (10.6%) required dose modifications during cycles 3–4, and three patients (7.8%) needed changes in palbociclib dose beyond cycle 5. The most common reason for modifications in dose and schedule was toxicity, being grade 3–4 neutropenia the most common (54.8%) followed by grade 3–4 thrombocytopenia (11.8%), grade 2–3 mucositis (9.5%), and grade 2–3 fatigue (4.8%). Consistently with Rugo and colleagues,[21] age >65 did not affect treatment compliance.[34]

In a trial by Watson and colleagues of palbociclib and ET, 28 patients on 64 had treatment deferrals due to neutropenia, with a median time to first deferral of 4 weeks. Fifteen patients required dose adjustments; however, there was no association with an increased risk of progressive disease. For the first time, a high incidence of thromboembolic events was reported (11 *versus* 2% of PALOMA-3 trial). However, it is difficult to establish whether these events were drug related or disease related.[35]

Additional studies[36,37] are summarized in Table 2 and are consistent with the data previously reported in activity and safety. Interestingly, Pizzuti and colleagues reported a reduced ORR in patients with prior exposure to everolimus/exemestane (16.7 *versus* 34.5%, respectively, $p=0.002$) and a higher ORR and CBR in patients without visceral metastasis ($p=0.0004$ and 0.04, no data available). On the other hand, no statistically significant difference in ORR was observed according to previous fulvestrant exposure (31.7 *versus* 29.6%, $p=0.72$) and menopausal status. The study also supports the use of palbociclib in an elderly population (≥75 years) with no differences in the toxicity profile depending on treatment line and patients' age.[37]

Quality of life

In the study by Darden and colleagues, the treatment satisfaction of patients receiving palbociclib was evaluated using the Cancer Therapy Satisfaction Questionnaire (CTSQ), a validated instrument that measures patients' expectations and satisfactions with treatments. It was developed for the use in patients with any type of cancer regardless of the stage and type of treatment used.[43] The trial was a web-based survey including 604 patients from six countries (the United States, Canada, Germany, Netherlands, Argentina, and Denmark). The questionnaire was translated into the appropriate native language for each country. They found that more than 96% of patients enrolled met or exceeded their expectations regarding the treatment. These results were not influenced by the type of the combination treatment (AI or fulvestrant) or by visceral involvement.[38]

Conclusions

The introduction of CDK 4/6 inhibitors in combination with ET is considered the most important advance in recent years for the management of luminal MBC.[2] Palbociclib is the first member of the CDK4/6 inhibitors entering the clinical arena. With more than a 10-month improvement in mPFS when added to letrozole or fuvestrant, it represents one of the

best steps forward in the treatment of luminal breast cancer. The significant improvement in mPFS demonstrated across the PALOMA trials occurred in all subgroups, regardless of stratification factors or other baseline characteristics. In addition, a recent update suggests that the use of palbociclib plus fulvestrant provides a substantial survival benefit, especially in patients with disease recurrence during adjuvant ET for at least 2 years, or in patients who received ET for metastatic disease with a high CBR.[14] However, despite improved clinical outcomes, PD eventually occurs, and women with HR+ MBC require multiple lines of therapy. Identifying response predictors will be essential for rational use of the drug to avoid unnecessary toxicity and costs.

Beyond results from randomized clinical trials, on which guidelines are based, clinicians in daily practice encounter a wide array of clinical presentations. With this in mind, the increasing body of data from real-world studies provide important information regarding the performance of the drug. Collectively, the real-life studies confirm the results of the randomized trials, as palbociclib plus ET appear to be effective and safe also in unselected patients. The primary objectives of these trials were activity and efficacy of the palbociclib combinations. Secondary endpoints were toxicity and, in one trial,[38] patients' treatment satisfaction according to CTSQ. As expected, activity and efficacy were related to the line of treatment in which palbociclib was used; trials enrolling heavily pretreated patients reported a low activity and efficacy of the combination. As in the phase II–III trials, no clinical subgroup depending on age, menopausal status, endocrine resistance, pretreatment, disease site, and its extension has been found to be related with a specific outcome.

Further, a systematic approach will likely be necessary to better identify the range of biomarkers associated with response or resistance, as well as the optimal sequence to use for the best benefit in each patient.

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