Original article

Palbociclib combined with endocrine therapy in heavily pretreated HR+/HER2- advanced breast cancer patients: Results from the compassionate use program in Spain (PALBOCOMP)

Luis Manso [a], Cristina Hernando [b], María Galán [c], Mafalda Oliveira [d], Miguel A. Cabrera [e], Raquel Bratos [f], César A. Rodríguez [g], Manuel Ruiz-Borrego [h], Salvador Blanch [i], Antonio Llombart-Cussac [j], Juan I. Delgado-Mingorance [k], Iñaki Álvarez-Busto [l], Isabel Gallegos [m], Lucía González-Cortijo [n], Serafín Morales [o], Elena Aguirre [p], Blanca A. Hernando [q], Ana Ballesteros [r], José E. Alés-Martínez [s], Cristina Reboredo [t], Amparo Oltra [u], María González-Cao [v], Marta Santisteban [w], Diego Malón [x], Isabel Echeverría [y], Elisa García-Garre [z], Estela Vega [aa], Sònia Servitja [ab], Raquel Andrés [ac], Carlos E. Robles [ad], Rafael López [ae], Elena Galve [af], María J. Echarri [ag], Marta Legeren [ah], Fernando Moreno [ai], *

[a] Hospital Universitario 12 de Octubre, Madrid, Spain
[b] Hospital Clínico Universitario de Valencia, Valencia, Spain
[c] Hospital Universitario Son Llàtzer, Palma, Spain
[d] Hospital Universitari Vall D'Hebron, Barcelona, Spain
[e] Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain
[f] Hospital MD Anderson Cancer Center, Madrid, Spain
[g] Hospital Universitario de Salamanca, Madrid, Spain
[h] Hospital Universitario Virgen del Rocío, Sevilla, Spain
[i] Instituto Valenciano de Oncología, Valencia, Spain
[j] Hospital Arnau de Vilanova, Valencia, Spain
[k] Hospital Universitario de Badajoz, Badajoz, Spain
[l] Hospital Universitario Miguel Servet, Zaragoza, Spain
[m] Hospital General de Segovia, Segovia, Spain
[n] Hospital Universitario Quirónsalud, Madrid, Spain
[o] Hospital Universitario Arnau de Vilanova, Lleida, Spain
[p] Hospital Quirónsalud, Zaragoza, Spain
[q] Hospital Universitario de Burgos, Burgos, Spain
[r] Hospital Universitario de La Princesa, Madrid, Spain
[s] Hospital Nuestra Señora de Sonsoles, Ávila, Spain
[t] Complejo Hospitalario Universitario A Coruña, A Coruña, Spain
[u] Hospital Virgen de Los Lirios, Alcoy, Alicante, Spain
[v] Hospital Universitario Dexeus, Barcelona, Spain
[w] Clínica Universidad de Navarra, Pamplona, Spain
[x] Hospital Universitario de Fuenlabrada, Madrid, Spain
[y] Hospital General Universitario Gregorio Marañón, Madrid, Spain
[z] Hospital General Universitario Morales Meseguer, Murcia, Spain
[aa] Hospital Universitario HM Sanchinarro, Madrid, Spain
[ab] Hospital Del Mar, Barcelona, Spain
[ac] Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain
[ad] Hospital Universitario Virgen de Valme, Sevilla, Spain
[ae] Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain
[af] Hospital Universitario de Basurto, Bilbao, Spain
[ag] Hospital Universitario Severo Ochoa, Madrid, Spain
[ah] Hospital Universitario Clínico San Cecilio, Granada, Spain
[ai] Hospital Clínico San Carlos, Madrid, Spain

* Corresponding author. Department of Oncology, Hospital Clínico San Carlos, IDISSC, C/ Profesor Martín Lagos S/N, 28040 Madrid, Spain ORCID: 0000-0001-8933-0687
E-mail address: fmorenoa@salud.madrid.org (F. Moreno).

A B S T R A C T

Background: This study evaluated efficacy and safety of palbociclib, a CDK4/6 inhibitor, in heavily-pretreated hormone receptor-positive and human epidermal growth factor receptor 2-negative (HR$^+$/HER2$^-$) metastatic breast cancer (mBC) patients during the compassionate use program in Spain from February 2015 to November 2017.
Patients and methods: Patient data were collected retrospectively from 35 hospitals in Spain. Patients with HR$^+$/HER2$^-$ mBC who had progressed on ≥4 treatments for advanced disease were eligible.
Results: A total of 219 patients received palbociclib in combination with aromatase inhibitors (110; 50.2%), fulvestrant (87; 39.7%), tamoxifen (8; 3.6%) or as single agent (10; 4.6%). Mean age of the patients was 58 years; 31 patients (16.1%) were premenopausal and 162 (83.9%) were postmenopausal at the beginning of treatment with palbociclib. Patients had received a median of 3 previous lines of endocrine therapy (ET) for advanced disease. Real-world tumor response (rwTR) and clinical benefit rate were 5.9% (n = 13) and 46.2% (n = 101), respectively. The median real world progression-free survival (rwPFS) was 6.0 months (95% CI 5.7—7.0) and the median overall survival was 19.0 months (95% CI 16.4—21.7). Subgroup analysis revealed a significant difference in median rwPFS in patients treated with palbociclib plus fulvestrant depending on the duration of prior treatment with fulvestrant monotherapy (>6 versus ≤6 months; HR 1.93, 95% CI 1.37—2.73, p < 0.001). The most frequently reported toxicities were neutropenia, asthenia, thrombopenia and anemia.
Conclusions: Palbociclib can be an effective and safe treatment option in patients with heavily pretreated endocrine-sensitive mBC, especially in those with longer PFS to previous ET.

1. Introduction

Endocrine therapy (ET) is the preferred option for hormone receptor-positive and human epidermal growth factor receptor 2-negative (HR$^+$/HER2$^-$) metastatic breast cancer (mBC) patients [1]. Despite the effectivity of ET, it is often associated with the appearance of acquired resistance after exposure to one or more lines of treatment [2]. Some resistance is driven from alterations of the cell cycle due to upregulation of the cyclin pathway [3,4]. Palbociclib is a small molecule with highly specific and selective inhibitory activity against CDK4 and CDK6, and its therapeutic potential for HR$^+$/HER2$^-$ mBC has been extensively studied in the last decade [5]. A synergistic anti-tumor activity between palbociclib and ET was initially observed in HR$^+$ breast cancer cell lines [6]. In February 2015 palbociclib (Ibrance®, Pfizer) in combination with letrozole received accelerated approval by the US Federal Drug Administration (FDA) [7,8], and in November 2016 the European Medicine Agency (EMA) granted regular approval to palbociclib for HR$^+$/HER2$^-$ mBC patients in combination with an aromatase inhibitors (AIs) as a first line treatment and with fulvestrant in those who had received prior hormone therapy [9].

Although palbociclib has shown activity as single agent in endocrine-resistant populations [10], the combination of palbociclib with ET significantly increases progression-free survival (PFS) compared to first- and second-line ET in HR$^+$/HER2$^-$ mBC. In postmenopausal women, the PALOMA-2 study showed that the addition of palbociclib to letrozole had a median PFS of 24.8 months compared to 14.5 months for letrozole alone (HR 0.58; 95% CI 0.46—0.72, p < 0.001) [11]. The PALOMA-3 trial showed that, after progression to previous ET, palbociclib and fulvestrant increased PFS compared to fulvestrant alone (9.5 vs. 4.6 months; HR 0.46; 95% CI 0.36—0.59, p < 0.0001) in pre and postmenopausal women [12,13]. These studies confirmed that the benefit of palbociclib associated with ET is independent of age, functional status, location of metastases, previous ET and relapse-free interval from adjuvant therapy.

Palbociclib toxicity is predictable, particularly asymptomatic neutropenia manageable with delays and/or dose reductions [14]. In addition to neutropenia, frequent adverse effects of palbociclib reported in the clinical trials are leukopenia, fatigue, and nausea [11,12,15].

Palbociclib was marketed in Spain in November 2017, but a compassionate use (CU) program was underway since February 2015. This program allowed access to the drug to approximately 400 patients with HR$^+$/HER2$^-$ mBC treated with at least 4 lines of prior therapy for advanced disease. Here, we report the results of efficacy and safety of palbociclib combined with fulvestrant, AIs, or tamoxifen in this patient population.

2. Methods

The CU program for palbociclib was implemented in 35 public and private hospitals throughout Spain and included patients between January 2015 and November 2017. Only those centers that treated 2 or more patients with palbociclib in the CU program were offered participation in PALBOCOMP. All patients provided signed informed consent and ethical approval was given by the Biomedical Research Foundation of the Hospital Clínico San Carlos (Madrid, Spain). Patient data were obtained retrospectively from the clinical history. This study was registered in ClinicalTrials.gov with identifier NCT04109261.

The patients included in the CU program were women diagnosed with HR$^+$/HER2$^-$ mBC who had received at least 4 previous standard treatments for mBC and were not eligible to receive palbociclib in a clinical trial. Patients who received a combination of palbociclib with ET despite previous resistance to the same ET were eligible. Other inclusion criteria were: absolute neutrophil count ≥1500/mm^3 (1.5 × 10^9/L); platelet count ≥100,000/mm^3 (100 × 10^9/L); hemoglobin ≥9 g/dL; serum creatinine ≤1.5 x upper limit of normal (ULN) or creatinine clearance ≥60 mL/min; total serum bilirubin ≤1.5 x ULN (≤3.0 x ULN if Gilbert's disease); aspartate transaminase and/or alanine transaminase ≤3 x ULN (≤5.0 x ULN if liver metastasis); and alkaline phosphatase ≤2.5 x ULN (≤5.0 x ULN if liver or bone metastasis).

Exclusion criteria were major surgery, chemotherapy, radiotherapy, administration of investigational drugs or any active cancer therapy during the two weeks prior to the start of treatment; previous treatment with radiotherapy on ≥25% of the bone
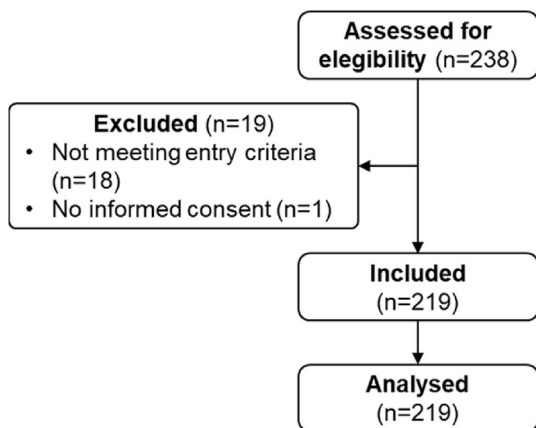
Fig. 1. Consort diagram.

marrow; QTc >480 ms, personal or family history of long or short QT syndrome, Brugada syndrome, or a history of QT interval prolongation or Torsade de Pointes (TdP) tachycardia; history during the 6 months prior to the start of treatment of myocardial infarction, unstable angina, grade ≥2 arrhythmias according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0), atrial fibrillation, coronary or peripheral arterial bypass, symptomatic congestive heart failure, stroke or pulmonary thromboembolism; known hypersensitivity to palbociclib; or current or recent suicidal ideation or behavior.

Palbociclib was administered orally at an initial dose of 125 mg

daily for 21 consecutive days, followed by 7 days off-period (28-day cycle).

The primary endpoints of this study were real-world progression free survival (rwPFS), real-world tumor response (rwTR) and duration of response to palbociclib in patients included in the CU program. The rwPFS time frame was considered from start of treatment to death, disease progression, or end of study. rwTR was defined as complete response or partial response, based on treating clinician's assessment of radiological evidence for change in burden of disease over the course of treatment.

The secondary endpoints were the assessment of the safety profile of palbociclib and overall survival (OS). To study the safety profile, all adverse events (AEs) identified since the start of treatment with palbociclib and related to the drug were collected. AEs were classified according to CTC-AE v4. The safety assessment was based on the frequency and severity of AEs.

As data from the CU program were collected retrospectively, all the statistical analyses were descriptive. All patients treated with palbociclib who met all the inclusion criteria and none of the exclusion criteria were included for analysis. Survival analysis was carried out using Kaplan-Meier curves. A Cox regression model was applied to find independent variables associated with OS or rwPFS between the groups. Hazard ratios with 95% confidence intervals were reported.

3. Results

A total of 238 patients were initially evaluated for the CU program but only 219 were included, as 18 did not meet inclusion criteria and one did not sign informed consent (Fig. 1). The

Table 1
Characteristics of the patients.

	n = 219
Age, years, mean (range)	58.0 (33–80)
Age at initial diagnosis, years, mean (range)	46.7 (27–84)
Stage at initial diagnosis (N = 214), N (%)	
I-III	162 (75.7)
IV	52 (24.3)
Sites of metastatic disease, N (%)	
Visceral	104 (47.5)
Hepatic	47 (21.5)
Lung	51 (23.3)
Brain	5 (2.3)
Other	49 (22.4)
Hormone receptor status at initial diagnosis, N (%)	
Estrogen receptor positive	199 (90.9)
Progesterone receptor positive	174 (79.5)
Prior lines of chemotherapy in metastatic disease, median (range)	3 (2–4)
Prior lines of ET in metastatic disease, median (range)	3 (2–3)
Prior ET for advanced disease, N (%)	215 (98.2)
Tamoxifen	85 (43.8)
Fulvestrant	163 (78.0)
Aromatase inhibitor	194 (91.5)
mTOR inhibitor plus ET	118 (55.9)
ECOG status at beginning of treatment, N (%)	
0-1	175 (90.2)
2-3	19 (9.8)
Palbociclib endocrine partner	
AIs	110 (50.2)
Fulvestrant	87 (39.7)
Tamoxifen	8 (3.6)
None	10 (4.6)
Others	4 (1.9)
Previous exposure to endocrine partner	
Yes	216 (98.6)
No	3 (1.4)

Abbreviations: AIs, aromatase inhibitors; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; mTOR, mammalian target of rapamycin.
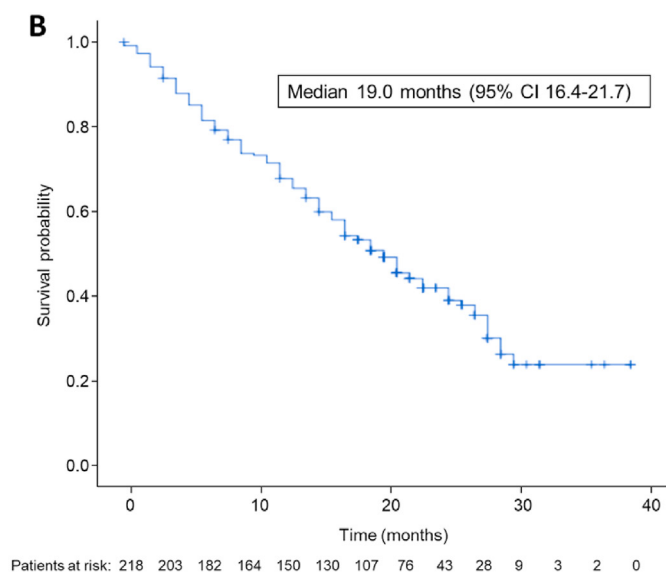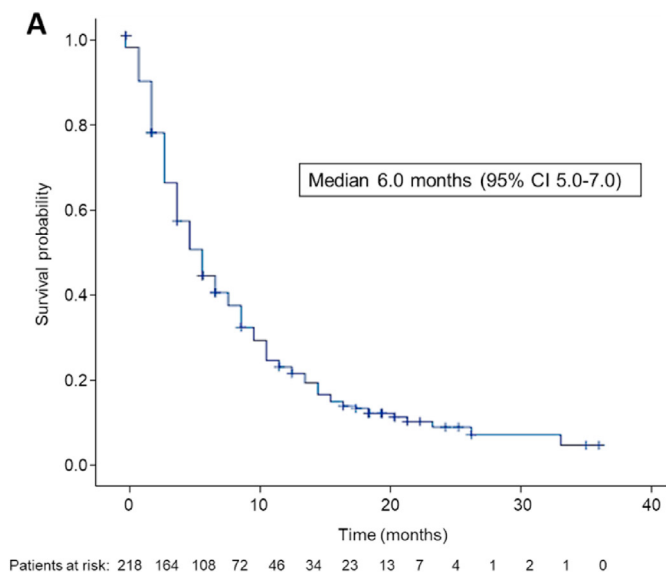
A

Median 6.0 months (95% CI 5.0-7.0)

Patients at risk: 218 164 108 72 46 34 23 13 7 4 1 2 1 0

B

Median 19.0 months (95% CI 16.4-21.7)

Patients at risk: 218 203 182 164 150 130 107 76 43 28 9 3 2 0

Fig. 2. Kaplan–Meier curves for PFS (A) and OS (B) of patients in the CU program.

	No. of patients		HR for rwPFS (95% CI)
Previous fulvestrant treatment (yes/no)	163/46		1.16 (0.82-1.65)
In patients treated with palbociclib + fulvestrant, previous fulvestrant monotherapy (≤6/>6 months)	61/100		1.93 (1.37-2.73)
Age at start of palbociclib (≤70/>70 years)	185/34		1.45 (0.96-2.20)
Everolimus prior to palbociclib (yes/no)	118/93		0.97 (0.73-1.31)
Visceral involvement (yes/no)	104/115		1.02 (0.77-1.36)
Chemotherapy in metastatic disease (yes/no)	143/76		0.90 (0.66-1.21)
Concomitant treatment with palbociclib (yes/no)	208/11		1.19 (0.63-2.25)

Fig. 3. Subgroup analysis of patients in the study (n = 219). Hazard ratios for rwPFS are shown. CI, confidence interval; HR, hazard ratio; rwPFS, real world progression-free survival.

A

HR=1.93 (95% CI 1.37-2.73), p<0.001

Fulvestrant >6 months

Fulvestrant ≤6 months

Patients at risk:
Fulvestrant >6 months 60 36 17 10 6 5 4 2 1 0
Fulvestrant ≤6 months 98 85 59 44 28 22 13 6 3 0

B

HR=1.70 (95% CI 1.14-2.55), p=0.01

Fulvestrant >6 months

Fulvestrant ≤6 months

Patients at risk:
Fulvestrant >6 months 60 54 45 37 32 27 19 9 3 0
Fulvestrant ≤6 months 98 92 81 75 64 47 24 14 2 0

Fig. 4. Kaplan-Meier curves for subgroup analysis of PFS (A) and OS (B) of patients who had received fulvestrant monotherapy for ≤6 months (n = 61, blue line) or for >6 months (n = 100, green line). CI, confidence interval; HR, hazard ratio.

characteristics of the patients included are shown in Table 1. The mean age of the patients were 58 years, mostly with good performance status (ECOG 0–1, 90.2%). At baseline, 104 patients (47.5%) presented with visceral disease and 162 (83.9%) were postmenopausal. Patients had received a median of 3 (range 2–4) previous lines of chemotherapy and 3 (range 2–3) previous lines of ET for advanced disease.

Patients received a median of 6 cycles of palbociclib. Most patients (n = 205; 95.0%) received concomitant ET with AIs (n = 110, 50.2%), fulvestrant (n = 87; 39.7%), or tamoxifen (n = 8; 3.6%). A total of 10 patients received palbociclib as a single agent (4.6%) and 4 patients received it with different combinations of ET. The most frequent reasons for treatment discontinuation were disease progression (89.9%) and toxicity (6.0%).

The median rwPFS was 6.0 (95% CI 5.7–7.0) months and the median OS was 19.0 (95% CI 16.4–21.7) months (Fig. 2). Subgroup analysis did not show differences in rwPFS according to age (≤70 years vs > 70 years), visceral metastasis, endocrine partner, and previous treatment with fulvestrant, everolimus or chemotherapy (Fig. 3). Duration of previous treatment with fulvestrant could be
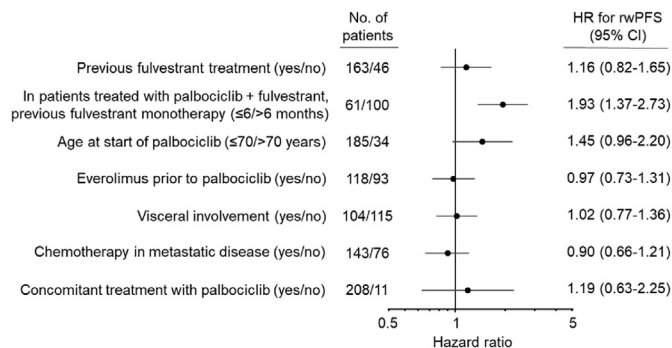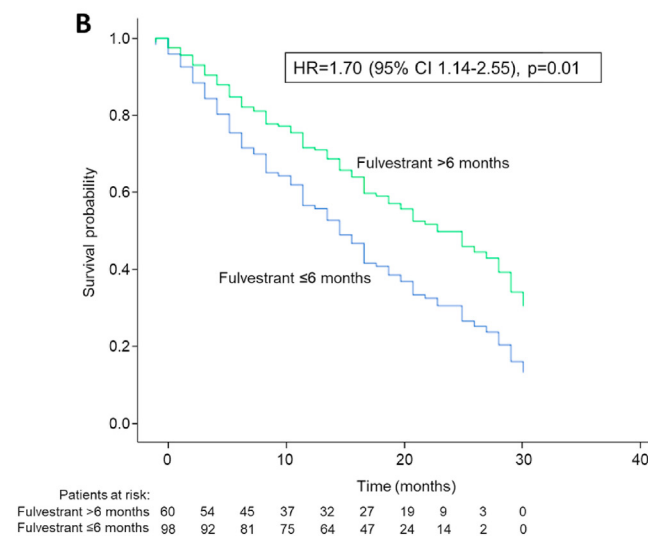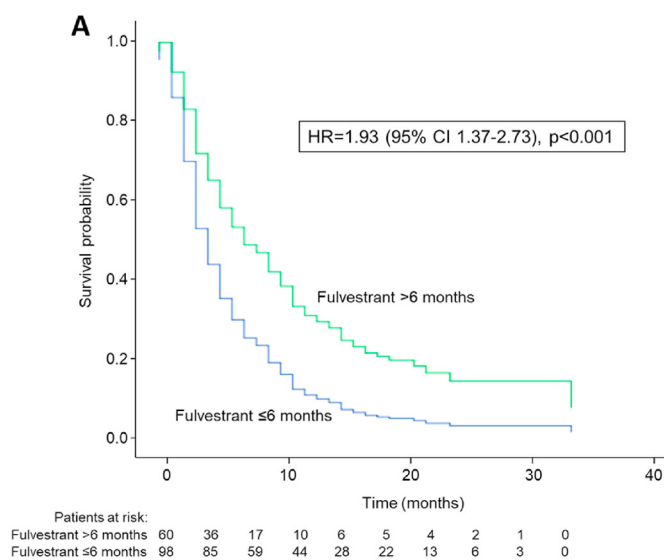
Table 2
Adverse events (n = 219).

Adverse event	All grades n (%)	Grades 3–4 n (%)
Neutropenia	128 (58.4)	83 (37.9)
Asthenia	68 (31.1)	7 (3.2)
Thrombopenia	31 (14.2)	7 (3.2)
Anemia	31 (14.2)	4 (1.8)
Nausea	14 (6.4)	0
Diarrhea	10 (4.6)	1 (0.5)
Constipation	8 (3.7)	0
Vomiting	6 (2.7)	1 (0.5)

helpful to identify patients who experience more benefit with palbociclib. Patients who had received previous fulvestrant monotherapy for >6 months, (n = 100) compared to those who had received this therapy for ≤6 months (n = 61), presented an improvement in median rwPFS (HR 1.93; 95% CI 1.37–2.73, p < 0.001), and median OS (HR 1.70; 95% CI 1.14–2.55, p < 0.01) (Fig. 4). However, duration of previous treatment with tamoxifen and AIs in the metastatic setting (≤ 6 months vs > 6 months) did not show differences in median rwPFS with palbociclib (HR 1.25, p = 0.39, and HR 1.18, p = 0.56, respectively).

A total of 196 (89.5%) patients were evaluable for response. Thirteen patients (5.9%) presented partial or complete response, with a median duration of response of 9.0 (5.5–19.0) months. Objective response was similar for patients with and without visceral metastasis (46.2% and 53.8% respectively), but the median response duration was significantly longer for patients with no visceral metastasis (5.6 ± 3.2 vs 11.9 ± 4.1, p = 0.013). The clinical benefit rate, defined as having a best response of complete response, partial response, or stable disease for at least 24 weeks, was 46.2% (n = 101).

Adverse events were reported in 175 (79.9%) patients (Table 2). The most frequently reported treatment-related non-hematologic adverse events of any grade were asthenia, diarrhea, and nausea. The most frequently reported hematologic toxicities of any grade were neutropenia, thrombopenia and anemia. Dose reductions were required by 58 (26.6%) patients.

4. Discussion

In this study, we present data on the efficacy and toxicity of palbociclib in heavily treated HR$^+$/HER2$^-$ mBC patients in a real-world multicentric setting. With 219 patients included, this is the largest study of palbociclib from a CU program reported in Europe. A median rwPFS of 6.0 (95% CI 5.7–7.0) months was observed, and the rate and severity of adverse events comparable to previous studies.

The cyclin-dependent kinases regulating cell-cycle progression have been considered as promising targets for breast cancer therapy because they were shown to contribute to the development of resistance to ET [4,16]. Palbociclib was the first third-generation and highly-selective oral CDK4/6 inhibitor discovered that demonstrated a substantially improved PFS for HR$^+$/HER2$^-$ breast cancer. Palbociclib, together with the others CDK4/6 inhibitors ribociclib and abemaciclib, received FDA and EMA approval for the treatment of HR$^+$/HER2$^-$ mBC in combination with either AIs or fulvestrant based on the PALOMA-2, MONALEESA 2 and the MONARCH 2 randomized clinical trials, respectively [12,15,17,18]. These studies demonstrated significant improvements in PFS and tolerable safety profiles [4]. For palbociclib, the pivotal registration trials PALOMA-2 and PALOMA-3 evaluated its efficacy and safety in combination with letrozole and fulvestrant in first- and second-line settings, respectively [11,12,19]. Data on the efficacy and safety of palbociclib in later lines of treatment have also been provided by several observational studies such as the Phase II TREnd trial [20], studies from the US [21,22], and CU programs in Europe [23–28] and Turkey [29]. The retrospective studies with data derived from heavily pretreated patients have reported median PFSs ranging from 2.9 to 7.6 months, comparable to the results observed in the present study (Table 3).

In PALBOCOMP, a significant improvement in median rwPFS in patients on palbociclib plus fulvestrant was observed depending on the time of prior exposure to fulvestrant monotherapy. Longer fulvestrant treatment (> 6 months versus ≤ 6 months) resulted in longer median rwPFS (p < 0.001), suggesting that higher sensitivity to previous ET predicts a higher benefit of palbociclib. Indirectly, this result can be compared to the results of the PALOMA-3 trial in which a higher benefit of palbociclib is observed in patients with secondary resistance to ET than in those with primary resistance [12]. A similar pattern was observed in the TREnd trial in women treated with palbociclib plus ET [20], where an advantage in PFS was observed in the subgroup of patients who had received prior ET (aromatase inhibitor or fulvestrant) for > 6 months (HR = 0.53, 95%

Table 3
Summary of studies of CU programs.

Study	Patients	Prior ET[a]	Combination therapy	PFS, median (95% CI)
Ban et al., 2018 [26]	24	3 (0–4)	PA + AI	4.8
Battisti et al., 2019 [25]	118	1-2, 42.4% 3-5, 54.2% 6-7, 1.7%	PA + AI, 48.3% PA + FU, 47.5% PA + TA, 4.2%	4.5 (3.7–5.9)
Demir et al., 2020 [29]	43	≥3	PA + TA, 44.1% PA + LE, 13.9% PA + AN, 6.9%	7 (4–10)
Du Rusquec et al., 2018 [27]	60	3 (1–7)	PA + FU	5.8 (3.9–7.3)
Herrscher et al., 2020 [28]	77	2	PA + FU	7.6 (4.6–10.4)
Hoste et al., 2018 [24]	82	4 (1–7)	PA + LE, 89.0% PA + FU = 3.7% PA + other, 7.2%	3.1 (2.7–4.7)
Maurer et al., 2018 [23]	34	3 (1–6)	PA + LE, 44.1% PA + FU, 23.5% PA + AN, 20.6% PA + other, 11.8%	3.1 (2.5–5.5)
PALBOCOMP	219	3 (2–3)	PA + AI, 50.2% PA + FU, 39.7% PA + TA, 3.6%	6.0 (5.7–7.0)

Abbreviations: AI = aromatic inhibitors; AN = anastrozole; CU = compassionate use; ET = endocrine therapy; FU = fulvestrant; ET = endocrine therapy; LE = letrozole; PA = palbociclib; PFS = progression free survival; TA = tamoxifen.
[a] Median (range) unless specified.

CI 0.3—0.9, p = 0.02), and was not observed in patients who had received prior ET for ≤ 6 months (HR 1.59; 95% CI 0.6—4.0, p = 0.33). This study also suggested that clinical benefit may be longer when palbociclib is combined with the same ET received beyond progression, leading to the hypothesis that palbociclib could actually reverse resistance to prior ET [20]. Improved PFS depending on length of prior ET was also observed in the UK CU program (5.9 months PFS if prior therapy was ≥6 months versus 3.7 months if prior therapy was <6 months, p = 0.055) [25]. However, other authors did not found differences in PFS depending on prior fulvestrant treatment [27].

We have not observed significant difference in rwPFS between patients who had received prior everolimus treatment compared with those who had not, a result similar to that reported from Belgian CU program [23].

The hematologic safety profile of palbociclib in our study was similar to that of other reports. However, the frequency of grade 3—4 neutropenia and of dose reductions was lower than in the PALOMA-2 and 3 trials, which could be related to less strict monitorization in real-world clinical practice, leading to under detection of this common AE.

In conclusion, the findings of PALBOCOMP suggest that palbociclib can be an effective and safe treatment option in later lines of systemic treatment.

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Ethical approval

Ethical permission was received from the Biomedical Research Foundation of the Hospital Clínico San Carlos (Madrid, Spain). All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in this study.

Declaration of competing interest

L. Manso reports consulting or advisory roles from Roche, AstraZeneca, Novartis, Tesaro, and Pfizer; speaker's bureau participation from Roche, AstraZeneca, Novartis, Tesaro, and Pfizer; research funding from Tesaro; travel expenses from Roche, Novartis, and Tesaro.

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