Breast Cancer Research and Treatment (2019) 174:731–740
https://doi.org/10.1007/s10549-019-05134-x

CLINICAL TRIAL

Palbociclib and endocrine therapy in heavily pretreated hormone receptor-positive HER2-negative advanced breast cancer: the UK Compassionate Access Programme experience

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Received: 7 January 2019 / Accepted: 9 January 2019 / Published online: 17 January 2019

Abstract

Purpose Palbociclib is approved in 1st line for hormone receptor (HR)-positive HER2-negative advanced breast cancer (ABC). A Compassionate Access Programme previously allowed patients to receive it in 4th line. However, Palbociclib has not been specifically tested in this population. We aimed to determine the safety and efficacy profile of Palbociclib within the Programme across ten institutions in the United Kingdom.

Methods We retrospectively identified HR-positive HER2-negative ABC patients on the Programme between December 2015 and September 2017. Demographics, disease characteristics, prior treatments, blood tests, toxicities, treatment delays and responses were recorded. Simple statistics, Fisher's exact test, χ^2 method and Cox regression were used.

Results 118 patients identified had a median age of 59. 82.2% were postmenopausal and 92.4% performance status 0–1. 81.4% had visceral involvement and 6.8% bone-only disease after a median of 5 prior treatments and 3 prior chemotherapies. Clinical benefit rate was 47.5%, overall response rate 15.8%, median PFS 4.5 months and median OS 15.8 months. Longer progression-free survival on prior endocrine therapy was a predictor of longer PFS and OS. 89.7% developed neutropenia (grade ≥ 3 in 56.8%). 5.1% experienced febrile neutropenia. 48.3% had dose reductions and 3.4% discontinued Palbociclib following toxicity. No statistically significant difference in grade ≥ 3 neutropenia was observed according to metastatic sites nor previous treatments.

Conclusions This is the most extensive analysis of palbociclib in ≥ 4th-line setting. Clinical benefit was confirmed particularly for endocrine-sensitive, predominantly bony disease and in earlier lines of treatment. Safety was similar to PALOMA trials with higher febrile neutropenia rate.

Keywords Breast cancer · ER-positive · Palbociclib · Advanced stage · Pretreated

Introduction

Resistance to endocrine therapy has been a major hurdle in the management of metastatic oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer, leading to treatment failure and progression of disease for patients [1]. However, many cases of ER-positive, HER2-negative breast cancer continue to be hormone dependent even upon disease progression on hormonal treatment and may respond to additional endocrine therapies. The possibility of continuing to target the hormone receptor is appealing since endocrine therapy is very likely to be beneficial for these

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patients, with fewer side effects compared with chemotherapy [2].

Research has focused on developing new strategies to overcome endocrine resistance and prolonging progression-free survival (PFS) on endocrine treatments. One such strategy has been the addition of the cyclin-dependent kinase (CDK)4/6 inhibitor palbociclib to conventional endocrine therapy. Palbociclib acts by inhibiting the interaction of cyclins 4 and 6 with cyclin D, thereby preventing the hyperphosphorylation of retinoblastoma (Rb) and preventing the cell from progressing through the G1 checkpoint [3]. Palbociclib was designated a 'breakthrough therapy' by the Food and Drug Administration (FDA) in 2013, and was subsequently licenced to be given in combination with an aromatase inhibitor [4] and fulvestrant [5] for the first- and second-line treatments of advanced ER-positive, HER2-negative metastatic breast cancer.

The FDA approval for the combination of palbociclib with an aromatase inhibitor as a first-line treatment in metastatic ER-positive breast cancer followed the results of the phase 2 PALOMA-1 and the phase 3 PALOMA-2 studies [6, 7]. The PALOMA-2 trial, which enrolled 666 postmenopausal women with advanced ER-positive, HER2-negative advanced breast cancer, showed a significant improvement of the median PFS to 24.8 months in the combination arm versus 14.5 months in the endocrine treatment alone arm [7]. The combination of palbociclib with fulvestrant in second line was approved by the FDA based on the PALOMA-3 trial findings, which confirmed improved PFS at 9.2 months in the combination arm compared to 3.8 months in the endocrine treatment alone group [8, 9]. Common side effects of palbociclib seen in trials are neutropenia, leukopenia, fatigue, nausea and alopecia [10]. Grade 3–4 neutropenia occurred in 66.4% and 62.0% of patients enrolled in the PALOMA-2 and PALOMA-3 studies, respectively, whereas febrile neutropenia was experienced by 1.8% and 0.6% of patients [7–9].

The experience of an Expanded Access Programme previously available in Northern America as an interim measure to provide patients suitable for letrozole as first or later line of therapy access to palbociclib before commercial availability has been reported [11]. In the meantime, in the United Kingdom, a Compassionate Access Programme (CAP) allowed patients with advanced ER-positive HER-negative breast cancer who have progressed on at least four lines of treatment to access palbociclib in combination with standard endocrine treatment. To date, however, no trials have established the toxicity and efficacy in this heavily pretreated patient population. We therefore evaluated the efficacy and the safety profile of palbociclib within the UK CAP.

Methods

The primary aim of our analysis was to assess the efficacy and safety of palbociclib given along with endocrine treatment within the fourth-line setting and beyond in terms of clinical benefit rate (CBR) and rate of grade ≥ 3 neutropenia. Secondary endpoints were efficacy outcomes (including overall response rate [ORR], progression-free survival [PFS] and overall survival [OS]), and further safety data (including: rates of other adverse events [AEs] such as neutropenia of any grade, anaemia, thrombocytopenia, stomatitis, diarrhoea, nausea, fatigue, skin rash, deranged liver function and infections; rate of dose reductions).

We identified a list of centres participating in the Pfizer Palbociclib Compassionate Access Programme (CAP) that enrolled patients in the United Kingdom between December 2015 and September 2017. Ten different Institutions agreed to participate in the analysis and each centre retrospectively identified HR-positive HER2-negative advanced breast cancer patients who commenced Palbociclib within the CAP.

Eligible breast cancer patients were required to meet the following criteria: disease progression on at least four previous lines of standard-of-care therapy for metastatic disease (apart from trial treatments); non-eligibility for ongoing palbociclib clinical trials; adequate bone marrow, renal and liver function; no concurrent medications inhibiting/inducing CYP3A4 or CYP3A4 substrates with narrow therapeutic window or prolonging QTc interval; no prior surgery, systemic treatment or radiotherapy within two weeks before treatment initiation; QTc interval measured ≤ 480 ms; no family history or personal history of long or short QT syndrome, Brugada syndrome, QTc prolongation or torsade de pointes; no prior myocardial infarction, severe or unstable angina, cardiac dysrhythmias of NCI CTCAE grade ≥ 2, atrial fibrillation, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or symptomatic pulmonary embolism within six months; no known hypersensitivity to the product; no suicidal ideation or behaviour.

Enrolled patients received palbociclib as 75, 100 or 125 mg capsules to be taken with food and administered orally daily at a starting dose of 125 mg per day on a 3 weeks on, 1 week off schedule (i.e. for 21 days followed by 7 days off treatment for each 28-day cycle). Palbociclib was given along with endocrine treatment according to physician's choice and choices may include aromatase inhibitors (letrozole, anastrozole or exemestane), fulvestrant or tamoxifen with or without ovarian function suppression.

Patient demographics including age, menopausal status and Eastern Cooperative Oncology Group (ECOG)

performance status (PS) were recorded, along with sites of disease. Prior treatments and their duration were also registered, along with data regarding endocrine treatment companions, blood test results over the first 3 months of treatment, radiological tumour assessments, toxicities, palbociclib dose reductions and delays.

We used simple statistics to describe the rates of AEs (with comparison among different subgroups), discontinuation, dose delays and disease response (according to RECIST). Fisher's exact test or χ^2 method were used as appropriate. PFS and Overall survival were calculated using the Kaplan–Meier method. Median PFS and overall survival will be presented with 95% confidence intervals. The rates of PFS and overall survival at 12 and 24 months were also reported. Comparisons of PFS and overall survival between different patient groups (number of prior lines of therapy, disease sites) were made using Cox regression to explore if there are differences in rates of disease progression and death between the groups. Hazard ratios with 95% confidence intervals were reported.

Results

Study population

118 patients received palbociclib within the CAP within ten participating Institutions across the UK between December 17th, 2015 and September 27th, 2017.

Baseline patient demographics and disease characteristics are summarized in Table 1. Median age was 59 years (range 32–82) and 37 patients (31.3%) were aged 65 and older. 97 patients (82.2%) were postmenopausal. 96 patients had visceral disease (81.4%), 8 (6.8%) had bone-only disease and only 1 patient had nodal/chest wall disease only. This patient population was heavily pretreated, with 114 (96.6%) patients having previously received four or more lines of treatment in the advanced setting (including endocrine therapy and chemotherapy). Three patients (3.4%) were granted access to the CAP after receiving only 3 prior lines of palliative treatment as they developed a relapse on adjuvant endocrine therapy. 75 patients (63.6%) had 3 or more prior lines of palliative chemotherapy. 66 patients (55.9%) had previously 3 or more lines of palliative endocrine therapy, and the median duration of their last line of endocrine therapy was 6 months (range 1–96). Palbociclib was given alongside an aromatase inhibitor in 57 patients (48.3%), with fulvestrant in 56 patients (47.5%), and with tamoxifen in 5 patients (4.2%). 13 patients (11.0%) received concomitant ovarian function suppression.

Table 1 Patient characteristics

Variables	*N*	%
Age		
Median (range)_	59 (32–82)	
65+	37	31.3
Menopausal status		
Premenopausal[a]	16	13.6
Perimenopausal	5	4.2
Postmenopausal	97	82.2
ECOG performance status		
0	38	32.2
1	71	60.2
2	9	7.6
Sites of disease		
Bones	100	84.7
Visceral	96	81.4
Nodes	63	53.4
Chest wall/skin	24	20.3
Bone only	8	6.8
Nodal/chest wall/skin only	1	0.8
Prior systemic Rx lines		
3	4	3.4
4–6	79	66.9
7–9	28	23.7
10–11	7	5.9
Prior endocrine Rx lines (including maintenance and rechallenges)		
None	2	1.7
1–2	50	42.4
3–5	64	54.2
6–7	2	1.7
Prior chemo lines		
None	6	5.1
1–2	37	31.3
3–5	63	53.4
6–8	12	10.2
Duration of prior endocrine Rx (months)		
Median	6 (1–96)	
Mean	10.5	
Endocrine agent companion		
Tamoxifen	5	4.2
AI	57	48.3
Fulvestrant	56	47.5
Ovarian function suppression	13	11.0

[a]Premenopausal patients received either Tamoxifen alone or endocrine therapy with ovarian function suppression

Efficacy evaluation

Overall, the median duration of palbociclib was 119 days (range 21–594). At the time of the analysis in May 2018, 12 patients (10.2%) were still on treatment. Among 101 patients

Table 2 Radiological responses at first radiological assessment at 3 months

	N	%
Clinical benefit rate	48	47.5
Overall response rate	16	15.8
Complete response	1	1.0
Partial response	15	14.8
Stable disease	32	31.7
Disease progression	53	52.5

who received a first radiological tumour assessment at a median of 3 months, one patient had a complete response, 15 (14.8%) had a partial response, 32 (31.7%) had stable disease and 53 (52.5%) had disease progression. As shown in Table 2, ORR was 15.8% and CBR was 47.5% at 12 weeks.

Median PFS was 4.5 months (95% confidence interval [CI] 3.7–5.9) in the overall population. Median PFS was longer in patients who had received less than 3 prior lines of chemotherapy compared to more heavily pretreated patients (5.9 months [95% CI 3.7–11] vs 4.3 months [95% CI 3.3–5.5], *p* 0.159), despite this was not statistically significant (Table 3). No significant difference in median PFS was detected in patients who had received less than 3 lines of prior endocrine therapy compared to those treated with more lines (4.5 months [95% CI 3.0–5.5] vs 5.8 months [95% CI 3.6–7.4], *p* 0.327). Although the number of patients with bone-only disease was very small, they had a statistically significantly longer median PFS compared to those with other sites of disease (11.0 months [95% CI 2.3-not reached] vs 4.4 months [95% CI 3.6–5.5], *p* 0.024). Similarly, patients with visceral disease had a significantly shorter median PFS compared to those without any evidence of visceral involvement (3.9 months [95% CI 3.4–4.9] vs 11.0 months [95% CI 7.4–17.6], *p* 0.002). Patients free from disease progression for more than 6 months on their previous line of endocrine therapy experienced a longer median PFS compared to those who remained on prior endocrine therapy for a shorter period of time and this finding neared statistical significance (5.9 months [95% CI 4.4–8.0] vs 3.7 months [95% CI 2.8–4.5], *p* 0.055). Kaplan–Meier estimates for PFS and OS are illustrated in Figs. 1 and 2.

In the overall population, median OS was 15.8 months (95% CI 13.3–18.7). Median OS was longer in patients who had received less than 3 prior lines of chemotherapy compared to more heavily pretreated patients (not reached (NR) [95% CI 15.4-NR] vs 13.4 months [95% CI 9.5–17.7], *p* 0.016). Likewise, median OS was longer in patients with bone-only involvement compared to those with other sites of metastatic disease (NR [95% CI 13.4-NR] vs 15.2 months [95% CI 12.8–18.3], *p* 0.048). Moreover, median OS was longer in patients achieving a progression-free interval on their previous line of endocrine therapy greater that 6 months compared to those progressing earlier (18.1 months [95% CI 13.0-NR] vs 14.4 months [95% CI 7.7–18.3], *p* 0.052). At 18 months of follow-up, 44.5% were alive (95% CI 34.4–54.1). The 18-month OS rate was also significantly higher in patients who had received less than 3 prior lines of chemotherapy compared to more heavily pretreated patients (Table 3).

Table 3 Progression-free and overall survival

	Outcome	95% CI	*p* value
Median PFS			
Overall	4.5 months	3.7–5.9	–
< 3 chemo lines	5.9 months	3.7–11.0	0.159
3 + chemo lines	4.3 months	3.3–5.5	
< 3 ET lines	4.5 months	3.3–5.5	0.271
3 + ET lines	5.8 months	3.6–7.4	
Bone only	11.0 months	2.3–NR	0.024
Non-bone only	4.4 months	3.6–5.5	
Visceral only	3.9 months	3.4–4.9	0.002
Non-visceral only	11.0 months	7.4–17.6	
Prior ET < 6 months	3.7 months	2.8–4.5	0.055
Prior ET ≥ 6 months	5.9 months	4.4–8.0	
6-month PFS rate			
Overall	41.0%	32.0–49.8	–
Bone only	87.5%	38.7–98.1	0.024
Non-bone only	37.5%	28.4–46.6	
Median OS			
Overall	15.8 months	13.3–18.7	–
< 3 chemo lines	NR	15.4-NR	0.016
3 + chemo lines	13.4 months	9.5–17.7	
< 3 ET lines	14.2 months	8.4–18.7	0.134
3 + ET lines	17.7 months	13.3–NR	
Bone only	NR	13.4–NR	0.048
Non-bone only	15.2 months	12.8–18.3	
Visceral only	14.2 months	10.6–18.0	0.002
Non-visceral only	NR	15.7-NR	
Prior ET < 6 months	14.4 months	7.7–18.3	0.052
Prior ET ≥ 6 months	18.1 months	13.0-NR	
18-month OS rate			
Overall	44.5%	34.4–54.1	–
< 3 chemo lines	60.3%	42.4–74.2	0.016
3 + chemo lines	35.2%	23.5–47.1	
Bone only	75.0%	31.5–93.1	0.048
Non-bone only	42.0%	31.6–52.1	
Visceral	38.3%	27.4–49.1	0.003
Non-visceral	69.5%	44.2–85.0	

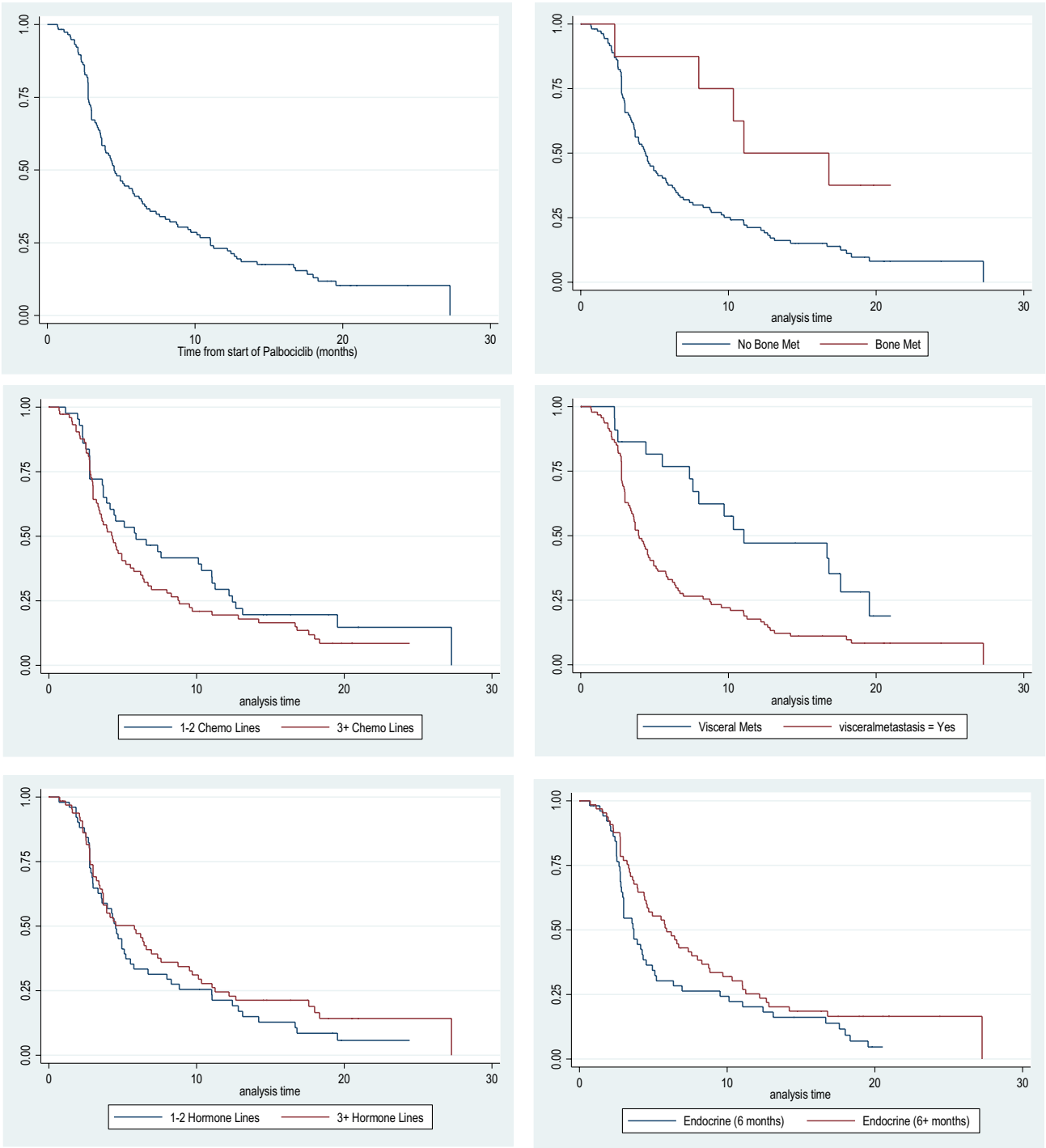

Fig. 1 Kaplan–Meier curve for PFS in the overall population and according to previous lines of chemotherapy, previous lines of endocrine therapy, presence of bony metastases, presence of visceral involvement and duration of previous endocrine therapy

Safety evaluation

Safety findings are presented in Table 4. In the overall population, 68 patients (57.6%) experienced grade 3–4 AEs (all causes). The most common AEs (experienced by > 20% of the overall population) were neutropenia (89.7%), anaemia (66.9%), fatigue (53.4%), thrombocytopenia (50.0%) and deranged liver function (32.2%). Grade 3–4 AEs included neutropenia (56.8%), thrombocytopenia (9.3%), transaminitis (5.1%), anaemia (4.2%), fatigue (1.7%), nausea (1.7%),

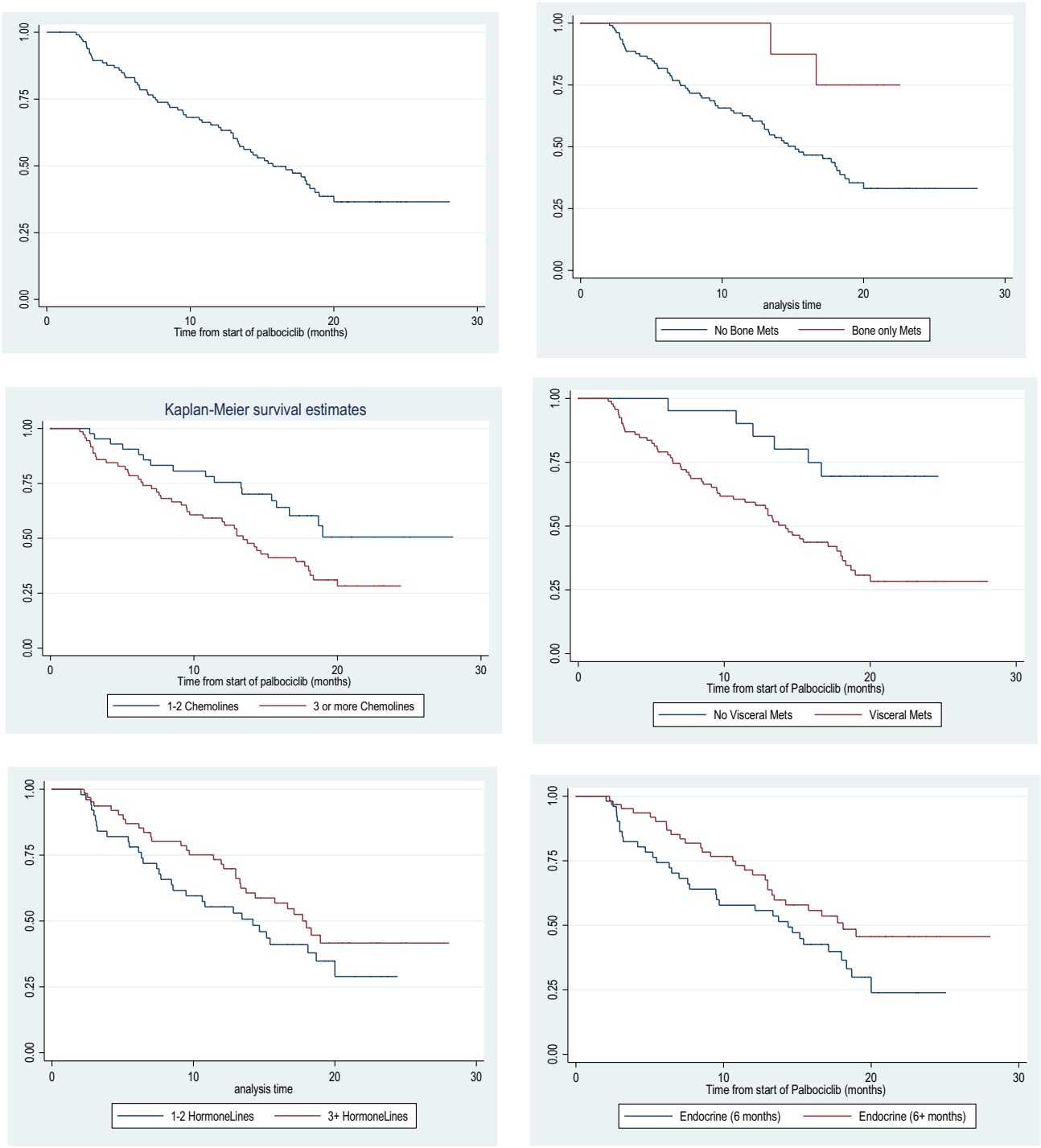

Fig. 2 Kaplan–Meier curve for OS in the overall population and according to previous lines of chemotherapy, previous lines of endocrine therapy, presence of bony metastases, presence of visceral involvement and duration of previous endocrine therapy

stomatitis (0.8%) and diarrhoea (0.8%). Infections requiring antibiotics occurred in 28 patients (23.7%) and febrile neutropenia in 6 (5.1%).

At least one dose reduction was required in 57 patients (48.3%). The final dose administered was 100 mg for 48 patients (40.7%) and 75 mg for 9 patients (7.6%). Out of 57 patients requiring a lower dose of palbociclib, dose reductions were due to haematologic toxicity in 46 (80.7%). Dose delays were required in 58 patients (49.1%) with a median 7 days of delay (range 0–56). Treatment was discontinued

Table 4 Adverse events

	N	%
Neutropenia		
Any grade	105	89.7
Grade 3–4	67	56.8 (95% CI 45.1–73.0)
Febrile neutropenia	6	5.1
Anaemia		
Any grade	79	66.9
Grade 3–4	5	4.2
Thrombocytopenia		
Any grade	59	50.0
Grade 3–4	11	9.3
Stomatitis		
Any grade	20	16.9
Grade 3–4	1	0.8
Diarrhoea		
Any grade	9	7.6
Grade 3–4	1	0.8
Nausea		
Any grade	23	19.5
Grade 3–4	2	1.7
Fatigue		
Any grade	63	53.4
Grade 3–4	2	1.7
Skin rash		
Any grade	4	3.4
Grade 3–4	0	0
Deranged LFTs		
Any grade	38	32.2
Grade 3–4	6	5.1
Infections requiring Abx while on Palbociclib	28	23.7
Dose reductions	57	48.3
Lowest dose of Palbociclib given		
125 mg	61	51.6
100 mg	48	40.7
75 mg	9	7.6
Reason for dose reduction		
Hematologic toxicity	46	80.7
Non-hematologic toxicity	11	19.3
Dose delays (days)		
Median	7 (0–56)	
Proportion	58	49.1
Reason for discontinuation		
Toxicity	4	3.4
PD	97	82.2

owing to toxicity in only 4 patients (3.4%) (prolonged grade 3 neutropenia in two cases) and to disease progression in 102 (86.4%). The rates of grade 3–4 neutropenia were not influenced by number of previous lines of chemotherapy nor by sites of metastatic involvement as shown in Table 5.

Table 5 Grade 3–4 neutropenia rates in different subgroups

1–2 previous chemotherapy lines	22	51.2	0.351
3 + previous chemotherapy lines	45	60.0	
1–2 previous endocrine therapy lines	33	63.5	0.193
3 + previous endocrine therapy lines	34	51.5	
Visceral involvement	54	56.2	0.808
No visceral involvement	13	59.1	
Bone only	6	75.0	0.281
No bone only	61	55.4	

Discussion

CDK4/6 inhibitors have reshaped the therapeutic landscape for advanced ER-positive, HER2-negative breast cancer. Palbociclib has been extensively investigated in the first- and second-line settings in the PALOMA-2 and PALOMA-3 studies [7–9]. However, there are no data regarding its efficacy and safety in later lines of treatment.

Our study is the most comprehensive analysis of outcomes of palbociclib in the fourth-line setting and beyond, although it has some limitations. First, this analysis was retrospective and therefore may be affected by reporting bias. Secondly, despite the median time to the first radiological assessment was 3 months, restaging was conducted according to local routine practice and physician's judgement, which is likely to have influenced the response rate analysis. Nonetheless, our analysis suggests that palbociclib remains a potentially effective treatment option in later lines of treatment.

These findings are particularly relevant to patients more likely to have endocrine-sensitive disease, such as predominantly bony metastatic involvement, fewer lines of prior chemotherapy and longer progression-free interval to previous hormonal treatment. In this population, there is a potential of maximizing the chances of long-term disease control with CDK4/6 inhibition and to defer the time to more intensive and potentially less well-tolerated forms of treatment such as chemotherapy.

Palbociclib is an important treatment option for patients who did not have the opportunity to receive CDK4/6 inhibitors in the first two lines of treatment as these drugs were not previously available. Further, palbociclib may be particularly important for older patients [12], who are more likely to experience toxicities from cytotoxic treatment.

The safety profile of palbociclib in this setting was consistent with the findings of the PALOMA trials [7–9]. The main toxicity of palbociclib remained myelosuppression

resulting in neutropenia and leukopenia, whereas anaemia and thrombocytopenia were less common. Overall, recovery from these side effects is prompt with dose delays or reductions. Nonetheless, the higher incidence of febrile neutropenia in our population needs to be carefully considered especially since these patients may be more likely to experience bone marrow suppression also as a consequence of more diffuse bony metastatic involvement or of previous myelosuppressive treatments. The treatment discontinuation rate due to toxicity remained low and is consistent with the data from PALOMA-2 and PALOMA-3 trials. Moreover, a patient-reported outcomes analysis of the PALOMA-3 study demonstrated that patients on palbociclib experience less reduction in global quality of life from baseline, along with a longer time to its deterioration compared to those on endocrine treatment alone [13]. Although our study did not report quality of life data, we hypothesize that this benefit is maintained in later lines of treatment. Our analysis also provided outcomes which are likely to apply to patients seen in everyday clinical practice and adds to the amount of real-world evidence confirming the safety and efficacy of CDK4/6 inhibitors [14–17].

Cytotoxic chemotherapy can provide ORRs of 10–20% with a median duration of response of 4–6 months [18–22] and can be associated with marked toxicities impacting on patients' quality of life [23]. In our analysis, palbociclib provided an ORR of 15.8%, which is similar to the historical outcome with cytotoxic therapy, along with a CBR of 47.5% and a safety profile consistent with previous findings.

Attempts to identify predictive biomarkers to guide patient selection for CDK4/6 blockade have not yet been successful [24]. Extensive research on candidate biomarkers may provide future insight into patients who are likely to respond to this approach also in later lines of treatment [25, 26]. Likewise, the ongoing studies on the mechanisms of primary and acquired resistance to CDK4/6 inhibition are likely to provide further guidance in decision-making [27, 28]. To this purpose, results from ongoing trials on combinations of inhibitors of the CDK4/6 and the PI3K–AKT–mTOR pathways are eagerly awaited in view of the profound crosstalk existing between these systems [29]. Also, the results of the PHYTHIA study (NCT02536742) on pretreated patients receiving an extensive molecular profiling under the AURORA initiative [30] to identify biomarkers of response to palbociclib and fulvestrant are likely to provide useful information. Although our patient population was CDK4/6 inhibition-naïve, the question of their use beyond progression is also being investigated by a number of ongoing trials (NCT02632045 [MAINTAIN study], NCT02871791, NCT01857193, NCT02732119 [TRINITI-1 study] and NCT03147287 [PACE study]) that might provide further rationale for the use of CDK4/6 inhibitors in this setting.

In conclusion, our analysis shows that palbociclib remains a potentially effective and safe treatment option in later lines of systemic treatment, especially in patients whose disease maintains endocrine sensitivity. Interestingly, palbociclib was beneficial even to patients who had received more lines of chemotherapy and the number of previous lines of endocrine treatment did not impact on this finding. Further research on potential approaches to overcome endocrine resistance and more insight into the mechanisms of resistance to CDK4/6 inhibition as well as the correct sequencing of treatment options are warranted and may help establish the role of palbociclib in more heavily pretreated patients.

Acknowledgements The authors wish to acknowledge the support of Pfizer in providing a list of centres enrolling patients within the Compassionate Access Programme. Prof Johnston, Dr Ring, Dr Battisti and Dr Kingston wish to acknowledge the support of The Royal Marsden NIHR Biomedical Research Centre for Cancer.

Conflict of interest Prof Johnston has received consulting and advisory board fees from Eli Lilly, AstraZeneca and Puma Biotechnology, speaker fees from Pfizer and Novartis and research funding from Pfizer. Dr Ring has received advisory board fees from Novartis, Pfizer and Lilly and speaker fees from Novartis and Pfizer. Dr Roylance has received an institutional educational grant from Pfizer and honoraria from Pfizer for advisory board and educational meetings. Dr Waters has received speaker and advisory fees from Genomic Health International, Novartis UK and Eisai Ltd. Dr Battisti, Dr Kingston, Dr Harper, Dr King, Dr Denton, Dr Sita-Lumsden, Dr Rehman, Dr Stavraka, Dr Kristeleit, Prof Sawyer, Dr Houghton, Prof Davidson, Dr Howell, Ms Choy, Dr Fharat and Mr Mohammed have no conflict of interest.

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