The efficacy and safety of palbociclib combined with endocrine therapy in patients with hormone receptor-positive HER2-negative advanced breast cancer: a multi-center retrospective analysis

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To explore the efficacy and safety of palbociclib combined with endocrine therapy (ET) in advanced breast cancer (ABC). We conducted a retrospective study involving patients with hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2—) ABC who received palbociclib combined with ET in the first- to third-line at three centers in China between January 2018 and October 2020. A total of 151 patients were included in this study. The median age of the patients at palbociclib initiation was 56 years (range 30–86 years) with a median follow-up of 10.9 months (range 2.0–41.2 months). Among these patients, 88 patients received palbociclib combined with ET as first-line therapy, and achieved a median progression-free survival (mPFS) of 19.8 months and an objective response rate (ORR) of 40.9%, meanwhile, in the first-line setting, 62 patients received palbociclib at an initial dose of 125 mg, achieving a mPFS of 20.9 months and an ORR of 46.8%. There were 39 and 24 patients who received palbociclib combined with ET as second- and third-line therapy, the mPFS were 10.0 months and 6.1 months, respectively. The most common and serious adverse events (AEs) were leukopenia and neutropenia. A total of 64 patients (42.4%) underwent palbociclib dose reduction due to AEs. Palbociclib combined with ET is an effective therapeutic regimen for HR+/HER2— ABC, particularly in the first-line setting with palbociclib initial dose of 125 mg, and AEs were manageable. *Anti-Cancer Drugs* 33: e635–e643 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Female breast cancer has now surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases, according to the Global cancer statistics [1]. The National Cancer Center of China reported in January 2019 that the incidence of breast cancer in China is increasing, as illustrated by an increase in new cases from about 279 900 in 2014 to about 304 000 in 2015 [2,3]. Although the majority of patients are diagnosed with breast cancer at an early stage, approximately 20% of victims will possibly relapse and develop metastatic disease [4]. Among patients with advanced breast cancer (ABC), the most prevalent molecular subtype based on immunohistochemistry study proved to be hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2–) accounting for about 60–70% [5]. For most patients with HR+/HER2– ABC, endocrine therapy (ET) is the backbone of the treatment. Although the development of resistance to ET has posed a major challenge, the clinical prognosis has been dramatically improved by the recent introduction of new and effective treatment modalities. Among these, the cyclin-dependent kinase 4/6 (CDK4/6) inhibitors have shown advantageous efficacy with manageable adverse events (AEs) when used in combination with ET [6].

CDK4/6 inhibitors block the DNA synthesis and cell proliferation by interfering with the cyclin D-CDK4/6-retinoblastoma pathway while avoiding the serious cytotoxicity associated with pan-CDK inhibitors [7]. The CDK4/6 inhibitors that are currently available include

palbociclib, ribociclib, and abemaciclib. Evidence from the PALOMA-2 trial (phase III, double-blind, randomized study) showed that in patients who had not received prior systemic therapy for HR+/HER2– ABC, the median progression-free survival (mPFS) following treatment with palbociclib-letrozole versus placebo-letrozole was 24.8 months and 14.5 months, respectively [hazard ratio (HR) = 0.58, 95% confidence interval (CI) 0.46–0.72; $P < 0.001$] [8]. Moving forward to the PALOMA-3 trial (phase III, double-blind, randomized study), in patients who had progressed or relapsed during previous ET, the median overall survival (mOS) after treatment with palbociclib-fulvestrant versus placebo-fulvestrant was 34.9 months and 28.0 months, respectively (HR for death = 0.81, 95% CI 0.64–1.03; $P = 0.09$; absolute difference = 6.9 months) [9]. In the MONALESSA-2 trial (phase III, double-blind, randomized study), in patients who had not received prior systemic therapy for HR+/HER2– ABC, the mPFS following treatment with ribociclib-letrozole versus placebo-letrozole was 25.3 months and 16.0 months, respectively (HR = 0.568, 95% CI 0.457–0.704; $P = 9.63 \times 10^{-8}$) [10]. In the MONARCH-3 trial (phase III, double-blind, randomized study), in patients who had not received prior systemic therapy for HR+/HER2– ABC, the mPFS following treatment with abemaciclib-nonsteroidal aromatase inhibitor (AI) versus placebo-nonsteroidal AI was 28.2 and 14.8 months, respectively (HR = 0.54, 95% CI 0.418–0.698; $P = 0.000002$) [11]. Based on these results, in 2015, palbociclib (IBRANCE; Pfizer Inc., New York, USA) in combination with letrozole was approved as first-line therapy for HR+/HER2– ABC by the US Food and Drug Administration, and in 2016, the indication was subsequently expanded to include combination regimen of fulvestrant-palbociclib for advanced disease after ET [12]; followed by ribociclib (KISQALI; Novartis Pharmaceuticals Corp., Basel, Switzerland) and abemaciclib (VERZENIO; Eli Lilly and Company, Indianapolis, Indiana, USA) being approved since 2017 for treatment of HR+/HER2– ABC [13, 14]. Notably, the efficacy data of the PALOMA-2 and PALOMA-3 trials were not significantly different in Asian patients ($n = 95$ and 105, respectively) and non-Asian patients ($n = 571$ and 416, respectively) [15,16]. Accordingly, palbociclib in combination with AI was approved as the first-line treatment for women with HR+/HER2– ABC in China since 2018. Nevertheless, little information is available regarding the safety and efficacy of palbociclib combined with ET in the real-world setting, particularly among Chinese patients.

To address this unmet need, we performed a large-scale specific retrospective study of palbociclib in China.

Patients and methods

Patients

Eligible patients were women with HR+/HER2– ABC who initiated palbociclib combined with ET between January 2018 and October 2020 at Peking University Cancer Hospital, Peking University First Hospital, and Peking University Third Hospital (all in Beijing, China). HR+ was defined as estrogen receptor- or progesterone receptor-positive status by immunohistochemistry [17]. HER2 status was determined by immunohistochemistry or fluorescence in situ hybridization [18]. Characteristics of the patients were reviewed from the electronic medical record system. Sensitivity to ET was defined as: a documented clinical benefit [complete response (CR), partial response (PR), or stable disease (SD) sustained for ≥24 weeks) from at least one previous ET regimen in the context of metastatic disease; or the receipt of at least 24 months of adjuvant ET before recurrence; otherwise, it was defined as endocrine resistance. Women were defined as postmenopausal if they were at least 60 years of age, had undergone bilateral oophorectomy, or were younger than 60 years of age and had had cessation of regular menses for at least 12 consecutive months with no alternative pathologic or physiologic cause and had serum levels of estradiol and follicle-stimulating hormone in the postmenopausal range.

Treatment protocols

Patients were administered oral palbociclib once daily (QD) with food, starting at initial doses of 125 mg or 100 mg depending on the general condition of the patient, for 21 consecutive days followed by 7 days off (28-day cycle). During the treatment, patients who experienced grade 1 or 2 AEs proceeded with the same dose of palbociclib in the next cycle and the AEs were carefully monitored. Treatment would be temporarily suspended for patients who experienced grade 3 or 4 AEs: if the AEs subsided to ≤grade 2 within 1 week, the immediate next cycle was resumed at the same dose; otherwise, the dosage of palbociclib would be stepped down (to 100 mg, then 75 mg). The selection of ET was at the physician's discretion, meanwhile premenopausal or perimenopausal patients were required to receive ovarian suppression with subcutaneous goserelin every 28 days initiated at least 4 weeks prior to the start of palbociclib combined with ET and thereafter throughout the treatment. Palbociclib combined with ET was continued until disease progression or intolerable AEs.

Evaluation of efficacy and safety

Patients had baseline radiologic evaluation of the primary and metastatic lesions (CT, MRI, or both) before the start of palbociclib combined with ET, and repeated every 2–3 months until disease progression. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (version 1.1) [19]. Efficacy was evaluated by the progression-free survival (PFS, defined as the time from treatment initiation to the first occurrence of disease progression or death), objective response rate (ORR, defined as the percentage of CR and PR), and disease control rate (DCR, defined as the percentage of CR, PR,

and SD). The definitions were as follows: CR, disappearance of all target lesions; PR, ≥30% reduction in the sum of diameters of the baseline lesions; progressive disease (PD), ≥20% increase in the sum of diameters of the baseline lesions or the appearance of new lesions; and SD, did not meet the criteria of PR or PD. AEs were graded and recorded continuously throughout the treatment, according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. All information on the efficacy and safety of palbociclib combined with ET was retrieved from the electronic medical record system.

Statistical analysis

All data were analyzed using SPSS 26.0 software (SPSS, Chicago, Illinois, USA). The Kaplan–Meier product limit method was used to estimate mPFS and generate time-to-event curves. The log-rank test was used for all comparisons. The Cox proportional hazards regression model was used to calculate HR and multivariate analysis of PFS. The chi-square test was used to compare the distribution of AEs and ORRs among the initial dose groups. $P < 0.05$ was considered statistically significant.

Results

Patient clinical and pathologic characteristics

Between January 2018 and October 2020, a total of 151 patients received palbociclib combined with ET at Peking University Cancer Hospital, Peking University First Hospital, and Peking University Third Hospital (all in Beijing, China) were included in the study. The median follow-up was 10.9 months (range 2.0–41.2 months) and the median age at enrollment was 56 years (range 30–86 years). Among these 151 patients, 90 (59.6%) had visceral metastases, 64 (42.4%) were sensitive to ET, 111 (73.5%) were postmenopausal, and 25 (16.6%) had de-novo stage IV disease (presented with metastatic disease ab initio, considered to be sensitive to ET) (Table 1). A total of 133 patients (88.1%) had at least one measurable lesion, and 18 patients (11.9%) had evaluable bone-only metastasis. Palbociclib combined with ET was administered as first-line therapy in 88 patients (58.3%), as second-line therapy in 39 patients (25.8%), and as third-line therapy in 24 patients (15.9%) (Table 1).

Treatment

The date of last follow-up was 8 July 2021. From this retrospective study, 94 events of disease progression or death had occurred (disease progression in 84 patients and death in 10 patients), 57 patients continued to receive treatment of palbociclib combined with ET. The initial dose of palbociclib was 125 mg QD for 99 patients (65.6%), and 100 mg QD for 52 patients (34.4%) (Table 1). A total of 64 patients (42.4%) had a reduction in palbociclib dose due to AEs. Among these 64 patients, 39 (25.8%) had palbociclib reduced from 125 mg QD to 100 mg QD, 12 (7.9%) had it reduced from 125 mg QD to 75 mg QD, and 13 (8.6%) had it reduced from 100 mg QD to 75 mg QD. The final maintenance doses were 125 mg QD for 48 patients (31.8%), 100 mg QD for 78 patients (51.7%), and 75 mg QD for 25 patients (16.6%) (Table 1). Eighty-seven patients (57.6%) received palbociclib in combination with AI and 64 patients (42.4%) received palbociclib in combination with fulvestrant (at a dose of 500 mg, administered intramuscularly on day 1 of each 28-day cycle, with an additional dose on day 15 of cycle 1) (Table 1).

Efficacy

Tumor response rate

Among the 88 patients who received palbociclib in the first-line setting, PR was observed in 36 patients (40.9%), SD in 49 patients (55.7%), and CR in no patients, resulting in an ORR of 40.9% (36/88) and a DCR of 96.6% (85/88). In the first-line cohort, 62 patients received palbociclib with an initial dose of 125 mg and obtained an ORR of 46.8% (29/62), while 26 patients received palbociclib with an initial dose of 100 mg and the ORR was 26.9% (7/26), with no significant difference ($P = 0.08$).

Of the 39 patients who received palbociclib as second-line therapy, PR was observed in four patients, SD in 32 patients, and CR in no patients, yielding an ORR of 10.3% (4/39) and a DCR of 92.3% (36/39), and among these 39 patients, 25 received an initial dose of palbociclib 125 mg with an ORR of 12.0% (3/25), while 14 patients received an initial dose of palbociclib 100 mg with an ORR of 7.1% (1/14). Of the 24 patients with treatment-refractory disease who received palbociclib as third-line therapy, PR was achieved in only one patient and SD in 17 patients, yielding an ORR of 4.2% (1/24) and a DCR of 75.0% (18/24), and among these 24 patients, 12 received an initial dose of palbociclib 125 mg with an ORR of 0.0% (0/12), while the counterpart 12 received an initial dose of palbociclib 100 mg with an ORR of 8.3% (1/12).

Association of progression-free survival with different lines of therapy and initial dose of palbociclib

Among entire patients ($n = 151$), the mPFS were statistically significantly different between patients receiving palbociclib combined with ET as first-line (19.8 months), second-line (10.0 months), and third-line (6.1 months) therapy ($P < 0.001$; Fig. 1a). Similarly, in the cohort of patients who received palbociclib with an initial dose of 125 mg ($n = 99$), the mPFS in first-line (20.9 months), second-line (10.0 months), and third-line (5.7 months) settings were statistically significantly different ($P = 0.003$; Fig. 1b); however in the cohort of patients who received palbociclib with an initial dose of 100 mg ($n = 52$), the mPFS in first-line (12.3 months), second-line

Table 1 Analysis of patients clinical and pathologic characteristics

Characteristic	*n* (%)[a]	mPFS (95% CI)	*P*-value	
			Univariate analysis	Multivariate analysis
Age				
Median (range) (years)	56 (30–86)			
<55 years	65 (43.0)	11.5 (2.31–20.70)	0.78	
≥55 years	86 (57.0)	12.8 (9.44–16.16)		
Menopausal status				
Postmenopausal	111 (73.5)	12.4 (8.57–16.17)	0.87	
Premenopausal or perimenopausal	40 (26.5)	11.5 (5.15–17.85)		
ECOG performance status				
0	105 (69.5)	12.1 (9.91–14.35)	0.09	0.39
1	43 (28.5)	17.3 (8.16–26.44)		
2	3 (2.0)	6.2 (5.22–7.24)		
Disease stage at initial diagnosis				
I	19 (12.6)	11.5 (4.22–18.78)	0.75[b]	
II	54 (35.8)	10.9 (8.55–13.20)		
III	47 (31.1)	14.7 (8.51–20.83)		
IV	25 (16.6)	13.4 (6.76–19.98)		
Unknown	6 (4.0)			
Histologic type of tumor				
Invasive ductal carcinoma	134 (88.7)	12.3 (9.23–15.38)	0.42	
Invasive lobular carcinoma	12 (7.9)	9.1 (NE)		
Mucinous adenocarcinoma	2 (1.3)	NR		
Pure tubular carcinoma	3 (2.0)	4.8 (2.83–6.77)		
Estrogen receptor				
1–10%	8 (5.3)	15.5 (8.54–22.40)	0.60	
11–100%	143 (94.7)	12.3 (9.10–15.50)		
Progesterone receptor				
1–10%	26 (17.2)	12.1 (1.04–23.22)	0.31	
11–100%	106 (70.2)	13.0 (8.85–17.21)		
Negative	19 (12.6)	8.6 (2.91–14.23)		
Ki 67				
<20%	46 (30.5)	16.1 (8.34–23.86)	0.13[b]	
≥20%	99 (65.6)	10.9 (8.23–13.57)		
Unknown	6 (4.0)			
Disease-free survival				
≤24 months	19 (12.6)	4.9 (4.69–5.17)	<0.001[c]	0.009
>24 months	107 (70.9)	14.7 (10.55–18.79)		
De-novo stage IV[d]	25 (16.6)	13.4 (6.76–19.98)		
Metastatic site				
Visceral (brain, liver, lung)	90 (59.6)	11.5 (8.86–14.08)	0.38[e]	
Non-visceral	61 (40.4)	16.1 (10.55–21.65)		
Bone-only	18 (11.9)	16.8 (7.83–25.83)		
Line of therapy				
First-line	88 (58.3)	19.8 (12.49–27.05)	<0.001	0.006
Second-line	39 (25.8)	10.0 (6.70–13.30)		
Third-line	24 (15.9)	6.1 (4.45–7.81)		
Prior endocrine therapy				
Resistant	87 (57.6)	10.2 (7.40–13.00)	0.006	0.20
Sensitive	64 (42.4)	19.8 (10.80–28.74)		
Initial dose of palbociclib				
125 mg d1–d21, q28d	99 (65.6)	14.8 (8.42–21.24)	0.03	0.06
100 mg d1–d21, q28d	52 (34.4)	8.6 (4.00–13.14)		
Maintenance dose of palbociclib				
125 mg d1–d21, q28d	48 (31.8)	11.5 (6.27–16.73)	0.36	
100 mg d1–d21, q28d	78 (51.7)	14.7 (9.84–19.50)		
75 mg d1–d21, q28d	25 (16.6)	8.6 (3.67–13.47)		
Concomitant endocrine therapy				
Aromatase inhibitor	87 (57.6)	12.3 (5.70–18.90)	0.34	
Fulvestrant	64 (42.4)	12.4 (5.70–15.23)		
Prior neoadjuvant/adjuvant chemotherapy				
Anthracyclines	6 (4.0)	NR	0.47[b]	
Taxanes	16 (10.6)	11.5 (8.07–14.93)		
Anthracyclines + taxanes	56 (37.1)	9.1 (5.08–13.18)		
Fluorouracil + Adriamycin + cyclophosphamide	14 (9.3)	7.3 (0.00–17.07)		
Capecitabine/fluorouracil/thiotepa/cisplatin + vinorelbine	3 (2.0)	11.5 (NE)		
None	45 (29.8)	13.4 (7.94–18.80)		
Unknown	11 (7.3)			
Prior neoadjuvant/adjuvant endocrine therapy				
SERMs	49 (32.5)	8.7 (5.34–12.12)	0.11[b]	
Aromatase inhibitor	45 (29.8)	11.5 (8.45–14.49)		
SERMs followed by aromatase inhibitor	11 (7.3)	10.6 (0.00–21.28)		
None	40 (26.5)	19.8 (14.33–25.21)		
Unknown	6 (4.0)			

95% CI, 95% confidence interval; DFS, disease-free survival; ET, endocrine therapy; mPFS, median progression-free survival; NE, not evaluable; NR, not reached; SERMs, selective estrogen receptor modulators.

[a]Data are number (%), because of rounding, some percentages do not total 100% when summed.

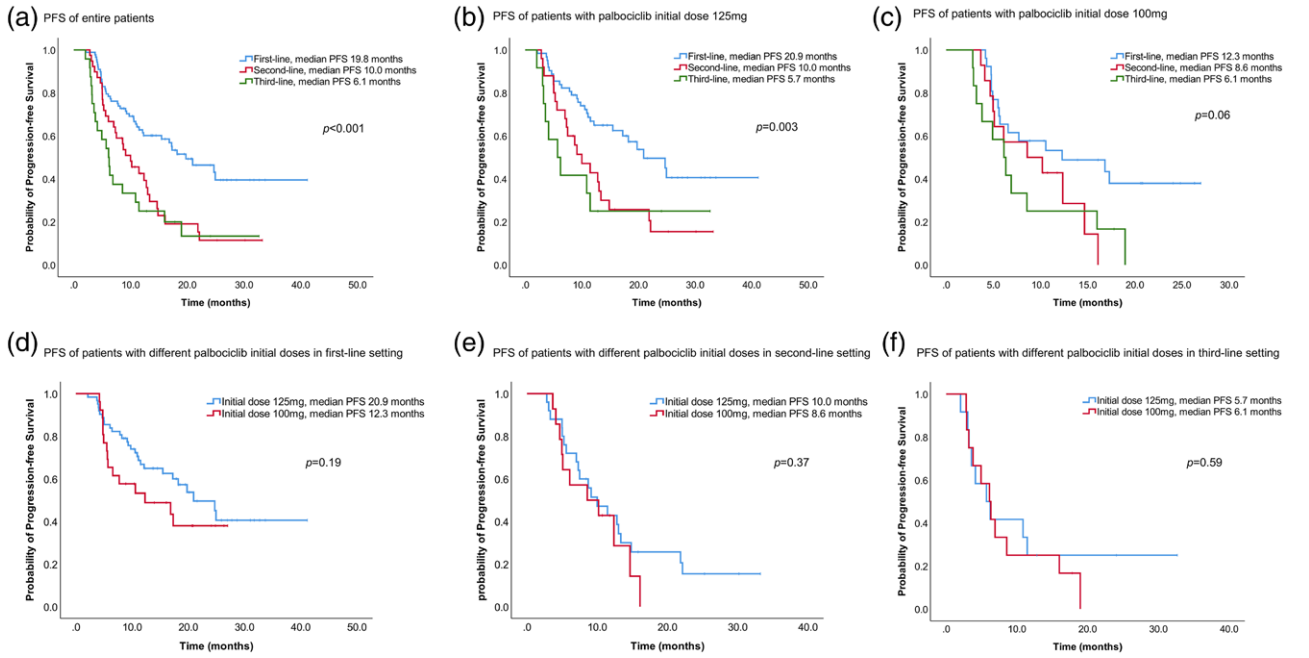
[b]These *P*-values are generated from comparing mPFS of each stratification factor excluding the factor of "unknown".

[c]This *P*-value is the result of comparing mPFS of DFS <24 months and DFS ≥24 months.

[d]The de-novo stage IV disease refers to metastatic disease ab initio, and is considered to be sensitive to endocrine therapy.

[e]This *P*-value is the result of comparing mPFS of visceral metastases and non-visceral metastases. The following factors achieved a *P*-value <0.10 through univariate analysis, including ECOG performance status, DFS, line of therapy, ET sensitivity, and initial dose of palbociclib; these factors have in turn been exposed to multivariate analysis.

Fig. 1



Progression-free survival of patients receiving palbociclib as first-, second-, and third-line therapy. (a) PFS of patients receiving palbociclib in first-line ($n = 88$), second-line ($n = 39$), and third-line ($n = 24$) settings in the entire cohort. (b) PFS of patients receiving palbociclib initial dose 125 mg in first-line ($n = 62$), second-line ($n = 25$), and third-line ($n = 12$) settings. (b) PFS of patients receiving palbociclib initial dose 100 mg in first-line ($n = 26$), second-line ($n = 14$), and third-line ($n = 12$) settings. (d) PFS of patients with different palbociclib initial doses in first-line setting. (e) PFS of patients with different palbociclib initial doses in second-line setting. (f) PFS of patients with different palbociclib initial doses in third-line setting. PFS, progression-free survival.

(8.6 months), and third-line (6.1 months) settings were not statistically significantly different ($P = 0.06$; Fig. 1c).

In the first-line cohort ($n = 88$), the mPFS for patients with palbociclib initial dose 125 mg ($n = 62$) versus 100 mg ($n = 26$) was 20.9 months (95% CI 14.75–27.11) and 12.3 months (95% CI 0.00–24.85), respectively ($P = 0.19$; absolute difference 8.6 months; Fig. 1d). In the second-line cohort, the mPFS for patients with palbociclib initial dose 125 mg ($n = 25$) versus 100 mg ($n = 14$) was 10.0 months (95% CI 5.77–14.23) and 8.6 months (95% CI 1.08–16.12), respectively ($P = 0.37$; Fig. 1e). In the third-line cohort, the mPFS for patients with palbociclib initial dose 125 mg ($n = 12$) versus 100 mg ($n = 12$) was 5.7 months (95% CI 2.14–9.27) and 6.1 months (95% CI 3.75–8.51), respectively ($P = 0.59$; Fig. 1f).

Meanwhile, in the first-line cohort, subgroup analyses of PFS according to stratification factors and other baseline characteristics confirmed a consistent benefit of palbociclib initial dose 125 mg (compared to 100 mg) across all subgroups (Fig. 2).

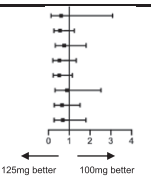
Association of progression-free survival with different metastatic sites, disease-free survival and endocrine therapy sensitivity

In the first-line cohort ($n = 88$), the mPFS was not statistically significantly different for patients with visceral metastases ($n = 48$) and with non-visceral metastases ($n = 40$) (20.9 months, 95% CI not evaluable and 18.2 months, 95% CI 10.50–25.91, respectively; $P = 0.87$). In the subgroups of the first-line cohort in which the initial dose of palbociclib was 125 mg ($n = 62$) or 100 mg ($n = 26$), the mPFS of patients with visceral metastases and with non-visceral metastases was not statistically significantly different (125 mg group: 20.9 months versus 24.7 months, $P = 0.92$, Fig. 3a; 100 mg group: 17.3 months versus 10.6 months, $P = 0.65$, Fig. 3b). Similarly, in the second- and third-line cohort, the mPFS was not statistically significantly different for patients with visceral metastases and with non-visceral metastases (second-line setting: 10.2 months versus 9.1 months, $P = 0.96$; third-line setting: 4.9 months and 8.6 months, $P = 0.26$).

In the first-line cohort, the mPFS of patients with disease-free survival (DFS) <24 months ($n = 9$) and with DFS ≥24 months ($n = 63$) was statistically significantly different (4.8 months versus 24.7 months; HR = 4.79, 95% CI 2.12–10.62; $P < 0.001$), and the mPFS of the corresponding patients in its subgroups for which the initial dose of palbociclib was125 mg or 100 mg were statistically significantly different (125 mg group: 4.0 months versus 24.7 months, $P = 0.003$; 100 mg group: 4.8 months versus 16.8 months, $P = 0.003$; Fig. 2). However, in the second- and third-line cohort, the mPFS was not statistically

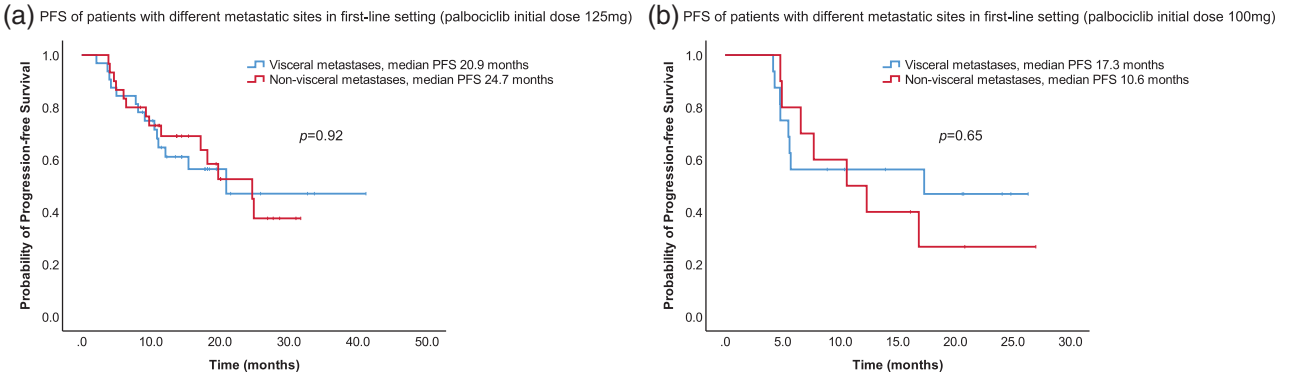
Fig. 2

Subgroups	palbociclib initial dose 125mg in first-line (n=62)			palbociclib initial dose 100mg in first-line (n=26)			HR (95% CI)	*p*-value§
	n (%)*	mPFS (95% CI)	*p*-value‡	n (%)*	mPFS (95% CI)	*p*-value¶		
DFS<24 months	6 (9.7)	4.0 (2.68-5.32)	0.003	3 (11.5)	4.8 (4.75-4.85)	0.003	0.61 (0.12-3.08)	0.54
DFS≥24 months	44 (71.0)	24.7 (NE)		19 (73.1)	16.8 (NE)		0.56 (0.26-1.24)	0.15
Visceral metastases (liver, lung, brain)	32 (51.6)	20.9 (NE)	0.92	16 (61.5)	17.3 (NE)	0.65	0.76 (0.32-1.81)	0.53
Non-visceral metastases	30 (48.4)	24.7 (17.46-31.94)		10 (38.5)	10.6 (3.44-17.70)		0.53 (0.21-1.33)	0.17
ET-resistant	28 (45.2)	18.2 (7.63-28.77)	0.16	14 (53.9)	5.7 (3.74-7.66)	0.05	0.52 (0.23-1.15)	0.10
ET-sensitive	34 (54.8)	NR		12 (46.2)	NR		0.89 (0.31-2.52)	0.82
Aromatase inhibitor	41 (66.1)	24.9 (NE)	0.17	15 (57.7)	17.3 (1.63-32.96)	0.49	0.65 (0.28-1.52)	0.32
Fulvestrant	21 (33.9)	15.5 (2.19-28.75)		11 (42.3)	10.6 (2.88-18.26)		0.69 (0.27-1.80)	0.45



Subgroup analysis of progression-free survival in first-line setting. The HR with 95% CI for disease progression in various subgroups in first-line setting is shown. Boxes represent HR for disease progression, with error bars indicating 95% CI. The stratification factors were DFS</≥24 months, with visceral metastases, with non-visceral metastases, ET sensitivity, and concomitant ET. *Data are number (%), because of rounding, some percentages do not total 100% when summed. ‡These *P* values are generated from comparing mPFS of each stratification factor in the 125 mg group. ¶These *P* values are generated from comparing mPFS of each stratification factor in the 100 mg group. §These *P* values are the results of comparing mPFS of palbociclib initial dose 125 mg and 100 mg in each subgroup. 95% CI, 95% confidence interval; DFS, disease-free survival; ET, endocrine therapy; HR, hazard ratio; mPFS, median progression-free survival; NE, not evaluable; NR, not reached.

Fig. 3



Progression-free survival of patients with different metastatic sites in first-line setting. (a) PFS of patients with visceral metastases ($n = 32$) or non-visceral metastases ($n = 30$) receiving palbociclib with initial dose of 125 mg in first-line setting. (b) PFS of patients with visceral metastases ($n = 16$) or non-metastases metastases ($n = 10$) receiving palbociclib with initial dose 100 mg in first-line setting. PFS, progression-free survival.

significantly different for patients with DFS <24 months and with DFS ≥24 months.

In the first-line cohort ($n = 88$), the mPFS for the patients with ET-resistant disease ($n = 42$) and ET-sensitive disease ($n = 46$) was statistically significantly different (12.1 months, 95% CI 5.59–18.67 and not reached; HR = 2.02, 95 CI 1.09–3.72, $P = 0.02$). However, in the subgroup of the first-line cohort in which the initial dose of palbociclib was 125 mg or 100 mg, the mPFS for the corresponding patients was not statistically significantly different (Fig. 2). And in the second- and third-line cohort, the mPFS was not statistically significantly different for patients with ET-resistant disease and ET-sensitive disease.

Independent risk factors for the efficacy of palbociclib combined with endocrine therapy

The univariate analysis of the influencing factors of mPFS for the entire patients ($n = 151$) is shown in Table 1. And the following factors achieved a *P*-value less than 0.10 through univariate analysis, including ECOG performance status, DFS, line of therapy, ET sensitivity, and initial dose of palbociclib. And these factors were exposed to multivariate analysis. The results of multivariate analysis showed that DFS ($P = 0.009$) and line of therapy ($P = 0.006$) were still statistically significantly different (Table 1).

Safety profile

Of the 151 enrolled patients, 148 experienced AEs. The most common and serious (grade 3–4) AEs were leukopenia and neutropenia (Table 2). Leukopenia at any grade occurred in 145 patients (96.0%) and at grade 3–4 in 61 patients (40.4%). Neutropenia at any grade occurred in 145 patients (96.0%) and at grade 3–4 in 89 patients (58.9%). Only two patients (1.3%) had febrile neutropenia. Other hematologic AEs included anemia (73 patients, 48.3%) and thrombocytopenia (29 patients, 19.2%).

Table 2 Adverse events in patients treated with palbociclib

	Overall		Grade 1		Grade 2		Grade 3		Grade 4	
Adverse events	Cases	Proportion (%)	Cases	Proportion (%)	Cases	Proportion (%)	Cases	Proportion (%)	Cases	Proportion (%)
Hematologic toxicities										
Leukopenia	145	96.0	10	6.6	74	49.0	53	35.1	8	5.3
Neutropenia	145	96.0	9	6.0	47	31.1	77	51.0	12	7.9
Anemia	73	48.3	24	15.9	8	5.3	4	2.6	0	0.0
Thrombocytopenia	29	19.2	15	9.9	8	5.3	3	2.0	3	2.0
Non-hematologic toxicities										
Asthenia	49	32.5	41	27.2	7	4.6	1	0.7	0	0.0
Alopecia	21	13.9	20	13.2	1	0.7	0	0.0	0	0.0
Diarrhea	17	11.3	17	11.3	0	0.0	0	0.0	0	0.0
Nausea	7	4.6	7	4.6	0	0.0	0	0.0	0	0.0
Vomiting	4	2.6	4	2.6	0	0.0	0	0.0	0	0.0
Decreased appetite	22	14.6	12	7.9	1	0.7	0	0.0	0	0.0
Stomatitis	26	17.2	22	14.6	4	2.6	0	0.0	0	0.0
Rash	8	5.3	4	2.6	0	0.0	0	0.0	0	0.0
Skin ulcer	4	2.6	1	0.7	2	1.3	1	0.7	0	0.0
Skin pruritus	2	1.3	2	1.3	0	0.0	0	0.0	0	0.0
Pulmonary interstitial changes	2	1.3	2	1.3	0	0.0	0	0.0	0	0.0
Epistaxis	1	0.7	0	0.0	1	0.7	0	0.0	0	0.0
Elevated hepatic enzymes	12	7.9	3	2.0	2	1.3	0	0.0	0	0.0
Cough	1	0.7	1	0.7	0	0.0	0	0.0	0	0.0
Pain	3	2.0	3	2.0	0	0.0	0	0.0	0	0.0
Insomnia	4	2.6	4	2.6	0	0.0	0	0.0	0	0.0

Non-hematologic AEs included asthenia, alopecia, and stomatitis, and were mostly of grade 1–2 (Table 2).

Among the 99 patients who received palbociclib with an initial dose of 125 mg QD, leukopenia and neutropenia occurred in 95 patients (96.0%) and 95 patients (96.0%), respectively (Table 3). Among the 52 patients who received palbociclib with an initial dose of 100 mg QD, leukopenia and neutropenia occurred in 50 patients (96.2%) and 50 patients (96.2%), respectively (Table 3). There was no significant difference in the AEs experienced by patients receiving different initial doses of palbociclib, except for anemia (Table 3).

Discussion

The management of HR+ ABC has seen tremendous evolution in recent years, with CDK4/6 inhibitors in combination with ET demonstrating significant efficacy in large prospective clinical trials [8,9,20,21]. These treatments have become the standard therapy for patients with HR+/HER2– ABC [22]. However, little information is available regarding the safety and efficacy of palbociclib combined with ET in the real-world setting, especially in Chinese patients.

In this multi-center retrospective study of palbociclib combined with ET, we analyzed 151 Chinese patients with HR+/HER2– ABC and found that the most consistent benefit was obtained by the 62 patients who received palbociclib with an initial dose of 125 mg in the first-line setting. These patients achieved an ORR of 46.8% with a mPFS of 20.9 months, which is consistent with the ORR of 42.1% and mPFS of 24.8 months in the intention-to-treat population and the ORR of 49% and mPFS of 25.7 months in the Asian subpopulation (n = 65, 14.6%) in the PALOMA-2 trial [8,15]. Meanwhile, in the first-line setting of our present study, the mPFS was longer in the palbociclib initial dose 125 mg group in comparison to the 100 mg group (20.9 months versus 12.3 months; absolute difference = 8.6 months), and similar results were obtained in the subgroups of first-line setting [the subgroups included: DFS </≥24 months, metastatic sites, ET-resistant, and concomitant ET (AI or fulvestrant)].

Comparing with the first-line cohort, the benefit obtained by the 25 patients in our study who received palbociclib with an initial dose of 125 mg in second-line setting was much rebated, with an ORR of 12.0% and a mPFS of 10.0 months. However, it was consistent with the ORR of 19% and mPFS of 9.5 months in the intention-to-treat population in the PALOMA-3 trial [23]. Meanwhile, PALOMA-3 enrolled 105 Asian patients (21.3%) who achieved comparable benefits to other ethnic groups [16].

In this study, the 29 patients who were treated with palbociclib combined with ET in the third-line setting also obtained beneficial effects. For this cohort, the mPFS was 6.1 months, ORR was 4.2%, and DCR was 75%. Although we did not collect data on OS, this result demonstrates the clinical benefit of CDK4/6 inhibitors when applied to late-line treatments. Our results are consistent with the data from a real-world study in the USA that showed a mPFS of 4.0 months with palbociclib administered in the third- and subsequent-line settings [24]. Our data thus confirm that Chinese patients will obtain the most significant benefit from palbociclib combined with ET when palbociclib is administered as first-line therapy with an initial dose of 125 mg.

Many patients with HR+/HER2– ABC present with visceral metastases, and their prognosis is generally worse

Table 3 Adverse events in patients administered with different initial doses of palbociclib

Adverse events	Palbocicilib initial dose 125 mg ($n = 99$)			Palbociclib initial dose 100 mg ($n = 52$)			*P*-value of any grade adverse events
	Any grade, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Any grade, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	
Hematologic toxicities							
Leukopenia	95 (96.0)	37 (37.4)	6 (6.1)	50 (96.2)	16 (30.8)	2 (3.8)	1.00
Neutropenia	95 (96.0)	55 (55.6)	9 (9.1)	50 (96.2)	22 (42.3)	3 (5.8)	1.00
Anemia	29 (29.3)	3 (3.0)	0	7 (13.5)	1 (1.9)	0	0.03
Thrombocytopenia	15 (15.2)	3 (3.0)	0	14 (26.9)	0	3 (5.8)	0.08
Non-hematologic toxicities							
Asthenia	30 (30.3)	1 (1.0)	0	19 (36.5)	0	0	0.44
Alopecia	14 (14.1)	0	0	7 (13.5)	0	0	0.91
Diarrhea	12 (12.1)	0	0	5 (9.6)	0	0	0.64
Nausea	3 (3.0)	0	0	4 (7.7)	0	0	0.23
Vomiting	3 (3.0)	0	0	1 (1.9)	0	0	1.00
Decreased appetite	5 (5.1)	0	0	8 (15.4)	0	0	0.06
Stomatitis	21 (21.2)	0	0	5 (9.6)	0	0	0.07
Rash	1 (1.0)	0	0	3 (5.8)	0	0	0.12
Skin ulcer	2 (2.0)	1 (1.0)	0	2 (3.8)	0	0	0.61
Skin pruritus	2 (2.0)	0	0	0	0	0	0.55
Pulmonary interstitial changes	2 (2.0)	0	0	0	0	0	0.55
Epistaxis	1 (1.0)	0	0	0	0	0	1.00
Elevated hepatic enzymes	5 (5.1)	0	0	0	0	0	0.17
Cough	1 (1.0)	0	0	0	0	0	1.00
Pain	3 (3.0)	0	0	0	0	0	0.55
Insomnia	4 (4.0)	0	0	0	0	0	0.30

than those with non-visceral involvement [25]. As we know, in the PALOMA-2 trial, the mPFS of patients with visceral disease receiving palbociclib combined with letrozole was 19.3 months, and in the PALOMA-3 trial, the mPFS of patients with visceral metastases receiving palbociclib combined with fulvestrant was 9.2 months [26]. In our present study, the mPFS of the patients with visceral metastases receiving palbociclib at an initial dose of 125 mg in the first-line cohort was 20.9 months, and the mPFS of patients with visceral metastases in second-line cohort was 10.2 months, which were consistent with the corresponding data in the PALOMA-2 and the PALOMA-3 trials. Meanwhile, our study showed there was no significant difference for patients with visceral metastases and with non-visceral metastases in the entire population and in the first- to third-line cohorts. Our results confirm that the clinical benefit of palbociclib combined with ET occurred irrespective of metastatic sites in Chinese patients.

In our present study, there was a statistically significant difference in mPFS between the patients with ET-sensitive and ET-resistant disease in the entire cohort and in the first-line cohort. Meanwhile, we found that there was a significant difference in mPFS between the patients with DFS <24 months and with DFS ≥24 months in the entire cohort and in the first-line cohort. These real-world observational findings are in concordance with data from the PALOMA-3 trial, which reported that patients with proven sensitivity to prior ET showed superior absolute mOS gain after treatment with palbociclib versus placebo (39.7 months versus 29.7 months), but no benefit was observed in patients who developed ET resistance (20.2 months versus 26.2 months); and patients with DFS >24 months obtained a longer mOS than patients with DFS ≤24 months (39.3 months versus 19.9 months) in palbociclib combined with fulvestrant group [9]. Our results suggest that ET-sensitive patients may benefit most from palbociclib combined with ET.

The addition of CDK4/6 inhibitors to ET can improve clinical outcomes but it also increases the incidence of AEs [27]. In our study, the highest initial dose of palbociclib (125 mg QD) was associated with the highest incidence of AEs, and among these patients (n = 99), there were 95 cases (96.0%) of neutropenia of any grade, 64 cases (64.6%) of grade 3–4 neutropenia, and two cases (2.0%) of febrile neutropenia. The incidences of severe AEs (grade 3–4) in our study were lower than those observed in the Asian populations in the PALOMA-2 and the PALOMA-3 trials [16,28]. Similarly, the incidence of non-hematologic AEs (mainly asthenia, alopecia, and stomatitis) observed in the palbociclib initial dose 125 mg group in our study was lower than the incidences in the Asian populations in the PALOMA-2 and the PALOMA-3 trials [16,28]. Overall, the results of our study have clarified that palbociclib is relatively well tolerated in the Chinese population.

Management of patients in the real world is complicated by preexisting comorbidities and compliance issues that necessitate modifications in treatment. This differs from the strictly monitored setting of a prospective clinical trial, highlighting the need for real-world data to obtain accurate information on efficacy and acute or chronic AEs for drugs used in routine clinical practice. The importance of our study lies in the analysis of both efficacy and safety data from a large cohort of Chinese women with HR+/HER2– ABC treated with palbociclib in combination with ET. Moreover, our subset analyses identified the impacts of therapy in different clinical scenarios. However, there are some limitations to our study, such as

the small sample size, short follow-up time and no randomization between the 125 mg and 100 mg cohort, therefore, the conclusions drawn from this study should be reevaluated in future with larger sample size and longer follow-up time. Meanwhile, some noteworthy concerns remain unaddressed, including the impact of palbociclib on overall survival and subsequent treatment options upon disease progression. To address these problems, we are expanding the sample size and continuing follow-up of the cases on an ongoing basis.

Conclusion

Palbociclib combined with ET is an effective therapeutic regimen for HR+/HER2– ABC, particularly in the first-line setting with palbociclib initial dose of 125 mg, and AEs were manageable.

Acknowledgements

H.L. planned the project and supervised the research. L.Z. collected, analyzed, and interpreted the data and wrote the manuscript under the supervision of H.L. Y.Z. responsible for the guidance of statistical analysis. All authors had full access to the data and agreed to the submission of the manuscript.

All procedures were performed in accordance with the ethical standards of the institution and national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent: Because this was a retrospective non-interventional study, informed consent was not required.

The datasets analyzed in this study are available from the corresponding author on reasonable request.

Conflicts of interest

There are no conflicts of interest.

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