Original Article

Efficacy and safety of palbociclib plus endocrine therapy for patients with HR$^+$/HER2$^-$ advanced breast cancer in real-world clinical practice

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Background: Palbociclib is the first cyclin dependent kinase 4/6 (CDK4/6) inhibitor approved in China to be combined with endocrine therapy (ET) for patients with hormone receptor-positive (HR$^+$)/human epidermal growth factor receptor 2-negative (HER2$^-$) metastatic breast cancer. However, palbociclib has only been used in China for a short amount of time, and there is limited data on its real-world applications. This study observed the efficacy and safety of palbociclib plus ET in a real-world setting in southwest China and we hope to provide some references for the treatment of patients with breast cancer in China.

Methods: This was an observational study of patients with HR$^+$/HER2$^-$ advanced breast cancer (ABC) who received palbociclib plus ET. The primary endpoint of the study was progression-free survival (PFS) and the 6- and 12-month progression-free rates. The secondary endpoint included the objective response rate (ORR) and the clinical benefit rate (CBR).

Results: A total of 64 patients were enrolled in this study, and 54.7% of them received palbociclib plus ET as the first-line treatment for ABC. The median PFS was 21.6 months (95% CI: 11.2–32.0 months) after a median follow-up period of 13.8 months (95% CI: 11.9–15.7 months). The 6-month progression-free rate was 75.4%, and 48.9% of patients remained progression-free at 12 months. Overall, the ORR was 21.6% and the CBR was 76.5%. Patients with the molecular typing of Luminal A (P=0.035), a lower Ki67 level (P<0.001), sensitivity or acquired resistance to ET (P=0.003), less than 3 visceral metastases lesions (P=0.001), and those who received palbociclib plus ET as first-line or second-line of treatment for ABC (P=0.001) showed longer PFS. A total of 53.1% of patients had grade 3–4 adverse events (AEs), but only 4.7% of patients experienced permanent discontinuation of treatment due to intolerable AEs.

Conclusions: The efficacy of palbociclib plus ET is worthy of recognition and the toxicity was acceptable in this study, which is similar to previously reported data from randomized clinical trials and other real-world evidence. Treatment for ABC using palbociclib plus ET should be recommended more widely in China due to the efficacy and safety.

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Keywords: Palbociclib; hormone receptor-positive (HR$^+$); human epidermal growth factor receptor 2-negative (HER2$^-$); advanced breast cancer (ABC); endocrine therapy (ET)

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Introduction

Global Cancer Observatory (GLOBOCAN) 2020 data estimated that the incidence of breast cancer in 2020 would exceed that of lung cancer for the first time, and that breast cancer now had the highest morbidity among all malignant tumors around the world (1). Patients with hormone receptor-positive (HR$^+$)/human epidermal growth factor receptor 2-negative (HER2$^-$) breast cancer represent approximately 70% of all the patients with breast cancer. Endocrine therapy (ET) has improved the outcomes of these patients significantly due to a high degree of therapeutic efficiency and safety. However, patients with HR$^+$/HER2$^-$ breast cancer who were in advanced stage often have a dismal prognosis and the third generation of aromatase inhibitor (AI) can only extend their progression-free survival (PFS) to 8–14 months as the first-line ET in advanced stage. Therefore, it is necessary to explore new treatment options on the basis of ET to improve the outcome of those patients (2,3). In recent years, with the development of research on signal transduction pathways, cyclin dependent kinase 4/6 (CDK 4/6) inhibitors have shown great potential in the treatment for HR$^+$/HER2$^-$ advanced breast cancer (ABC). This is because they can selectively inhibit CDK4/6 and obstruct the CDK-retinoblastoma (Rb)-early-region-2 transcription factor (E2F) pathway which can promote the transformation of cells from G1 phase to S phase, thereby restraining the unlimited proliferation of tumor cells, and there was research which have confirmed that the resistance of ET may also be related to the CDK-Rb-E2F pathway. Therefore, CDK4/6 inhibitors can significantly delay the ET resistance of patients with HR$^+$/HER2$^-$ ABC (4,5). On the basis of the theoretical basis above, CDK4/6 inhibitors combined with ET have gradually become the new choice of treatment for patients with HR$^+$/HER2$^-$ ABC.

Based on the results from the phase II and III randomized clinical trials (RCTs) known as PALOMA, palbociclib became the first CDK4/6 inhibitor approved by the China Food and Drug Administration for clinical applications in 2018. As reported in PALOMA-2, letrozole plus palbociclib have increased the median PFS of patients with HR$^+$/HER2$^-$ ABC who never received treatment in the advanced stage by 13.1 months compared with letrozole plus placebo (27.6 *vs.* 14.5 months). In PALOMA-3, the researchers concluded that fulvestrant combined with palbociclib could significantly prolong the PFS (median PFS: 9.5 *vs.* 4.6 months) and overall survival (OS) (median OS: 34.9 *vs.* 28 months) than fulvestrant combined with placebo of patients who progressed after prior ET (6-10). While some RCTs have been conducted to confirm its efficacy and safety, further data is needed to support those confirmations because RCTs were limited by strict inclusion and exclusion criteria and standardized intervention so that the results of RCT can't be fully inferred to the real world (11-13). Furthermore, palbociclib has only been approved by the China Food and Drug Administration for a short amount of time, therefore, there is a lack of real-world clinical data belonging to Chinese patients. So, we need more real-world evidence which may guide the clinical treatment of HR$^+$/HER2$^-$ ABC with palbociclib plus ET and make recommendations such as adaptive population, medication regimen and management of possible adverse effects in China.

In this study, we investigated the efficacy and safety of palbociclib plus ET for patients with HR$^+$/HER2$^-$ ABC in southwest China. By examining the clinical characteristics that could affect the efficacy of the treatment and analyzing treatment options for patients who were resistance to palbociclib, we hope to improve the application mode of palbociclib plus ET for patients in China. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1002/rc).

Methods

Study design and patients

This is an observational study conducted in southwest China. We retrospectively selected patients who met the inclusion and exclusion criteria from September 2018 to April 2021 at the First Affiliated Hospital of Chongqing

Medical University and Chongqing University Cancer Hospital. Eligible patients included patients with HR^+/$HER2^-$ ABC who were treated with palbociclib plus ET according to the China Food and Drug Administration-approved indication for palbociclib and they should have relatively complete clinical data such as basic information, clinical features, and detailed follow-up data. Patients with other primary malignancies or those lost to follow-up were excluded.

We continuously selected patients who met the inclusion and exclusion criteria from September 2018 to April 2021 in the order of the time starting medication with palbociclib during outpatient or inpatient treatment, and in this way to minimize potential selection bias. As this clinical practice was carried out in real-world setting, there were significant differences among samples, so it was necessary to select as many patients as possible to avoid bias. Therefore, the final sample size of this study was mainly determined by the number of cases who met the inclusion and exclusion criteria during the period of research, and finally a total of 64 patients were enrolled in the study which was sufficient for some preliminary analysis. All patients who did not experience disease progression were followed up for at least 6 months. The last follow-up time point was October 2021. The baseline characteristics of participants were collected through the hospital's electronic medical record system. The follow-up was achieved by an outpatient review, an inpatient examination, and feedback received by phone or email with patients.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (No. 2021-445) and the Chongqing University Cancer Hospital was informed and agreed the study. Informed consent was taken from all the patients.

Definition of clinical variables

According to the clinical, radiographic, and pathological findings, patients were staged based on the eighth edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system (14). ABC was defined as locally advanced, which was unresectable, or metastatic. Immunohistochemistry was used to determine the status of each patient's estrogen receptor (ER) and progesterone receptor (PR). A rate of nuclear staining ≥1% was defined as ER or PR positive. If a patient was ER or PR positive, they were defined as HR^+ (15). The evaluation of HER2 status was based on the standard recommended by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP): a patient with a staining score of 0, 1, or 2 without the *HER2* gene amplification as determined by fluorescence *in situ* hybridization (FISH) was defined as HER2 negative, while patients with a score of 2 with the *HER2* gene amplification as determined by FISH and a score of 3 were considered HER2 positive (16). Menopause was defined as the permanent termination of menstruation, which was divided into natural menopause and artificial menopause.

The baseline metastasis status of patients was determined by the results of imaging and pathology reports. Types of metastases were including local metastasis, bone-only metastasis, and visceral metastasis with or without bone metastasis. At least one measurable tumor lesion must be met by imaging examination in the follow-up for the best tumor responses which was assessed by the Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1) (17). Primary resistance to ET was defined as recurrence of disease occurring during the first 2 years of adjuvant ET, or disease progression within the first 6 months of first-line ET for an advanced stage of the disease. Acquired resistance to ET was defined as recurrence occurring after the first 2 years of adjuvant ET, or disease progression after the first 6 months of first-line ET for an advanced stage of the disease. Patients who relapsed after 1 year of completing adjuvant ET or who did not previously receive ET were considered sensitive to ET (18).

The emergence time and severity of AEs was graded according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) and recorded while each patient was on medication. There are three different dosage options for palbociclib including 125, 100, and 75 mg. The recommended starting dose of palbociclib was 125 mg (once daily for 3 weeks, followed by 1 week off treatment). Patients adjusted the dosage and medication cycle according to drug safety and medication tolerance, and terminated medication if necessary.

Endpoints

Computerized tomography or magnetic resonance imaging was carried out every 2 to 3 months during treatment until the disease progressed or the patient died. The tumor response was evaluated by the attending physician according to the RECIST 1.1.

The primary endpoint of the study was PFS, which was defined as the time from initiation of palbociclib treatment to disease progression or death, and the 6- and 12-month progression-free rates which were added to evaluate the efficacy for patients who did not reach PFS due to the short time of medication. The secondary endpoint included the objective response rate (ORR) and the clinical benefit rate (CBR).

All patients were divided into three subgroups. The first, second, and third subgroup received palbociclib plus ET as a first-line treatment, a second-line treatment, and a later-lines treatment for ABC, respectively. We analyzed the endpoints of each subgroup individually to observe the differences between each population. The safety of medication was assessed according to CTCAE 4.0, and the choices and efficacy of subsequent therapy after the progression of the disease while the patient was treated with palbociclib was our exploratory endpoint.

According to RECIST 1.1, the efficacy was divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). ORR was defined as the percentage of CR and PR, while CBR was defined as the percentage of CR, PR, and SD for at least 24 weeks.

Statistical analyses

All statistical analysis and graphs were performed with SPSS (version 25.0, IBM Corporation, Armonk, NY, USA) and GraphPad Prism (version 8.0.2, San Diego, CA, USA). Quantitative data conforming to a normal distribution were represented by mean ± standard deviation, and those disobeying the normal distribution were expressed as a median (lower quartile to upper quartile). Categorical data were described as the number of cases and the constituent ratio. The survival curves were plotted by the Kaplan-Meier method to analyze PFS, which was verified by the log-rank test during the univariate analysis. The clinical factors with statistical significance in univariate analysis were tested for collinearity diagnostics and those factors without multicollinearity could be selected for the Cox proportional hazards regression model which was used for multivariate analysis. The correlation analysis between clinical characteristics and tumor response was performed using the chi-square test or Fisher's exact test. Due to the small sample size of this study and the other complete data of samples with missing values, we chose imputation instead of deletion to ensure the integrity of data. All the missing data were categorical variables and were replaced by the median to reduce the disturbance to the results. The follow-up time was calculated by the time from the start of treatment to disease progression, death, or the date of the last follow-up. The reverse Kaplan-Meier method was used to estimate the median follow-up period. A two-sided P value <0.05 was considered to be statistically significant.

Results

Patients and treatment patterns

A total of 73 patients received palbociclib plus ET for treatment during the period. From this, 4 patients were excluded (3 patients lacked relatively complete clinical data, and 1 patient had another primary malignancy). After a median follow-up period of 13.8 months, 5 patients were loss to follow-up. By the beginning of our analysis, a total of 64 patients were enrolled in our study. Among all the participants, 62 patients (96.9%) had a metastatic stage of the disease, and 2 patients had a locally advanced stage of the disease. One male patient was also included. The age range of patients at the initiation of treatment with palbociclib plus ET was 34 to 81 years, and the average age was 54.2±11.3 years. A total of 11 patients (17.2%) were over 65 years old, and 48 patients (75.0%) were menopausal. There were 47 patients (73.4%) with visceral metastases, and patients with two or fewer visceral metastases sites accounted for 91.5% of these 47 patients (43/47). The remaining patients included those with metastases of a distant lymph node and bone-only, in addition to 2 locally advanced patients. A total of 54.7% (35/64) of the patients received palbociclib plus ET as the first-line treatment for the advanced stage of cancer, while 14 patients (21.9%) and 15 patients (23.4%) were in the second-line and later-lines setting, respectively. A total of 27 patients (42.2%) had undergone chemotherapy for ABC before treatment with palbociclib plus ET, 46 patients (71.9%) had previously received ET before they received palbociclib plus ET. A total of 59 patients (92.2%) started to receive a daily dose of palbociclib at 125 mg, and the remaining 5 patients (7.8%) started at 100 mg/d. Letrozole was the most common choice (48.4%) of the ET concomitant drug with palbociclib, followed by fulvestrant (34.4%), exemestane (9.4%), anastrozole (4.7%) and tamoxifen (3.1%).

A total of 30 patients (46.9%) were still receiving palbociclib plus ET by the end of the follow-up, and the other 34 patients (53.1%) had discontinued medication

for different reasons. The main reason for discontinuation was disease progression (42.2%), followed by financial issues (6.3%), or intolerable AEs (4.7%). Detailed clinical characteristics and post-treatment status of the patients are shown in *Table 1*.

Efficacy

The median PFS (mPFS) was 21.6 months (95% CI: 11.2–32.0 months) after a median follow-up period of 13.8 months (95% CI: 11.9–15.7 months). Among patients who received palbociclib plus ET as the first-line treatment for ABC, the median PFS was not reached due to the short time of follow-up, while the median PFS of patients who received that as more than a first-line of treatment for ABC was 7.9 months (the mPFS of the patients in the second-line and the later-lines setting was 16.9 and 4.9 months, respectively). Excluding those patients who discontinued medication due to financial issues or intolerable AEs within 6 and 12 months, we found that the 6-month PFS rate and the 12-month PFS rate was 75.4% and 48.9%, respectively. For patients in the first-line setting, the 6-month PFS rate was 93.9% and the 12-month PFS rate was 72.7%, and in the second-line setting, the 6-month PFS rate was 78.6% and the 12-month PFS rate was 50%, while the PFS was 28.6% and 7.7% in the later-lines setting, respectively. This confirmed the short-term efficacy of palbociclib plus ET.

Univariate analysis showed that the following factors were statistically significant in the subgroup analyses of PFS (P<0.05; *Table 2*): the range of Ki67, the molecular typing of breast cancer, whether a patient underwent chemotherapy for ABC, the lines of prior ET, the sensitivity to ET, the number of visceral metastases, whether or not the patient had liver metastasis, and the line of palbociclib plus ET for ABC. There was a statistical difference between Ki67 ≥20% and Ki67 <20%. A better prognosis was observed in the subgroup with a lower level of Ki67 (P=0.001). Patients with Luminal A had a better survival prognosis than those with Luminal B (P=0.004). Greater survival benefit was shown in patients who had not experienced chemotherapy for ABC rather than those who had undergone chemotherapy for ABC (P=0.004). In addition, more obvious survival benefits were observed in those patients who received prior ET ≤1 line (P<0.001), and who were without primary resistance to ET (P=0.001), had a fewer number of visceral metastasis sites (P<0.001), were without liver metastasis (P<0.001), or who received palbociclib as a first or second line of treatment for ABC (P<0.001) (there was no statistically significant difference between the first-line and the second-line while we can see significant difference between later-lines and first/second-line) (*Figure 1*). The clinical factors with statistical significance in univariate analysis were tested for collinearity diagnostics and we found that there was multicollinearity between whether underwent chemotherapy for ABC and the lines of palbociclib, so we excluded the factor of whether underwent chemotherapy for ABC and put other clinical factors into the Cox proportional hazards regression model which was used for multivariate analysis. The Cox regression multivariable analysis showed that the Ki67 level (P<0.001), the molecular typing (P=0.035), a patient's sensitivity to ET (P=0.003), the number of visceral metastases (P=0.001), and the line of palbociclib plus ET for ABC (P=0.001) were independent prognostic factors for patients (*Table 3*).

According to the standard of RECIST 1.1, 51 patients had measurable lesions (28 patients in the first-line setting, 12 patients in the second-line setting and 11 patients in the later-line setting), and among these patients, 21.6% (11/51) of them were with PR, 72.5% (37/51) of them were with SD and 5.9% (3/51) of them were with PD. Based on this, the ORR was 21.6% (11/51), and the CBR was 76.5% (39/51). The ORR and CBR of patients received palbociclib plus ET as the first-line treatment for ABC were 28.6% (8/28) and 96.4% (27/28), respectively. The ORR and CBR of the second-line population were 16.7% (2/12) and 75.0% (9/12), while the proportion were 9.1% (1/11) and 27.3% (3/11) in the later-lines. Among the patients who received palbociclib plus ET as more than a first-line of treatment for ABC, the ORR and CBR were 13.0% (3/23) and 52.2% (12/23), respectively. The specific distribution of patients with ORR and CBR in different clinical characteristics is shown in *Table 4*. We can see that no significant statistical difference was observed for the ORR of 51 patients in different clinical characteristics, but the higher CBR was observed in the subgroup whose range of Ki67 was lower (P=0.024) or whose molecular typing of breast cancer was Luminal A (P=0.027). At the same time, patients with fewer lines of chemotherapy for ABC (P<0.001) or prior ET (P<0.001), and the patients without endocrine resistance (P=0.026), had better CBR than other patients. In addition, as we expected, patients who received palbociclib plus ET as a first-line or second-line treatment for ABC had higher CBR than those who received palbociclib as a later-lines treatment.

Table 1 Patient demographic characteristics

Characteristic	All patients (n=64)	First-line patients (n=35)	Second-line patients (n=14)	Later-lines patients (n=15)
Age, mean (SD), years	54.2 (11.3)	52.0 (10.2)	57.4 (14.6)	56.6 (9.7)
Age group, n (%)				
<65 years	53 (82.8)	32 (91.4)	9 (64.3)	12 (80.0)
≥65 years	11 (17.2)	3 (8.6)	5 (35.7)	3 (20.0)
Menstruation status, n (%)				
Menopausal	48 (75.0)	24 (68.6)	11 (78.6)	13 (86.7)
Premenopausal	15 (23.4)	10 (28.6)	3 (21.4)	2 (13.3)
Male	1 (1.6)	1 (2.9)	0 (0.0)	0 (0.0)
ECOG PS, n (%)				
0	2 (3.1)	2 (5.7)	0 (0.0)	0 (0.0)
1	54 (84.4)	30 (85.7)	13 (92.9)	11 (73.3)
2	8 (12.5)	3 (8.6)	1 (7.1)	4 (26.7)
Disease stage at initial diagnosis, n (%)				
I	10 (15.6)	7 (20.0)	2 (14.3)	1 (6.7)
II	21 (32.8)	12 (34.3)	5 (35.7)	4 (26.7)
III	8 (12.5)	5 (14.3)	1 (7.1)	2 (13.3)
IV	18 (28.1)	9 (25.7)	5 (35.7)	4 (26.7)
Not documented	7 (10.9)	2 (5.7)	1 (7.1)	4 (26.7)
Molecular typing at initial diagnosis, n (%)				
Luminal A	36 (56.3)	21 (60.0)	8 (57.1)	7 (46.7)
Luminal B	28 (43.8)	14 (40.0)	6 (42.9)	8 (53.3)
Expression of Ki67, n (%)				
≤20%	39 (60.9)	22 (62.9)	9 (64.3)	8 (53.3)
>20%	25 (39.1)	13 (37.1)	5 (35.7)	7 (46.7)
Sensitivity to ET, n (%)				
Sensitivity	28 (43.8)	22 (62.9)	4 (28.6)	2 (13.3)
Acquired resistance	24 (37.5)	7 (20.0)	8 (57.1)	9 (60.0)
Primary resistance	12 (18.8)	6 (17.1)	2 (14.3)	4 (26.7)
Number of sites for visceral metastasis, n (%)				
0	17 (26.6)	13 (37.1)	2 (14.3)	2 (13.3)
1	33 (51.6)	15 (42.9)	10 (71.4)	8 (53.3)
2	10 (15.6)	6 (17.1)	2 (14.3)	2 (13.3)
≥3	4 (6.3)	1 (2.9)	0 (0.0)	3 (20.0)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	All patients (n=64)	First-line patients (n=35)	Second-line patients (n=14)	Later-lines patients (n=15)
Prior lines of chemotherapy for ABC, n (%)				
0	37 (57.8)	35 (100.0)	2 (14.3)	0 (0.0)
1	18 (28.1)	0 (0.0)	12 (85.7)	6 (40.0)
2	5 (7.8)	0 (0.0)	0 (0.0)	5 (33.3)
3	2 (3.1)	0 (0.0)	0 (0.0)	2 (13.3)
≥4	2 (3.1)	0 (0.0)	0 (0.0)	2 (13.3)
Prior lines of ET, n (%)				
0	18 (28.1)	12 (34.3)	4 (28.6)	2 (13.3)
1	32 (50.0)	22 (62.9)	7 (50.0)	3 (20.0)
2	10 (15.6)	1 (2.9)	2 (14.3)	7 (46.7)
≥3	4 (6.3)	0 (0.0)	1 (7.1)	3 (20.0)
Concomitant ET, n (%)				
Tamoxifen	2 (3.1)	1 (2.9)	0 (0.0)	1 (6.7)
Anastrozole	3 (4.7)	2 (5.7)	0 (0.0)	1 (6.7)
Letrozole	31 (48.4)	18 (51.4)	8 (57.1)	5 (33.3)
Exemestane	6 (9.4)	3 (8.6)	3 (21.4)	0 (0.0)
Fulvestrant	22 (34.4)	11 (31.4)	3 (21.4)	8 (53.3)
Initial dose of palbociclib, n (%)				
125 mg/d	59 (92.2)	34 (97.1)	12 (85.7)	13 (86.7)
100 mg/d	5 (7.8)	1 (2.9)	2 (14.3)	2 (13.3)
Treatment discontinuation, n (%)				
Yes	34 (53.1)	11 (31.4)	8 (57.1)	15 (100.0)
No	30 (46.9)	24 (68.6)	6 (42.9)	0 (0.0)
Reasons for treatment discontinuation, n (%)				
Disease progression	27 (42.2)	8 (22.9)	7 (50.0)	12 (80.0)
Financial issue	4 (6.3)	2 (5.7)	1 (7.1)	1 (6.7)
Toxicity	3 (4.7)	1 (2.9)	0 (0.0)	2 (13.3)

SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ET, endocrine therapy; ABC, advanced breast cancer.

Toxicity

The proportion of patients who experienced any AEs during the treatment of palbociclib plus ET is shown in *Figure 2*. AEs mainly manifested as hematological toxicity, of which neutropenia and leukopenia were the most dominant types of toxicity. Neutropenia was the most common hematological toxicity, with an incidence of 76.6% (49/64), while the incidence of leukopenia was 71.9% (46/64). Among all AEs of grade 3 or above, neutropenia and leukopenia also represented the largest proportion, but patients with anemia or thrombocytopenia almost only reached grade 1 or grade 2 (*Table 5*). The most

Table 2 Univariate analysis of PFS in different characteristics

Characteristic	N	mPFS	95% CI	χ^2	P
Age group				1.274	0.259
<65 years	53	16.9	4.4–29.4		
≥65 years	11	NR	NR		
Menstruation status				1.227	0.268
Menopausal	48	22.1	NR		
Premenopausal	15	11.9	7.3–16.5		
Male	1	–	–		
Expression of Ki67				10.669	0.001
≤20%	39	NR	NR		
>20%	25	7.9	4.8–11.0		
Molecular typing at initial diagnosis				8.373	0.004
Luminal A	36	NR	NR		
Luminal B	28	7.4	4.6–10.2		
Prior chemotherapy for ABC				17.773	<0.001
Yes	27	6.4	2.7–10.1		
No	37	NR	NR		
Prior lines of ET				15.267	<0.001
≤1	50	NR	NR		
>1	14	4.9	4.5–5.3		
Sensitivity to ET				11.265	0.001
Sensitivity or acquired resistance	52	NR	NR		
Primary resistance	12	5.9	0.6–11.2		
Visceral metastasis				0.391	0.532
Yes	47	21.6	8.8–34.4		
No	17	16.9	10.6–23.2		
Number of sites for visceral metastasis				14.140	<0.001
≤2	60	22.1	NR		
>2	4	3.9	2.0–5.8		
Hepatic metastases				13.330	<0.001
Yes	19	5.9	4.0–7.8		
No	45	NR	NR		
Lines of palbociclib for ABC				29.343	<0.001
1	35	NR	NR		
2	14	16.9	5.6–28.2		
≥3	15	4.9	4.5–5.3		
Initial dose of palbociclib				<0.001	0.984
125 mg/d	59	21.6	11.4–31.8		
100 mg/d	5	NR	NR		

PFS, progression-free survival; mPFS, median progression-free survival; CI, confidence interval; ABC, advanced breast cancer; ET, endocrine therapy; NR, not reach.

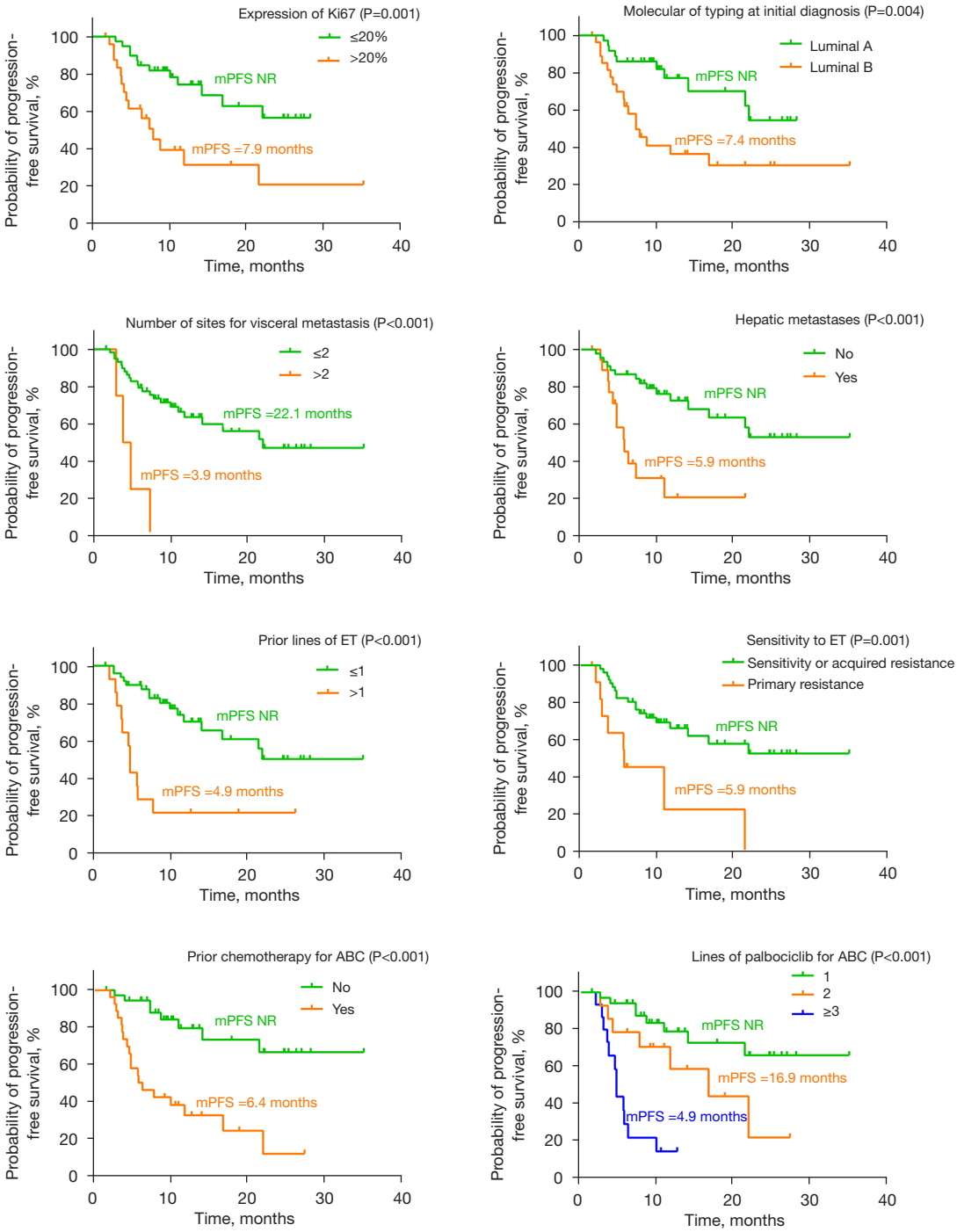

Figure 1 PFS of palbociclib plus ET stratified by different characteristics. PFS, progression-free survival; ET, endocrine therapy; ABC, advanced breast cancer; mPFS, median progression-free survival; NR, not reach.

Table 3 Cox regression multivariable analysis of PFS in different characteristics

Characteristic	HR	95% CI	P
Expression of Ki67	6.032	2.305–15.784	<0.001
Molecular typing at initial diagnosis	2.454	1.065–5.653	0.035
Prior lines of ET	1.707	0.562–5.187	0.346
Sensitivity to ET	4.504	1.675–12.108	0.003
Hepatic metastases	0.658	0.211–2.051	0.471
Number of sites for visceral metastasis	12.489	2.776–56.190	0.001
Lines of palbociclib for ABC	3.711	1.748–7.881	0.006

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ABC, advanced breast cancer; ET, endocrine therapy.

severe hematological toxicity mostly occurred in the early stage (after 1–2 medication cycles) (*Figure 3*). A total of 12 patients (18.8%) had dose reductions due to AEs, and 7 patients (10.9%) had dose interruptions or required a delay in the start of a subsequent treatment cycle because of AEs. Only 3 patients (4.7%) experienced permanent discontinuation due to intolerable AEs.

Patterns and efficacy of subsequent therapy

As an exploratory endpoint, we conducted a follow-up after the initial treatment with patients who were resistant to the treatment of palbociclib plus ET. We found that, after excluding patients who terminated medication due to AEs or economic reasons, a total of 27 patients discontinued medication due to disease progression. Among these patients, 3 patients were deceased, 4 patients received only palliative symptomatic treatment including local radiotherapy for metastases, analgesic treatment, and nutritional support, 6 patients were lost to follow-up, and 14 patients had follow-up records of their subsequent therapy. There were 10 patients who received chemotherapy as the first choice of subsequent therapy after they were found to resist palbociclib treatment, and the most common chemotherapeutic drug was taxane (n=4, including 2 patients with nab-paclitaxel and 2 patients with paclitaxel combined with platinum), followed by gemcitabine (n=3). The other 3 patients received capecitabine, methotrexate, and eribulin. A total of 4 patients received ET after finding out they were resistant to palbociclib. Among them, 2 patients were treated with fulvestrant alone, 1 patient was treated with fulvestrant plus chidamide, and 1 patient received tamoxifen (*Figure 4*).

We performed statistical analyses on the PFS of these patients who received therapy subsequent to the initial palbociclib plus ET treatment. The median PFS of the chemotherapy group was 8.3 months (95% CI: 2.9–13.7 months), and the median PFS of the ET group was 3.3 months (95% CI: 0.9–5.7 months). The difference between the two groups was not statistically significant (P=0.447).

Discussion

Among patients in our study who received palbociclib plus ET as the first-line treatment for ABC, the ORR was 28.6%, the CBR was 96.4%, and the median PFS was not reached. Compared with the results of PALOMA-2, which enrolled patients with $HR^+/HER2^-$ breast cancer who had not received prior treatment for an advanced stage of the disease, the ORR of patients in our study was not as high as that of patients in the PALOMA-2 study (ORR =43%), but the CBR of patients in our study was better than that of patients in the PALOMA-2 study (CBR =81%) (7). The efficacy results indicated that palbociclib plus ET is a viable treatment option for patients with ABC in China. The representative real-world research known as IRIS study reported the results of many countries, including the United States, Argentina, and Canada, among others (13,19,20). In the IRIS study, the CBR of patients who received palbociclib as initial treatment for ABC in almost all of these reports reached about 90%, which was similar to our study. The median PFS of the patients with ABC who received palbociclib plus letrozole in the first-line treatment setting in the PALOMA-2 study was 27.6 months. In our study, the PFS in patients in the first-line setting did not reach the mPFS, but the median follow-up time was only 13.8 months in our study, which was less than half the time of median follow-up time in the PALOMA-2 study. By

Table 4 Tumor response of palbociclib plus ET in different characteristics

Characteristic	ORR			CBR		
	N (%)	χ^2	P	N (%)	χ^2	P
Age group		0.526	0.468		0.314	0.575
<65 years	8 (18.6)			34 (79.1)		
≥65 years	3 (37.5)			5 (62.5)		
Menstruation status		1.018	0.769		0.777	0.784
Menopausal	9 (25.0)			28 (77.8)		
Premenopausal	2 (14.3)			10 (71.4)		
Male	0 (0.0)			1 (100.0)		
Expression of Ki67		2.881	0.090		5.086	0.024
≤20%	10 (30.3)			29 (87.9)		
>20%	1 (5.6)			10 (55.6)		
Molecular typing at initial diagnosis		0.140	0.904		4.917	0.027
Luminal A	6 (22.2)			24 (88.9)		
Luminal B	5 (20.8)			15 (62.5)		
Number of sites for visceral metastasis		2.313	0.547		2.821	0.386
0	3 (18.8)			14 (87.5)		
1	5 (18.5)			20 (74.1)		
2	2 (33.3)			4 (66.7)		
≥3	1 (50.0)			1 (50.0)		
Prior lines of chemotherapy for ABC		2.290	0.737		20.583	<0.001
0	8 (26.7)			29 (96.7)		
1	2 (13.3)			7 (46.7)		
2	1 (33.3)			1 (33.3)		
3	0 (0.0)			2 (100.0)		
≥4	0 (0.0)			0 (0.0)		
Prior lines of ET		2.129	0.522		18.943	<0.001
0	6 (33.3)			17 (94.4)		
1	4 (17.4)			20 (87.0)		
2	1 (12.5)			2 (25.0)		
≥3	0 (0.0)			0 (0.0)		
Sensitivity to ET		2.750	0.253		6.694	0.035
Sensitivity	8 (30.8)			23 (88.5)		
Acquired resistance	2 (12.5)			12 (75.0)		
Primary resistance	1 (11.1)			4 (44.4)		
Lines of palbociclib for ABC		1.694	0.487		19.389	<0.001
1	8 (28.6)			27 (96.4)		
2	2 (16.7)			9 (75.0)		
≥3	1 (9.1)			3 (27.3)		

ET, endocrine therapy; ORR, objective response rate; CBR, clinical benefit rate; ABC, advanced breast cancer.

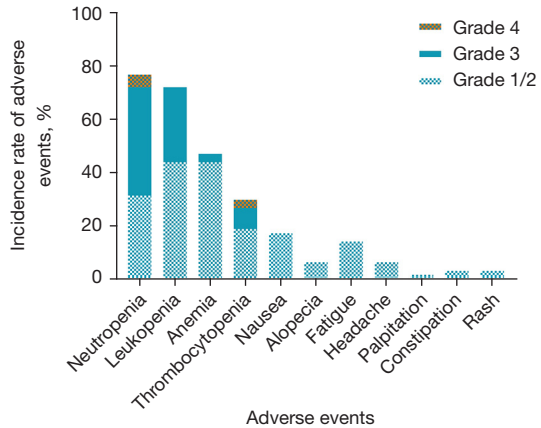

Figure 2 Incidence of adverse events with palbociclib.

the end of our study, there were still 30 patients (46.9%) continuing to receive medication, of which 24 patients were in the first-line setting, accounting for 68.6% of the total number of first-line medication. Therefore, the follow-up time was relatively short for the patients who received palbociclib plus ET as the first-line treatment for ABC, and in order to reach the mPFS for these patients, longer follow-up time is needed. However, we observed that the 6- and 12-month PFS rate of patients treated with palbociclib plus ET in the first-line setting in our study was 93.9% and 72.7%, respectively. In the IRIS study, the 6-month PFS rate of patients in the first-line setting in Argentina and Canada were 94% and 96.2%, respectively, while the 12-month PFS rate was 85.0% and 90.3%, respectively. This shows that the PFS rates in the IRIS study were better than our results. It's noteworthy that the proportion of patients with visceral metastases in our study was 62.9% in the first-line setting, which was higher than the proportion in the IRIS study (46.4% in the United States) and this may lead to the difference of PFS rate between IRIS study and our study. Further, the reason why the PFS rates in the IRIS study were better than our results may be also related to the difference in the treatment pattern between the IRIS study and this study. The patients who received palbociclib as a first-line treatment for ABC were all combined with AI in the IRIS, whereas only 65.7% of the patients received AI as the first-line ET combined with palbociclib in this study; the other 31.4% and 2.9% of patients in a first-line setting received fulvestrant and tamoxifen as ET combined with palbociclib. Further, the proportion of patients with visceral metastases in our study was 62.9% in the first-line setting, which was higher than the proportion in the IRIS study (46.4% in the United States).

PALOMA-3 enrolled patients with disease progression who had previously received ET and treated them with palbociclib plus fulvestrant and most of the patients (79%)

Table 5 Specific toxicity with palbociclib

Adverse event	All grades, n (%)	Grade 1/2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Any	57 (89.1)	23 (35.9)	29 (45.3)	5 (7.8)
Hematologic				
Neutropenia	49 (76.6)	20 (31.3)	26 (40.6)	3 (4.7)
Leukopenia	46 (71.9)	28 (43.8)	18 (28.1)	0 (0.0)
Anemia	30 (46.9)	28 (43.8)	2 (3.1)	0 (0.0)
Thrombocytopenia	19 (29.7)	12 (18.8)	5 (7.8)	2 (3.1)
Nonhematologic				
Nausea	11 (17.2)	11 (17.2)	0 (0.0)	0 (0.0)
Alopecia	4 (6.3)	4 (6.3)	0 (0.0)	0 (0.0)
Fatigue	9 (14.1)	9 (14.1)	0 (0.0)	0 (0.0)
Headache	4 (6.3)	4 (6.3)	0 (0.0)	0 (0.0)
Palpitation	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)
Constipation	2 (3.1)	2 (3.1)	0 (0.0)	0 (0.0)
Rash	2 (3.1)	2 (3.1)	0 (0.0)	0 (0.0)

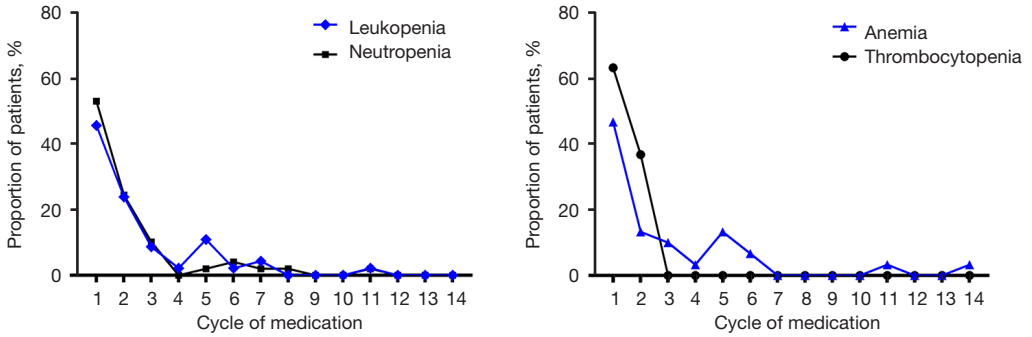

Figure 3 Proportion of patients with most severe hematological toxicity in different cycle of medication.

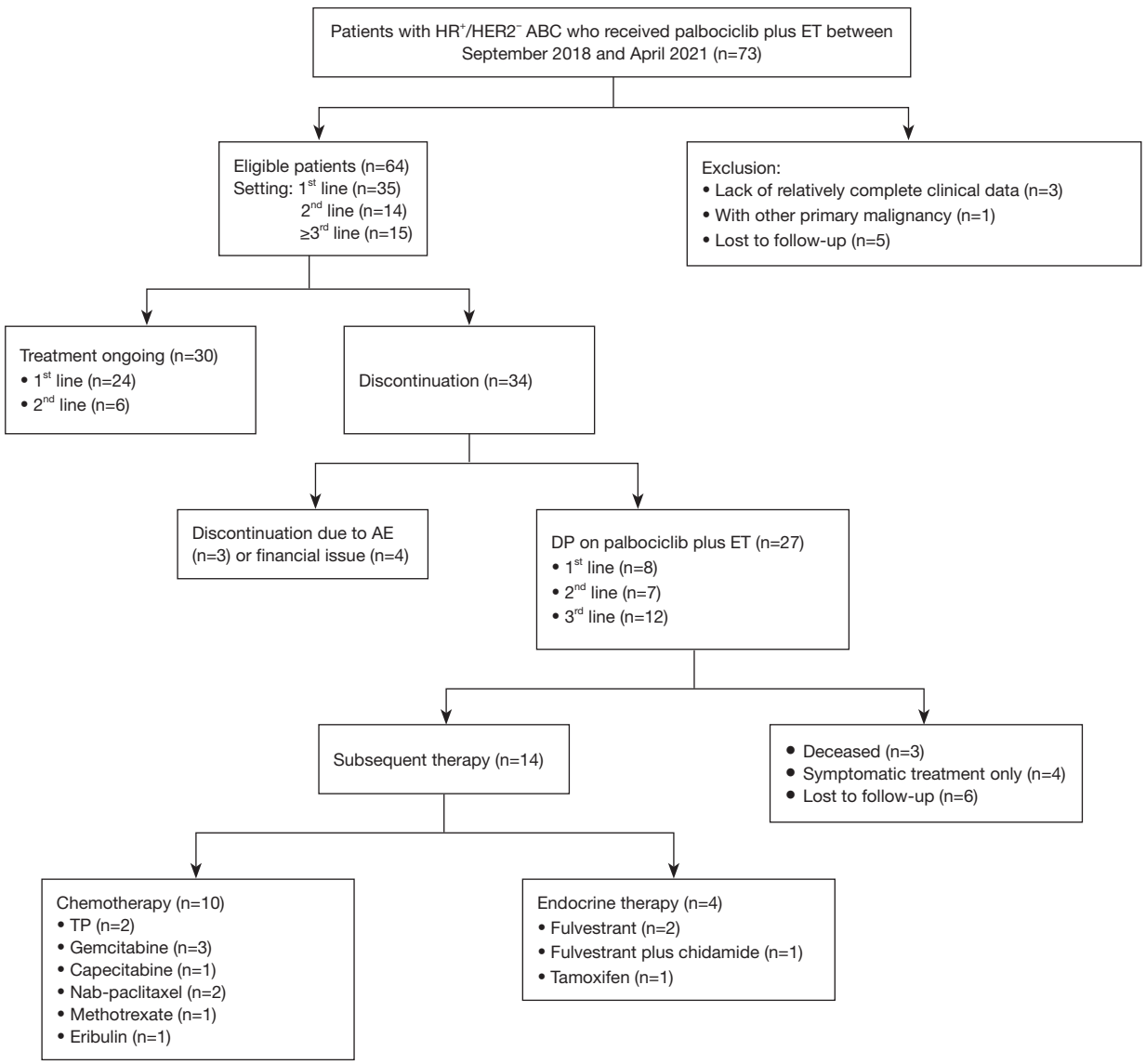

Figure 4 Flowchart of the treatment pattern of palbociclib plus ET and subsequent therapy. HR+, hormone receptor-positive; HER2−, human epidermal growth factor receptor 2-negative; ABC, advanced breast cancer; ET, endocrine therapy; AE, adverse event; DP, disease progression; TP, taxanes plus platinum.

were those received palbociclib plus ET as second-line or later-lines in advanced stage. In the PALOMA-3 study, the ORR and CBR were 19% and 67% and the median PFS was 9.5 months. Compared with the ORR (13.0%), CBR (52.2%), and median PFS (7.9 months) of patients in the second-line or later-lines setting in our study, the results of PALOMA-3 were better than ours. It should be noted that researchers only checked whether the participants had gone through endocrine resistance during prior ET in PALOMA-3 as an important inclusion criterion, and there was no strict requirement on whether endocrine resistance appeared during the adjuvant treatment stage or the advanced stage. Therefore, PALOMA-3 included patients who were treated with palbociclib plus fulvestrant as a first-line therapy for ABC, which may be the reason why the results in the PALOMA-3 study were better than our results in the second-line or later-lines setting. In addition, we analyzed the clinical characteristics of patients in the later-lines setting and found that the proportion of patients with visceral metastases, multi-line chemotherapy for ABC, or the Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of ≥2 was higher than those in other subgroups. The mPFS of this subgroup was 4.9 months, which was comparable to the mPFS of 4.8 months for patients who received palbociclib after the failure of multi-line therapy in the research by Ban *et al.* (21).

Cox regression multivariate analysis found that patients with the molecular typing of Luminal A, a lower Ki67 level, sensitivity or acquired resistance to ET, less than 3 lesions of visceral metastases, and those who received palbociclib plus ET as a first-line or second-line of treatment for ABC had a better prognosis. The latter three factors were also verified in other real-world research such as a study conducted in Shanghai, China, which showed that a better effect of treatment was observed in patients without primary resistance to ET, with less than 3 metastatic sites, and in patients who did not receive chemotherapy in the advanced stage (22). Another real-world study carried out by Xi *et al.* (23) showed that, in the first-line, second-line, and later-lines setting, the median PFS of patients who received palbociclib plus ET was 20.7, 12.8, and 4.0 months, which supported our results, respectively. However, we have not found out other research mentioned whether patients with an initial molecular typing of Luminal A or a lower Ki67 level would have a better survival prognosis and our results may provide more reference for the treatment of palbociclib plus ET for patients with $HR^+/HER2^-$ ABC. Furthermore, we consider that the molecular typing and level of Ki67 may be related to the location of the biopsy, and it may easily fluctuate due to changes in the patient's condition. It is necessary to increase the sample size, continue to follow-up with patients, and formulate uniform standards for evaluating the level of Ki67 and molecular typing, then obtain more convincing results to support our study.

In this study, letrozole (48.4%) was the most common ET in combination with palbociclib, followed by fulvestrant (34.4%), and exemestane (9.4%). Letrozole was also the most used in patients who were in the first-line setting. The majority of patients (92.2%) started treatment with palbociclib at a dose of 125 mg/d, and only 5 patients (7.8%) started treatment with a dose of 100 mg/d. Among these 5 patients, 4 patients were older than 65 years old, and 3 patients were even over 70 years old. Another commonality was that patients who received 100 mg/d as the initial dose all had visceral metastases and varying degrees of organ function impairment. In this study, 18.8% of patients experienced dose reduction due to AEs, 10.9% of patients interrupted or postponed the treatment cycle, and only 4.7% of patients permanently discontinued the medication due to AEs. The main reason for discontinuation was hematologic toxicities, which was consistent with the results of a large number of clinical trials and real-world studies. The proportions of dose reduction, interruption, and postponement of treatment with palbociclib plus ET in our study were significantly lower than that in PALOMA trials (36% of patients experienced dose reduction, 67% of patients interrupted or postponed the treatment cycle in the PALOMA-2 study while the data in the PALOMA-3 study were 34% and 54%, respectively) (7,10). The difference may be because doctors can start treatment at a lower dose according to the specific conditions of the patients. However, PALOMA-2 and PALOMA-3 uniformly followed the prescribed dose of 125 mg/d as the initial dose. Therefore, dose reduction, interruption, and postponement of treatment with palbociclib plus ET due to AEs was more likely to occur. Due to the limited size of the sample in our study, the number of patients with 100 mg/d as the initial dose as relatively small. Examining whether the medication adjustment is closely related to the initial dose still needs more research.

In the exploratory analysis about subsequent therapy, we found that more patients were willing to choose chemotherapy as the preferred subsequent treatment after finding that they were resistant to palbociclib, but the efficacy of both chemotherapy and ET was limited, and the difference between the two groups was not

statistically significant. The research by Xi *et al.* (23) analyzed the subsequent therapy after palbociclib resistance was identified and found that more patients preferred chemotherapy than ET (67% *vs.* 31%). Further research performed in China showed that the median PFS of the chemotherapy group and ET group was 4.0 and 5.1 months, respectively, but the difference was also not statistically significant (22). This implies that both chemotherapy or ET can be used as the subsequent therapy after a patient experiences palbociclib resistance, and there is no significant difference of efficacy between chemotherapy and ET. However, the small sample size and the complex clinical characteristics of patients with ABC who might have experienced multiple treatments leading to multi-drug resistance make it difficult to accurately evaluate the efficacy of each drug of chemotherapy and ET, and more research data is still needed to support our results.

The limitations of this study also should not be ignored. First, the selection of the patients enrolled in the study was all carried out by the physicians willing to participate in the study, which might cause a selection bias. To minimize potential selection bias to the greatest extent possible, physicians were asked to sort patients according to the order of the time starting medication with palbociclib from September 2018 to April 2021 during outpatient or inpatient treatment consecutively and selected patients who met the requirements according to the inclusion and exclusion criteria of this study. Second, patients' clinical data was collected from the electronic medical record system by researchers retrospectively, which may lead to a lack of data. We supplemented these missing data by contacting patients, but this may lead to recall bias. Third, the number of patients enrolled in this study was relatively small, and the follow-up time was short. It is necessary to continue to expand the sample size, then keep following up cases and updating data. However, this study confirmed the efficacy and safety of palbociclib plus ET in southwest China. The usual modes and the efficacy of subsequent therapy after a patient had palbociclib resistance were also discussed, however, there was not an accurate conclusion about the specific best mode of subsequent therapy. We will keep enlarging the size of sample and continue following up the clinical data of patients to explore the efficacy of subsequent therapy in depth in the future.

Conclusions

The efficacy of palbociclib plus ET was worthy of recognition and the toxicity was acceptable in our study which was similar to previously reported data from phase 2 and 3 trials and other real-world evidence. Treatment for $HR^+/HER2^-$ ABC using palbociclib plus ET should be recommended more widely in China due to the efficacy and safety especially for those patients with the molecular typing of Luminal A, a lower Ki67 level, sensitivity or acquired resistance to ET, less than 3 lesions of visceral metastases, and those who received palbociclib plus ET as a first-line or second-line of treatment for ABC. However, due to the relatively short time for which palbociclib has been approved by the China Food and Drug Administration, there are currently limited real-world studies on palbociclib plus ET for the Chinese population. We hope to give some references for the best application mode of palbociclib plus ET for patients in China through our study and provide more practical guidance about the use of palbociclib for patients with $HR^+/HER2^-$ ABC in the future by expanding the sample size, keeping follow-up, and updating data.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1002/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1002/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (No. 2021-445) and the Chongqing University Cancer Hospital was informed and agreed the study. Informed consent was taken from all the patients.

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