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Clinical Outcomes of 130 Patients with Hormone Receptor-Positive and Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer Treated with Palbociclib plus Endocrine Therapy and Subsequent Therapy: A Real-World Single-Center Retrospective Study in China

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Study Design A
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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: This retrospective single-center study conducted in China aimed to investigate the clinical outcomes of patients with hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2–) metastatic breast cancer (MBC) treated with palbociclib plus endocrine therapy (ET) and subsequent therapy.

Material/Methods: Eligible patients were women with HR+ and HER2– MBC who initiated palbociclib plus ET between September 2016 and August 2019 at Fudan University Shanghai Cancer Center. Clinical characteristics and efficacy data were retrospectively recorded from the electronic medical record system.

Results: In total, 130 patients were included in the study, of whom 87.0% of patients started palbociclib on 125 mg/day, 8.5% of patients had dose reduction, and 2.3% of patients discontinued the treatment because of toxicity. Overall, the disease control rate was 77.4% and clinical benefit rate was 63.4%. After a median follow-up period of 10.6 months, the median progression-free survival was 9.2 months. There was limited efficacy in patients who received palbociclib as no less than a fourth line of ET, except for patients who added palbociclib to the ET, which they had acquired resistance to. After disease progression on palbociclib, further treatment with chemotherapy and ET had similar efficacy (P=0.571).

Conclusions: The findings from this real-world single-center study in China showed that treatment with palbociclib plus ET exhibited favorable efficacy and good tolerance in patients with HR+ and HER2– MBC, even in patients who were initially resistant to endocrine therapy, and there was no difference in outcomes between subsequent treatment with chemotherapy and ET.

MeSH Keywords: Breast Neoplasms • Cyclin-Dependent Kinase Inhibitor Proteins • Pragmatic Clinical Trials as Topic

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Background

Breast cancer is the most common malignancy in women and one of the three most common malignant tumors worldwide [1]. Today, metastatic breast cancer (MBC) remains incurable and is the leading cause of death among breast cancer patients. Endocrine therapy (ET) is the basis and first choice of palliative treatment for patients with hormone-receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2–) MBC, except for patients with symptomatic visceral metastases. However, resistance to ET eventually results in disease progression and the use of chemotherapy. Much effort has been made to enhance the sensitivity of ET and overcome patient resistance to it in recent years.

Palbociclib, an oral inhibitor of cyclin-dependent kinase (CDK) 4/6, prevents cancer cell proliferation by blocking the cell cycle from the G1 to the S phase. The prospective TREnd trial confirmed the efficacy of palbociclib as a single agent for HR+ and HER2– MBC and its ability to reverse resistance to ET in patients. The clinical benefit rate was 60% in the single agent group and 54% in combination with the same ET that the patient had progressed on previously [2]. Additionally, in the well-designed prospective PALOMA trials, palbociclib showed great improvement on progression-free survival (PFS), manageable toxicity, and good life quality in treating patients with HR+ and HER2– MBC [3–6]. In the PALOMA-2 trial, palbociclib given concomitantly with letrozole in the first-line setting had a median PFS of 24.8 months, compared to 14.5 months in the placebo-letrozole group (hazard ratio= 0.58, $P<0.001$) [5]. In the PALOMA-3 trial, which included patients who had progressed on previous ET, the median PFS was 9.5 months in the palbociclib-fulvestrant group, which was significantly longer than the PFS of 4.6 months in the placebo-fulvestrant group (hazard ratio=0.46, $P<0.0001$) [3]. Based on these encouraging results, palbociclib was approved for the treatment of HR+ and HER2– MBC in the first-line setting when given concomitantly with letrozole, or when given concomitantly with fulvestrant in patients who progressed on ET.

In the real-world setting, although the efficacy of palbociclib differed due to the differences in treatment patterns and patient characteristics, palbociclib still showed good results in reports from the Americas and Europe [7–11]. In the Ibrance Real World Insights (IRIS) study [8,10], the clinical benefit rates of palbociclib plus letrozole or fulvestrant were all more than 90%, regardless of the treatment line, which were better than the results of the PALOMA studies (85% in PALOMA-2 and 67% in PALOMA-3). The 12-month PFS rates were approximately 85% for patients treated with palbociclib plus letrozole and 80% for patients treated with palbociclib plus fulvestrant. In China, there is limited data on the efficacy of palbociclib plus ET in patients with MBC in a real-world practice, especially in those who had progressed on multiple lines of ET previously. In addition, the treatment pattern and efficacy of subsequent therapy beyond disease progression on palbociclib remains unknown.

Therefore, in this retrospective study conducted at a single center in China, we aimed to investigate the clinical outcomes of patients with HR+ and HER2– MBC treated with palbociclib plus ET and subsequent therapy in a real-world setting.

Material and Methods

Patients

Eligible patients were women with HR+ and HER2– MBC who initiated palbociclib plus ET between September 2016 and August 2019 at the Fudan University Shanghai Cancer Center. Patients with breast cancer were staged according to the 8th edition of the American Joint Committee on Cancer TNM staging system [12]. Those with metastases in distant organs or non-regional nodes detected by clinical, radiographic, or pathological means were diagnosed with MBC. HR+ was defined as estrogen receptor- or progesterone receptor-positive status by immunohistochemistry [13]. HER2 status was determined by immunohistochemistry or fluorescence *in situ* hybridization [14]. Patients who did not progress on the most recent treatment in a metastatic setting were excluded. Patients without measurable lesions defined by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [15] were also excluded. The treatment patterns of palbociclib plus ET and subsequent therapy are shown in Figure 1. ET for breast cancer was defined as treatment targeting estrogen receptor signaling, including selective estrogen receptor modulators (SERM) (tamoxifen and toremifene), non-steroidal aromatase inhibitors (AI) (anatrozole and letrozole), steroidal AIs (exemestane), and selective estrogen receptor degraders (SERD) (fulvestrant). Patients were treated as per the National Comprehensive Cancer Network guidelines [16] or the physician's choice for compassionate use. Characteristics of the patients were retrospectively collected from the electronic medical record system. Primary resistance to ET was defined as recurrence during the first 2 years of adjuvant ET or progression within the first 6 months of the most recent palliative ET. Acquired resistance to ET was defined as recurrence during adjuvant ET after the first 2 years, recurrence within the first year of completing adjuvant ET, or progression after 6 months of the most recent palliative ET [17]. Patients who relapsed after 1 year of completing adjuvant ET or did not receive ET previously were considered sensitive to ET.

Efficacy

Patients received computed tomography or magnetic resonance imaging every 2 to 3 months during treatment until disease progression. Tumor response was assessed by the attending

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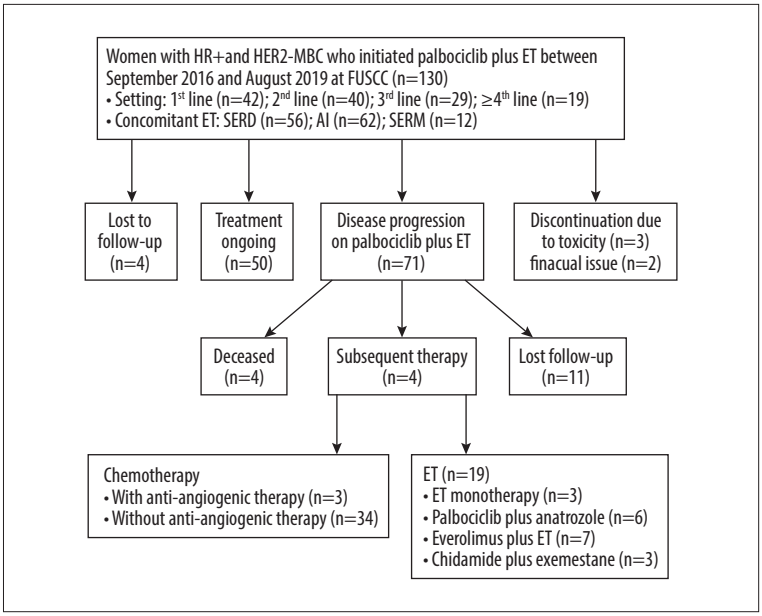

Figure 1. Flowchart of the treatment pattern of palbociclib plus endocrine therapy and subsequent therapy. ET – endocrine therapy; HR+ – hormone receptor-positive; HER2 – human epidermal growth factor receptor 2; MBC – metastatic breast cancer; FUSCC – Fudan University Shanghai Cancer Center; SERD – selective estrogen receptor degrader; AI – aromatase inhibitor; SERM – selective estrogen receptor modulator

physician according to RECIST 1.1 [15]. All information on the efficacy of palbociclib plus ET and subsequent therapy was retrospectively acquired from the electronic medical record system. Efficacy was evaluated by the clinical benefit rate, disease control rate, and PFS. The clinical benefit rate was defined as the percentage of complete response, partial response, and stable disease for at least 24 weeks. The disease control rate was defined as the percentage of complete response, partial response, and stable disease. PFS was defined as time from initiation of palbociclib to progression of disease or death.

Statistical analyses

Correlation analyses between patient characteristics and tumor response were performed by Pearson's chi-square test or Fisher's exact test. The follow-up period was defined as time from initiation of one regimen to the earliest of disease progression, death, or last medical record. The median follow-up period was estimated by the reverse Kaplan-Meier method. Survival curves of PFS were plotted by the Kaplan-Meier method and compared by the log-rank test. For all tests, a 2-sided *P* value of less than 0.05 was considered statistically significant. All statistical analyses and graphics were performed with SPSS (version 22.0, IBM Corp, Armonk, NY, USA) and the GraphPad Prism software (version 5, GraphPad Software Inc, San Diego, CA, USA).

Results

Patient characteristics and treatment patterns

A total of 130 patients treated with palbociclib plus ET were included in the study. Table 1 shows the patients' baseline characteristics at the initiation of palbociclib. The median age was 56 (31 to 84) years. Most patients were menopausal (80.0%) and in good performance status (Eastern Cooperative Oncology Group score of 0–1, 98.5%). Nearly one-half of patients (47.7%) had at least 3 metastatic sites and the majority (72.3%) had visceral metastasis. More than half (54.6%) had received systemic chemotherapy once for MBC before the initiation of palbociclib. Only 3 patients (2.3%) had received everolimus previously. Primary and acquired resistance to the most recent ET accounted for 37.7% and 43.1% of the patients, respectively, and the remaining 19.2% were considered sensitive to ET.

The number of patients receiving palbociclib in the first-, second-, third-, and later-line setting were 42 (32.3%), 40 (30.8%), 29 (22.3%), and 19 (14.6%), respectively. For dosing, 113 patients (87.0%) started palbociclib at 125 mg/day, 11 patients (8.5%) had a dose reduction to 100 mg/day, and 3 patients (2.3%) discontinued treatment due to toxicity. Fifteen patients (11.5%) started palbociclib at 100 mg/day and 2 (1.5%) started at 75 mg/day, and none experienced dose reduction or drug discontinuance due to toxicity. The most common ET concomitant drug with palbociclib was AI (n=62, 47.7%), followed by SERD (n=56, 43.1%) and SERM (n=12, 9.2%). Details of the treatment pattern are shown in Table 2. A total of 19 patients (14.6%) received palbociclib in combination with the same ET that had been previously taken until disease progression. Premenopausal patients (20.0%) received ovarian function suppression during palbociclib plus ET.

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Table 1. Patient characteristics at palbociclib initiation in different treatment-line settings.

Characteristic	All patients (n=130)	1st line (n=42)	≥2nd line (n=88)	≥4th line (n=19)
Median age, years (range)	56.0 (31.0–84.0)	58.0 (35.0–78.0)	55.0 (31.0–84.0)	54.0 (32.0–84.0)
Menstruation status, n (%)				
Menopausal	104 (80.0%)	33 (78.6%)	71 (80.7%)	17 (89.5%)
Premenopausal	26 (20.0%)	9 (21.4%)	17 (19.3%)	2 (10.5%)
ECOG PS, n (%)				
0	1 (0.8%)	0 (0.0%)	1 (1.1%)	0 (0.0%)
1	127 (97.7%)	42 (100.0%)	85 (96.6%)	19 (100.0%)
2	2 (1.5%)	0 (0.0%)	2 (2.3%)	0 (0.0%)
DFS, n (%)				
≥1 year	98 (75.4%)	23 (54.8%)	75 (85.2%)	18 (94.7%)
<1 year	5 (3.8%)	3 (7.1%)	2 (2.3%)	0 (0.0%)
De novo MBC	27 (20.8%)	16 (38.1%)	11 (12.5%)	1 (5.3%)
Number of metastatic sites, n (%)				
<3	68 (52.3%)	26 (61.9%)	42 (47.7%)	4 (21.1%)
≥3	62 (47.7%)	16 (38.1%)	46 (52.3%)	15 (78.9%)
Visceral metastasis, n (%)				
Yes	94 (72.3%)	30 (71.4%)	64 (72.7%)	16 (84.2%)
No	36 (27.7%)	12 (28.6%)	24 (27.3%)	3 (15.8%)
Prior chemotherapy for MBC				
Yes	71 (54.6%)	11 (26.2%)	60 (68.2%)	16 (84.2%)
No	59 (45.4%)	31 (73.8%)	28 (31.8%)	3 (15.8%)
Prior lines of ET, n (%)				
0	42 (32.3%)	42 (100.0%)	0 (0.0%)	0 (0.0%)
1	40 (30.8%)	0 (0.0%)	40 (45.5%)	0 (0.0%)
2	29 (22.3%)	0 (0.0%)	29 (33.0%)	0 (0.0%)
≥3	19 (14.6%)	0 (0.0%)	19 (21.5%)	19 (100.0%)
Prior exposure to everolimus, n (%)				
Yes	3 (2.3%)	0 (0.0%)	3 (3.4%)	2 (10.5%)
No	127 (97.7%)	42 (100.0%)	85 (96.6%)	17 (89.5%)
Sensitivity to ET, n (%)				
Sensitivity	25 (19.2%)	25 (59.5%)	0 (0.0%)	0 (0.0%)
Acquired resistance	56 (43.1%)	11 (26.2%)	45 (51.1%)	6 (31.6%)
Primary resistance	49 (37.7%)	6 (14.3%)	43 (48.9%)	13 (68.4%)

SD – standard deviation; ECOG PS – Eastern Cooperative Oncology Group Performance status; DFS – disease-free survival; MBC – metastatic breast cancer; ET – endocrine therapy.

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Table 2. Treatment pattern of palbociclib-based treatment in different treatment-line settings.

Characteristic	All patients (n=130)	1st line (n=42)	≥2nd line (n=88)	≥4th line (n=19)
Concomitant ET, n (%)				
SERM	12 (9.2%)	0 (0.0%)	12 (13.6%)	7 (36.8%)
Tamoxifen	2 (1.5%)	0 (0.0%)	2 (2.3%)	2 (10.5%)
Toremifene	10 (7.7%)	0 (0.0%)	10 (11.4%)	5 (26.3%)
AI	62 (47.7%)	21 (50.0%)	41 (46.6%)	9 (47.4%)
Anatrozole	13 (10.0%)	5 (11.9%)	8 (9.1%)	2 (10.5%)
Letrozole	30 (23.1%)	12 (28.6%)	18 (20.5%)	6 (31.6%)
Exemestane	19 (14.6%)	4 (9.5%)	15 (17.0%)	1 (5.3%)
SERD	56 (43.1%)	21 (50.0%)	35 (39.8%)	3 (15.8%)
Palbociclib concomitant with prior ET, n (%)				
Yes	19 (14.6%)	1 (2.4%)	18 (20.5%)	6 (31.6%)
No	111 (85.4%)	41 (97.6%)	70 (79.5%)	13 (68.4%)
Dosage of palbociclib, n (%)				
Start at 125 mg/day	113 (87.0%)	33 (78.6%)	80 (90.9%)	16 (84.2%)
Reduction to 100 mg/day	11 (8.5%)	6 (14.3%)	5 (5.7%)	2 (10.5%)
Start at 100 mg/day	15 (11.5%)	7 (16.7%)	8 (9.1%)	3 (15.8%)
Start at 75 mg/day	2 (1.5%)	2 (4.8%)	0 (0.0%)	0 (0.0%)

ET – endocrine therapy; SERM – selective estrogen receptor modulator; AI – aromatase inhibitor; SERD – selective estrogen receptor degrader.

Efficacy of palbociclib plus ET

Tumor responses are shown in Table 3. Among 124 patients who had received tumor assessment once during palbociclib plus ET, 14 (11.3%) had partial response, 82 (66.1%) had stable disease, and 28 (22.6%) had disease progression. None had complete response. Consequently, the clinical benefit rate in this study was 63.4%, and the disease control rate was 77.4%.

As shown in Figure 2, better tumor responses were observed in those patients who had fewer than 3 metastatic sites (P=0.029), underwent no chemotherapy for MBC (P<0.001), or received palbociclib as an early line treatment (P<0.001). Also, better response to the most recent ET correlated with better response to palbociclib plus ET (P<0.001). Further, a higher proportion of patients receiving palbociclib concomitantly with SERD achieved disease control than did those receiving a combination of palbociclib with AI and SERM (P=0.043). It was noteworthy that palbociclib taken concomitantly with the previously administered ET showed similar tumor responses to those of switching to an alternative ET (P=0.433). Two patients who progressed on the ET monotherapy within 3 months had disease progression on palbociclib plus ET at their first tumor evaluation. Among the 4 patients with disease progression on monotherapy within 3 to 6 months, 2 patients achieved disease control but not clinical benefit and 2 patients achieved clinical benefit. All 13 patients who progressed on the monotherapy beyond 6 months had disease control and 12 of them achieved clinical benefit.

Among all 130 patients after a median follow-up period of 10.6 months, 71 patients had disease progression on palbociclib plus ET, and the median PFS was 9.2 months. Subgroup analyses of PFS confirmed a consistent benefit of the baseline characteristics mentioned above (Figure 3).

Since no statistically significant PFS benefit from the addition of palbociclib was observed in patients who received palbociclib as no less than the fourth line of ET in the PALOMA-3 trial [3], we further studied the efficacy of palbociclib plus ET in the 19 patients in this subgroup. Twelve (66.7%) patients achieved stable disease, 6 (33.3%) had disease progression at the first tumor evaluation, and 1 had an unknown tumor response. The median PFS was only 4.4 months.

Three patients who were exposed to everolimus progressed on everolimus-based treatment. One of the patients received palbociclib plus ET as the third line of ET and had a prolonged PFS of 11 months (treatment was ongoing). The other 2 patients received palbociclib plus ET as the fourth line of ET and had disease progression on palbociclib within 3 months.

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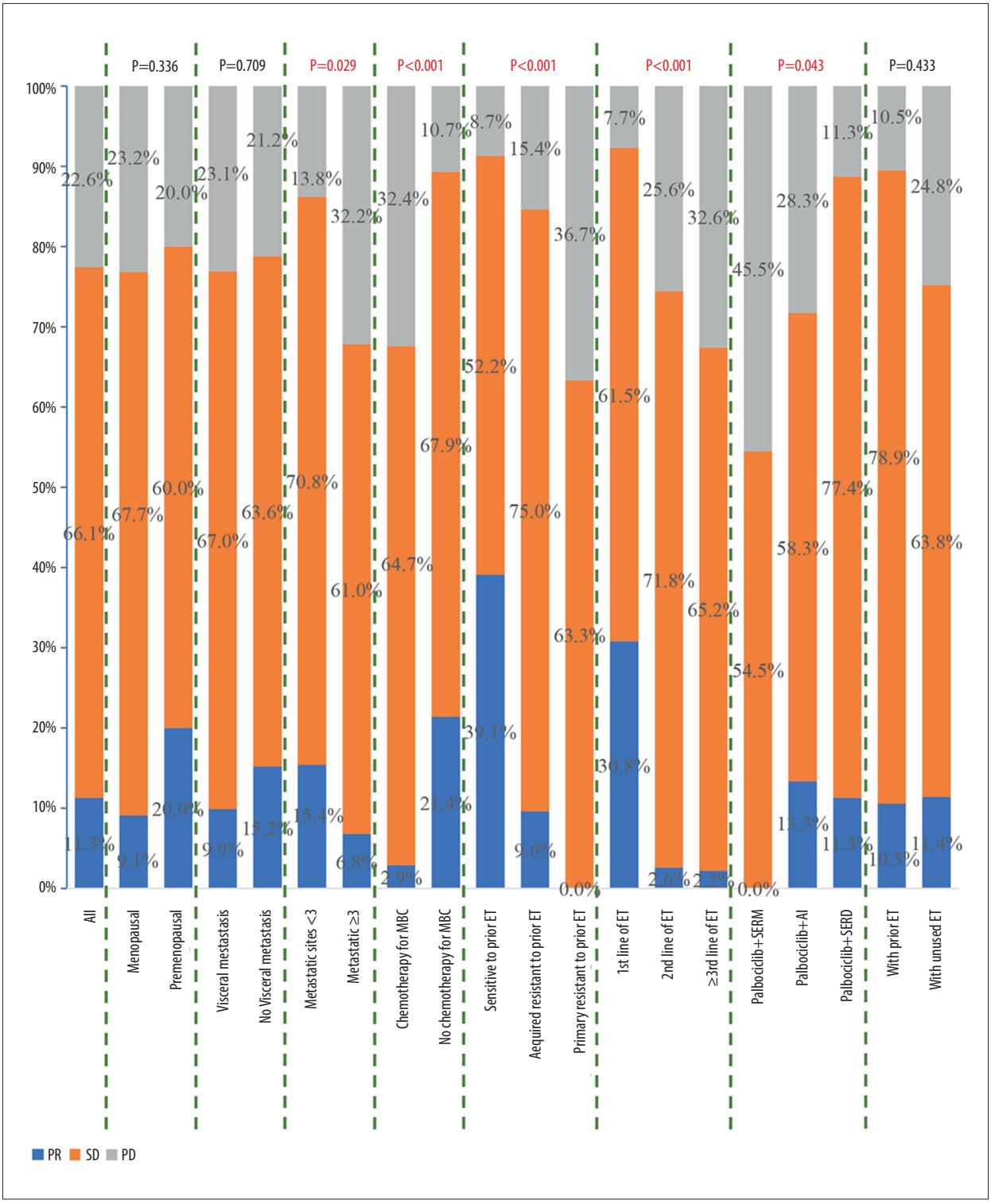

Figure 2. Tumor response to palbociclib plus endocrine therapy of patients with different characteristics. *P*-values of less than 0.05 indicate statistical significance and are marked in red. ET – endocrine therapy; MBC – metastatic breast cancer; SERM – selective estrogen receptor modulator; AI – aromatase inhibitor; SERD – selective estrogen receptor degrader; PR – partial response; SD – stable disease; PD – progression of disease.

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Table 3. Efficacy of palbociclib-based treatment in different treatment-line settings.

Characteristic	All patients	1st line	≥2nd line	≥4th line
Best response, n (%)				
CR	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PR	14 (11.3%)	12 (30.8%)	2 (2.4%)	0 (0.0%)
SD	82 (66.1%)	24 (61.5%)	58 (68.2%)	12 (66.7%)
PD	28 (22.6%)	3 (7.7%)	25 (29.4%)	6 (33.3%)
DCR	77.4%	92.3%	70.6%	66.7%
CBR	63.4%	78.9%	56.5%	44.4%
Median PFS, months	9.2	14.7	7.4	4.4
Median follow-up period, months	10.6	10.6	11.0	10.4

CR – complete response; PR – partial response; SD – stable disease; PD – progression of disease; ORR – objective response rate; DCR – disease control rate; CBR – clinical benefit rate; SD – standard deviation.

Efficacy of subsequent therapy following palbociclib plus ET

The subsequent treatment of 56 of the 71 patients who had disease progression on palbociclib was documented. Of the 56 patients, 37 switched to chemotherapy with an antiangiogenic agent (n=3) or without an antiangiogenic agent (n=34). Paclitaxel was the most common regimen (n=14), followed by vinorelbine (n=13). Nineteen patients continued ET, including ET alone (n=3), palbociclib plus ET (n=6), everolimus plus ET (n=7), and chidamide plus ET (n=3). The PFS rates were 119 days for chemotherapy and 154 days for ET; the difference was not statistically significant (P=0.571) (Figure 4).

Of the 6 patients who continued palbociclib in combination with another ET, 3 progressed on the new regimen after approximately 2 months, 1 experienced disease control for 10.3 months (treatment was ongoing), and the other 2 patients had initiated the new regimen later, resulting in the lack of tumor assessment. Among the 7 patients who received everolimus plus ET, 1 patient remained unevaluated on account of a short medication time, 1 had disease progression within 2 months, 1 progressed in the sixth month, and 4 had prolonged PFS, from 3.9 to 12.2 months (treatment was ongoing).

Discussion

This real-world single-center study in China retrospectively investigated the treatment patterns and clinical outcomes of the CDK 4/6 inhibitor, palbociclib, plus ET and subsequent therapy in 130 women with HR+ and HER2– MBC. Overall, the disease control rate of palbociclib plus ET was 77.4%, the clinical benefit rate was 63.4%, and the median PFS was 9.2 months. Despite the limited efficacy in the later-line treatment, patients who were resistant to prior ET could still benefit from palbociclib plus the same ET. Subsequent therapy of the physicians' choice showed no significant difference in efficacy between chemotherapy and ET. To the best of our knowledge, this study is the first report on the clinical practice of palbociclib in a Chinese real-world setting.

Because of the differences in treatment patterns and patient characteristics, the efficacy of palbociclib plus ET in the real-world setting differed. In the representative IRIS studies [8,10], the 12-month PFS rates of palbociclib plus AI were 85% in Argentina and 84.1% in the US, more than twice the PFS rate (38.2%) of our study. This could have resulted from the difference in treatment lines since only patients treated with palbociclib plus AI as first line of ET were included in IRIS studies, whereas only one-third of the patients in our study received this regimen as the first line of ET. The 12-month PFS rates of palbociclib plus SERD were 79.8% in the US and 64.3% in our study, possibly owing to the difference in the proportion of visceral metastasis (41.5% in IRIS and 72.3% in our study).

In the PALOMA trials, patients were required to initiate palbociclib at 125 mg/day, concomitantly with AI as first line of ET in PALOMA-2, and with fulvestrant for patients with disease progression on prior ET in PALOMA-3. In the present study, fulvestrant was the most common ET taken concomitantly with palbociclib, followed by letrozole and exemestane. Dosing of palbociclib for 87.0% of patients started on 125 mg/day, and the other patients started on 100 mg/day or 75 mg/day. The dose reduction rate and drug discontinuation rate due to toxicity were 8.5% and 2.3%, respectively, both of which were lower than those of the PALOMA trials (36% and 9.7% in PALOMA-2, respectively; 34% and 4% in PALOMA-3, respectively). The differences between the present study and the PALOMA studies could be due to differences in the follow-up period and dosage of palbociclib.

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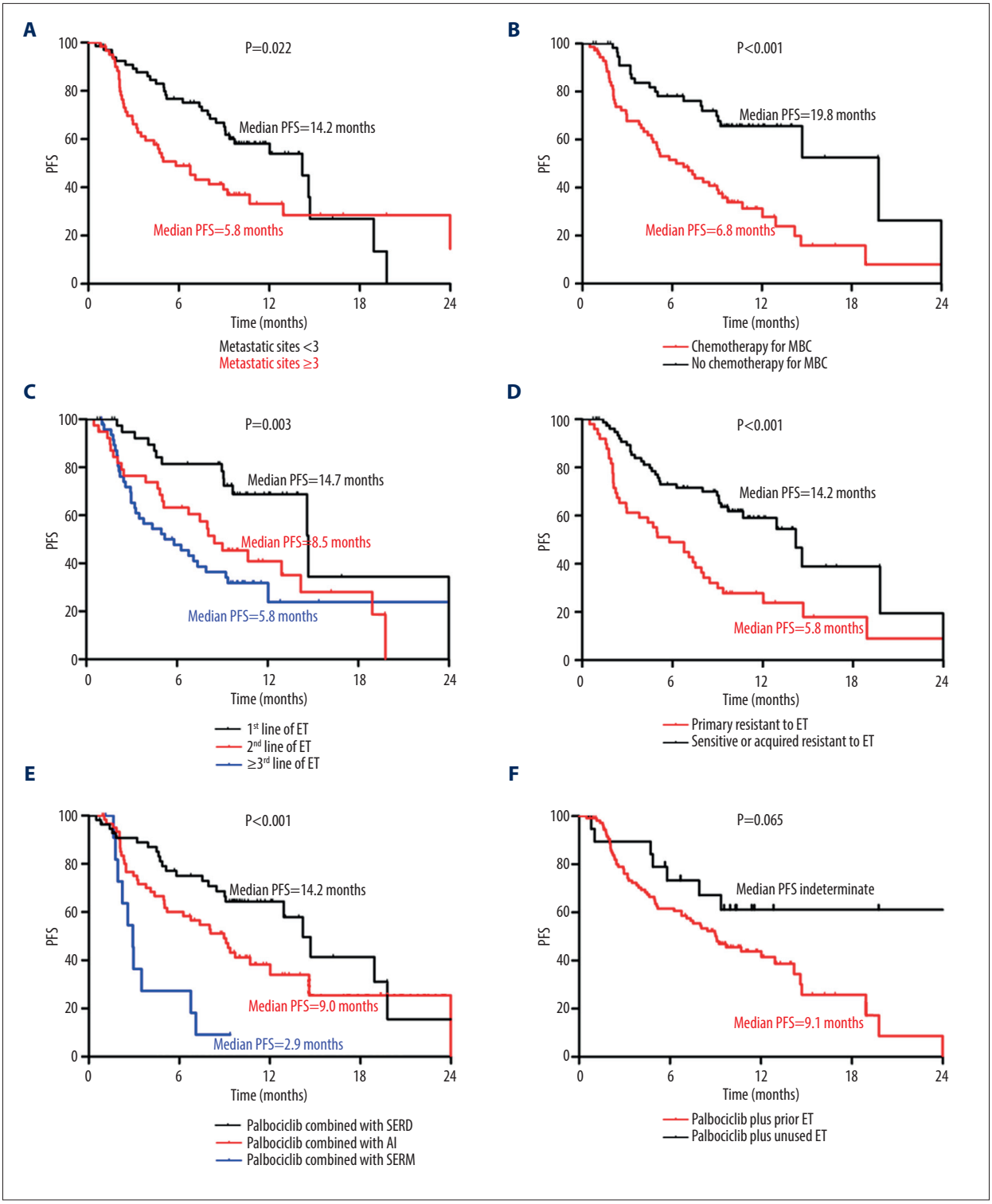

Figure 3. Progression-free survival of palbociclib plus endocrine therapy stratified by patient characteristics. (**A**) Number of metastatic sites; (**B**) Whether or not receiving chemotherapy for MBC; (**C**) Line of palbociclib in ET; (**D**) response to the most recent ET; (**E**) Type of combined ET; (**F**) Palbociclib combined with prior ET or unused ET. Survival curves of PFS were plotted by the Kaplan-Meier method and compared by the log-rank test. *P*-values of less than 0.05 indicate statistical significance. PFS – progression-free survival; ET – endocrine therapy; MBC – metastatic breast cancer; SERD – selective estrogen receptor degrader; AI – aromatase inhibitor; SERM – selective estrogen receptor modulator.

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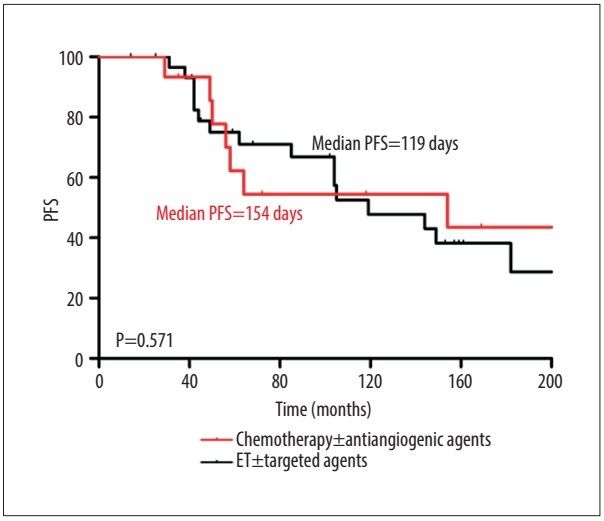

Figure 4. Progression-free survival of the subsequent therapy after progression on palbociclib-based treatment. Survival curve of PFS was plotted by the Kaplan-Meier method and compared by the log-rank test. *P*-values of less than 0.05 indicate statistical significance. PFS – progression-free survival; ET – endocrine therapy.

In the first-line setting of the present study, a clinical benefit rate was achieved in 78.9% of patients and the median PFS was 14.7 months, much lower than the results from the PALOMA-2 trial (85% and 24.8 months, respectively). However, it should be noted that the median follow-up period for this subgroup was only 10.6 months in our study, which was too short to reflect real-world survival. Also, the proportion of visceral metastasis in the present study (71.4%) was higher than that in PALOMA-2 (48.2%). Moreover, 26.2% of patients previously received systemic chemotherapy for MBC in our study, whereas none received prior palliative chemotherapy in the PALOMA-2 trial.

In the second- and later-line settings, 72.7% of the patients in the present study had visceral metastasis, which was higher than the 59% in the PALOMA-3 trial. In our study, 68.2% of patients had previously received systemic chemotherapy for MBC, twice that of the PALOMA-3 trial (33%). In addition, 48.9% of patients in our study had primary resistance to ET, compared to 21% of patients in the PALOMA-3 trial. However, the definitions of sensitivity were not quite the same: our study referred to the tumor response of the most recent ET and the PALOMA-3 study referred to the best tumor response of prior ET. Therefore, the clinical benefit rate and median PFS in our study were lower than those of the PALOMA-3 trial (56.6% *vs.* 67%, 7.4 months *vs.* 9.5 months, respectively).

As expected, better efficacy was observed in those patients who received palbociclib as an early line of treatment, showed no primary resistance to the most recent ET, had fewer than 3 metastatic sites, and had not undergone chemotherapy for MBC. Also, palbociclib plus SERD worked better than palbociclib in combination with AI or SERM. When the PALOMA-2 study was launched, fulvestrant was not recommended as the first-line ET for HR+ and HER2– MBC; therefore, the PALOMA-2 study was designed with palbociclib plus letrozole as the first-line ET. Since then, fulvestrant has been confirmed as superior to AI [18,19], and ribociclib, another CDK 4/6 inhibitor, plus fulvestrant has shown encouraging efficacy as a first-line ET [20]. Thus, we can speculate that palbociclib plus fulvestrant, a powerful combination, will lead to better efficacy in the first-line setting.

Among patients who received palbociclib plus the prior ET which they had progressed on, we further explored the duration of the prior monotherapy. Patients who were resistant to the prior ET could still benefit from palbociclib plus the same ET, regardless of the treatment line, and a longer PFS from the prior monotherapy indicated a better efficacy of the combination. Although the sample size of the present study was small, its results provide evidence that palbociclib could reverse resistance to ET, especially acquired resistance, which agrees with the results of the TREnd trial [2]. Compared with switching to an alternative ET and adding palbociclib, we observed improved PFS in patients adding palbociclib to the prior ET, although the difference was not statistically significant. Among patients who received palbociclib as no less than the fourth line of ET, palbociclib plus ET showed limited efficacy [21,22], with the median PFS of 4.4 months in our present study; whereas, all patients who added palbociclib to the ET which they had acquired resistance to benefited from a prolonged PFS of more than 6 months, and thereby delayed chemotherapy. This issue may be worth further studies in patients who experienced good efficacy from prior ET, especially for those who were heavily treated previously.

After the progression of disease on palbociclib, physicians suggest chemotherapy or ET as subsequent therapy, according to patient characteristics. Both chemotherapy and ET showed limited efficacy and no significant differences in the present study, in agreement with previous reports [12,23]. It should be pointed out that, in fact, the efficacy of subsequent chemotherapy and ET was not comparable because of patient heterogeneity.

There are some limitations in our study. First, this study was conducted in a single center and the study population was relatively small, which could have led to selection bias. Second, the follow-up period was relatively short; therefore, the conclusions drawn from this study should be reevaluated after longer follow-up. Third, all data on clinical characteristics and efficacy were retrospectively recorded, resulting in human error and missing data. Finally, some noteworthy concerns remain unaddressed, including the impact of palbociclib on overall

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survival, the potential of a better medication sequence of targeted drugs (including CDK4/6 inhibitor, mTOR inhibitor, and PIK3CA inhibitor) in ET, and the selection of populations benefiting from palbociclib across multiple lines. To address these problems, we are expanding the sample size and continuing follow-up of the cases on an ongoing basis at our institution. Nonetheless, our study provided valuable information on the real-world practice of palbociclib plus ET in women with HR+ and HER2– MBC in China.

Conclusions

The findings from this real-world study at a single center in China showed that treatment with palbociclib plus ET exhibited favorable efficacy and good tolerance in patients with HR+ and HER2– MBC, even in patients who were initially resistant to ET. Also, there was no difference in outcome between chemotherapy and ET used as subsequent therapy.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Fudan University Shanghai Cancer Center Institutional Human Ethics Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflicts of interest

None.

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