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Real-world effectiveness and sensitivity of palbociclib plus endocrine therapy in HR+/HER2– patients with metastatic breast cancer

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Abstract

Palbociclib has shown satisfactory outcomes when combined with endocrine therapy (ET) in hormone receptor–positive and human epidermal growth factor receptor 2–negative (HR+/HER2–) metastatic breast cancer (MBC). However, data in Asia are currently scarce.This retrospective study aimed to evaluate the real-world effectiveness, sensitivity, and toxicity of palbociclib plus ET in HR+/HER2– MBC in North China. We recruited patients with HR+/HER2– MBC from August 2018 to July 2020 across 7 hospitals in North China. The primary endpoint was to evaluate progression-free survival (PFS) after initial progress on palbociclib therapy. The secondary endpoints included determining predictive biomarkers of palbociclib sensitivity and toxicity of palbociclib.A total of 54 patients were analyzed in this cohort with an estimated median follow-up time of 14.3 months. Patients who received palbociclib as a first-line treatment showed significantly prolonged PFS compared with those who received palbociclib as a second-line or beyond treatment (21.8 months vs 15.9 months vs 6.8 months) ($P < .001$). Besides, patients with Ki67 <30% ($P = .024$) and PR ≥20% ($P = .041$) in metastatic tumors had significantly longer PFS. The Cox proportional-hazards regression analyses proved that different lines ($P = .001$ in multivariate analysis), Ki67 <30% ($P = .035$ in multivariate analysis), and PR ≥20% ($P = .045$ in univariate analysis) in metastatic tumors affected PFS significantly. The most common adverse events were hematologic, with 31.48% of patients having neutropenia.Palbociclib plus ET significantly prolonged PFS for patients with HR+/HER2– MBC who received first-line therapy, with manageable toxicity. The values of Ki67 and PR in metastatic tumors may be potential predictive biomarkers of palbociclib sensitivity.

Abbreviations: ABC = advanced breast cancer, AEs = adverse events, CBR = clinical benefit rate, CR = complete response, CDK4/6i = CDK4/6 inhibitor, ER = estrogen receptor, ET = endocrine therapy, HR+/HER2– = hormone receptor positive and human epidermal growth factor receptor 2 negative, MBC = metastatic breast cancer, PD = disease progression, PFS = progression-free survival, PR = progesterone receptor, RCTs = randomized clinical trials, SD = stable disease.

Keywords: effectiveness, metastatic breast cancer, palbociclib, real-world, sensitivity

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YL and XZ contributed equally to this study.

Statement of Ethics: This study was approved by the Institutional Ethics Committee of the Fourth Hospital Affiliated with Hebei Medical University (Shijiazhuang, China), and signed informed consent was provided by the participants. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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1. Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related deaths among women worldwide.[1] Hormone receptor–positive and human epidermal growth factor receptor 2–negative (HR+/HER2−) breast cancer, is the most common subtype of breast cancer expressing estrogen receptor (ER) and/or progesterone receptor (PR), accounting for approximately 70% of all breast cancers.[2] Endocrine therapy (ET) has consistently been the cornerstone of treatment in HR+/HER2− breast cancer. However, ET is not curative due to substantial heterogeneity and intrinsic or acquired drug resistance in a large subset of HR+/HER2− breast cancers.[3,4] The overall survival (OS) of patients with HR+/HER2− metastatic breast cancer (MBC) have shown no trend of improvement over the past decade due to ET resistance and frequent disease progression (PD),[5] necessitating the discovery of new approaches against HR+/HER2− MBC.

The dysregulation of the cell cycle is one of the defined hallmarks of breast cancer. Cyclin-dependent kinases are serine/threonine kinases that promote progression from the G1 phase to the S phase of the cell cycle.[6] The inhibition of CDK4/6 leads to the inhibition of retinoblastoma (Rb) phosphorylation of the cyclin-D CDK4/6 Rb pathway, thereby causing G1 arrest and suppressing cell proliferation.[7] The development of CDK4/6 inhibitor (CDK4/6i) for treating HR+/HER2− advanced breast cancer (ABC) was based on the findings of preclinical studies, suggesting that CDK4/6i had the potential to act synergistically with ET, and reverse endocrine resistance of HR+ breast cancer.[8] The clinical benefit of CDK4/6i combined with ET has been reported in multiple trials. The results from phase 3 randomized trials have provided consistent support for the use of CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) in patients with HR+/HER2− ABC, with substantial improvement in progression-free survival (PFS) and overall response rate and manageable toxicity.[9–12] No head-to-head trial comparing different CDK4/6 inhibitors was conducted, but subgroup analyses of a meta-analysis showed no significant difference in PFS among 3 CDK4/6 inhibitors.[13]

Palbociclib is the first-in-class oral small-molecule CDK4/6 inhibitor, which improves PFS when combined with letrozole or fulvestrant in clinical trials. The phase 2 study PALOMA-1 showed that the PFS was twice as long with the addition of palbociclib as a first-line treatment in HR+/HER2− ABC. Consequently, the US Food and Drug Administration (FDA) granted the approval of palbociclib plus letrozole as the first-line treatment in February 2015.[14] These clinical benefits were later confirmed in the subsequent phase 3 PALOMA-2 trial.[15] Meanwhile, the PALOMA-3 trial demonstrated that the addition of palbociclib and the selective ER downregulator (SERD) fulvestrant led to a significant improvement in median PFS in patients with HR+/HER2− ABC with PD while on or soon after a previous adjuvant ET or while receiving first-line ET,[9] leading to the FDA approval of palbociclib plus fulvestrant in February 2016. Besides, the toxicity of palbociclib was very manageable, with asymptomatic neutropenia being the most common side effect and a low incidence of febrile neutropenia.[16] Patients with ABC could achieve a better quality of life, with a low drug discontinuation rate.

However, renowned differences existed possibly emerging from the comparison between patients enrolled in randomized clinical trials (RCTs) and those from the real-life setting. Real-world data were critical to demonstrate the reproducibility of evidence and external generalizability of RCTs. Real-life reports from the Americas and Europe showed good results of palbociclib,[17–20] whereas data in Asia were scarce. In addition, currently no robust predictive biomarkers of CDK4/6i are available to help guide clinical medication. Exploring the potential clinical biomarkers of palbociclibis is necessary to help optimize patient selection in clinic. The predictive values of the statuses of Ki67 and HR status were controversial in previous studies.[21] In light of drug access in China, this study reported the real-world clinical outcomes of palbociclib in combination with ET in female patients with HR+/HER2− MBC treated at multiple cancer centers in Hebei Province of North China. This study aimed to assess the real-world clinical benefit, sensitivity, and tolerability of palbociclib combined with ET as first or subsequent endocrine lines of therapy in Chinese patients with HR+/HER2− MBC.

2. Patients and methods

2.1. Study design and patients

This retrospective study comprised 65 patients with HR+/HER2− ABC who received at least one cycle of palbociclib between August 2018 and July 2020. Patients were retrospectively and sequentially identified across 7 hospitals in North China's Hebei Province. All patients had histologically confirmed HR+ and HER2− MBC, while they were excluded if clinicopathological information (N=6) and follow-up data were not available or incomplete (N=2). Patients without measurable lesions defined by the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) were also excluded (N=3) (Fig. 1). Eventually, only 54 patients were enrolled in the present analysis. Palbociclib was given orally at 125 mg/d in 4-week cycles (3 weeks of treatment followed by 1-week off) for at least one cycle. All 54 patients were followed up until the date of first PD or July 2021. This present study was approved by the Medical Ethics Committee at each hospital, following the Declaration of Helsinki. Informed consent to data collection was obtained from all the participants involved.

2.2. Endpoints

The primary endpoint was progression-free survival (PFS), defined as the time from the initiation of palbociclib to radiologically or clinically confirmed PD or death. The secondary endpoints included: clinical benefit rate (CBR), defined as the percentage of complete response (CR) + partial response (PR) + stable disease (SD) for at least 6 months; overall response rate, defined as CR+PR; predictive biomarkers of palbociclib sensitivity; toxicity; and reasons for treatment discontinuation. Moreover, we aimed to evaluate the efficacy in subgroups defined according to relevant patient-related and tumor-related features.

2.3. Biomarker detection

ER, PR, HER2, and Ki67 expression were analyzed immunohistochemically on formalin-fixed, paraffin-embedded tumor sections (all 54 primary tumors and available 27 metastatic tumors) (all monoclonal antibodies were purchased from Abcam, Cambridge, UK), according to the recommended guidelines of the American Society of Clinical Oncology and College of American

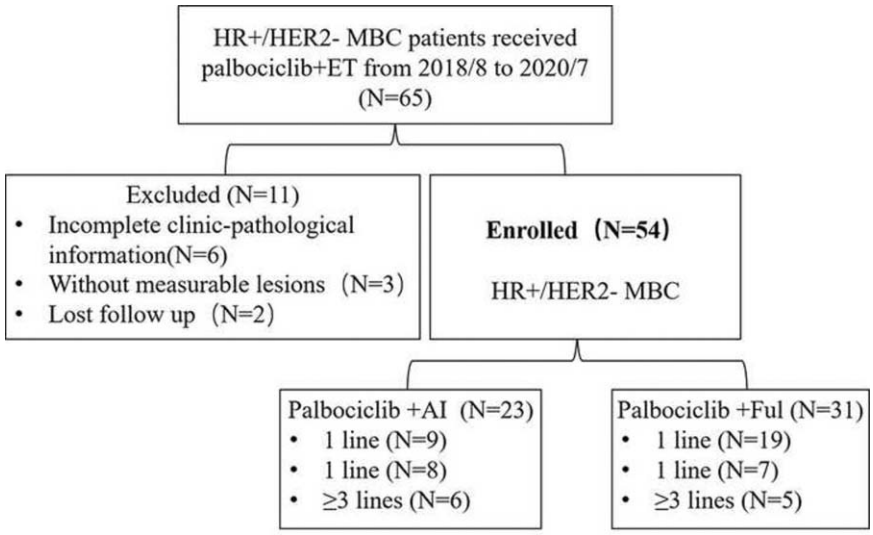

Figure 1. Flow diagram of the study cohort. AI = aromatase inhibitor, ET = endocrine therapy, Ful = fulvestrant, HR+ = hormone receptor positive, HER2− = human epidermal growth factor receptor 2 negative, MBC = metastatic breast cancer.

Pathologists. In patients with a score of HER2 IHC 2+, a fluorescent in situ hybridization (FISH) test was conducted. ER, PR, and Ki67 were analyzed both as continuous and dichotomized variables.

2.4. Efficacy and toxicity assessment

Imaging (computed tomography scans, magnetic resonance imaging, or bone scans) was performed every 2 months during treatment until disease progression. The treatment efficacy was evaluated by physicians according to RECIST1.1. Biochemical and hematologic laboratory tests were performed on days 1 and 15 of the first 2 cycles and subsequently on day 1 of subsequent cycles in most patients. Dose reductions/delay/discontinuations of palbociclib due to adverse events were recorded. Treatment was continued until disease progression, unacceptable toxicity, or patient refusal. Adverse events (AEs) were recorded and graded following the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0).

2.5. Statistical analysis

The SPSS software (SPSS version 22.0, IBM Corp, Armonk, NY) was used for all statistical evaluations. The Kaplan–Meier method was used for the calculation of PFS and the unstratified log-rank test for the comparison of the survival curves. The Cox proportional-hazards model was used to estimate the hazard ratio (HR) of each clinicopathological variables for PFS. All predictors with a P value $<.05$ in univariate Cox analyses or clinical significance were used in multivariate analysis. Multivariate Cox proportional-hazard models were developed using stepwise regression (forward selection). P values were 2 tailed and considered significant when $<.05$.

3. Results

3.1. Patients characteristics

Between August 2018 and July 2020, 54 patients with metastatic HR+/HER2− breast cancer patients were retrospectively enrolled across 7 hospitals in North China's Hebei Province eventually (Fig. 1). The main patient and tumor characteristics are listed in Table 1. The median age was 53.4 years (range 34–84). The majority of patients were menopausal (72.2%), and nearly one-half of patients (44.4%) had at least 2 metastatic organs and over a half (59.3%) had visceral metastasis. Further, 48.1% of patients had not received any treatment for MBC before the initiation of palbociclib. Patients who relapsed after 1 year of completing adjuvant ET or did not receive ET previously were considered sensitive to ET (46.3%). 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 (14.8%). 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 (38.9%).[22]

3.2. Efficacy

Figure 2 and Tables 2 and 3 demonstrate the therapeutic data of our study. The total estimated median follow-up time was 14.3 months, with a range of 2 to 29 months. All the patients included in the analysis were evaluable for efficacy. Overall, the estimated median PFS was 13.9 months in the total population, with the CBR of 57.4% (31/54). Among the total 54 patients, 23 patients were treated with palbociclib + AI achieved a CBR of 65.2% (15/23), while the other 31 patients were treated with palbociclib + fulvestrant with an CBR of 51.6% (16/31). In the palbociclib + fulvestrant group, the PFS was 14.8 months versus 9.5 months in the PALOMA-3 trial.[9] The PFS in patients treated with palbociclib + AI for the first-line treatment was 16.0 months, which was shorter than the PFS of 24.8 months in the PALOMA-2 trial,[16] but similar to the palbociclib + fulvestrant clinical outcome for the first-line treatment (17.6 months) (Table 3).

In the total population, 28 patients received palbociclib as a first-line treatment, 15 as a second-line treatment, and 11 as a third-line or beyond treatment. The estimated median PFS was 21.8 months, 15.9 months, and 6.8 months, respectively. It showed that patients without any treatment for MBC earlier had

Table 1

Main baseline characteristics of the study population (N = 54).

Characteristics	Patients, N (%)
Age	
<60	33 (61.1%)
≥60	21 (38.9%)
Menopausal status	
Postmenopausal	39 (72.2%)
Premenopausal or perimenopausal	15 (27.0%)
ECOG performance status	
0–1	50 (92.6%)
2	4 (7.4%)
Histology	
Ductal	49 (90.7%)
Lobular	2 (3.7%)
Other	3 (5.6%)
TNM stage at initial diagnosis	
I	7 (13.0%)
II	23 (42.6%)
III	20 (37.0%)
IV	4 (7.4%)
Adjuvant chemotherapy	
Yes	40 (74.1%)
No	14 (25.9%)
Type of adjuvant hormonal therapy	
Tamoxifen	33 (61.1%)
Letrozole	17 (31.5%)
Anastrozole	2 (3.7%)
Exemestane	2 (3.7%)
Sensitivity to ET	
Sensitivity	25 (46.3%)
Primary resistance	8 (14.8%)
Acquired resistance	21 (38.9%)
Biopsy of the metastasis tumor	
Yes	27 (50.0%)
No	27 (50.0%)
ER# status in primary tumor	
>10%	51 (94.4%)
≤10%	3 (5.6%)
PR# status in primary tumor	
≥20%	34 (63.0%)
<20%	20 (37.0%)
PR* status in metastasis tumor (n = 27)	
≥20%	12 (44.4%)
<20%	15 (55.6%)
Ki 67# status in primary tumor	
<30%	29 (53.7%)
≥30%	25 (46.3%)
Ki 67* status in metastasis tumor (n = 27)	
<14%	15 (55.6%)
≥30%	12 (44.4%)
DFS, mo	
≥60	25 (46.3%)
<60	29 (53.7%)
Metastatic sites	
Bone-only	12 (22.2%)
Visceral involvement	32 (59.3%)
Lung involvement	24 (44.4%)
Liver involvement	10 (18.5%)
Brain involvement	1 (1.9%)
Lymph node or soft tissue-only	9 (16.7%)
Number of organ metastases	
1	30 (55.6%)
≥2	14 (44.4%)
Previous treatment for MBC	
Yes	26 (48.1%)
No	28 (51.9%)
Previous chemotherapy for MBC	
No	37 (68.5%)
Yes	17 (31.5%)
Previous hormonal therapy for MBC	
None	38 (70.4%)
1 line	10 (18.5%)
≥2 lines	6 (11.1%)

AIs = aromatase inhibitors, DFS = disease-free interval, ECOG PS = Eastern Cooperative Oncology Group Performance Status, ER = estrogen-receptor, ET = endocrine therapy, PR = progesterone receptor, MBC = metastatic breast cancer.

a longer PFS than those with previous palliative treatment (21.8 months vs 12.3 months, $P = .003$) (Fig. 2A). Similarly, patients who received palbociclib as a first-line treatment had significantly prolonged PFS compared with those who received palbociclib as a second-line or beyond treatment ($P < .001$) (Fig. 2B). Both univariate ($P < .001$) and multivariate ($P = .001$) Cox proportional-hazards regression model analyses proved that received palbociclib in different lines significantly affected PFS (Table 4).

3.3. Predictive biomarkers of sensitivity

In total, 29 patients had tumors with Ki67 <30%, and 34 patients had tumors with PR ≥20% evaluated in the primary tumor samples. Due to the metastatic lesion accessibility and other realistic issues, only 27 patients underwent the re-biopsy of an amenable metastatic lesion to confirm the biomarker status. Among 27 metastatic tumors, 15 lesions (55.6%) had Ki67 <30% expression, and 12 lesions (44.4%) had PR ≥20% expression (Table 1). The Kaplan–Meier curve demonstrated that patients with Ki67 <30% had a longer PFS than those with Ki67 ≥30% in metastatic tumors (19.5 months vs 9.8 months, $P = .024$) (Fig. 3B). Patients with PR ≥20% showed prolonged PFS compared with those with PR <20% (20.2 months vs 10.6 months, $P = .041$) (Fig. 4B). However, different statuses of Ki67 ($P = .195$) and PR ($P = .253$) statuses in primary tumors did not affect PFS significantly (Figs. 3A and 4A). Both univariate ($P = .036$) and multivariate ($P = .035$) Cox proportional-hazards regression model analyses proved that Ki67 <30% in metastatic tumors significantly prolonged PFS. The univariate analysis showed that PR ≥20% in metastatic tumors affected PFS significantly ($P = .045$) (Table 4).

3.4. Toxicity

Data on toxicity are reported in Table 2. The main toxicity observed was hematological, with neutropenia of any grade occurring in 31.48% of patients. Fatigue was the most common documented nonhematologic adverse event in 22.22% of patients. Other less commonly reported toxicities included anemia, thrombocytopenia, pancytopenia, diarrhea, anorexia, dyspnea, elevated liver enzymes, oral mucositis, headaches, skin rash, and nausea were not found in our study. Among total 54 patients, 49 (90.7%) patients started palbociclib at 125 mg/d, and 5 (9.3%) patients started palbociclib at 100 mg/d. Further, 11 patients who started with a dose of 125 mg/d had a dose reduction to 100 mg/d due to toxicity (11/54 = 20.4%). Only one patient had discontinuation of palbociclib owing to AEs. Further, 2 patients had discontinuation of palbociclib because of the financial issues.

4. Discussion

This retrospective study investigated the real-world clinical outcomes of palbociclib pluls ET in patients with HR+/HER2− MBC treated at multiple cancer centers in Hebei Province of North China. It exhibited favorable clinical efficacy in patients treated with palbociclib + ET as a first-line treatment. Also, the statuses of Ki67 <30% and PR ≥20% in metastatic tumors may be potential predictive biomarkers of palbociclib sensitivity. In addition, AEs of palbociclib were generally manageable, with dose reductions and discontinued treatment in a few of patients due to AEs. The clinical outcomes from our study may help

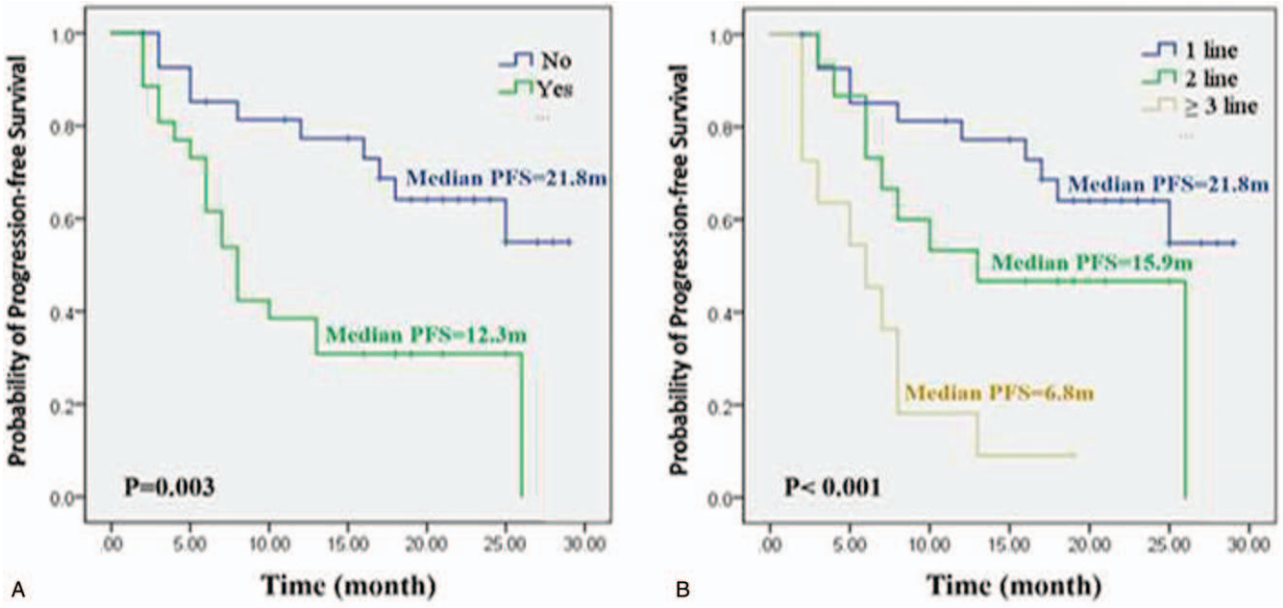

Figure 2. Progression-free survival for palbociclib plus endocrine therapy stratified by characteristics (N = 54). (A) Previous treatment for MBC or not; (B) line of palbociclib plus endocrine therapy. MBC = metastatic breast cancer.

physicians determine the most appropriate therapy for an individual patient with MBC, and optimize the patient selection of palbociclib treatment in the future.

Palbociclib is a highly selective inhibitor of CDK4/6, indicating satisfactory clinical benefits in patients with HR+/HER2−, advanced or MBC in combination with AI or fulvestrant. In previous RCTs, palbociclib in combination with letrozole as a first-line treatment in postmenopausal women[14,15] or in combination with fulvestrant in premenopausal, perimenopausal, or postmenopausal patients led to progression after ET.[9] The latest PARSIFAL trial presented in the 2020 ASCO showed that palbociclib plus fulvestrant demonstrated the same clinical outcome as palbociclib in combination with AI as a first-line treatment,[23] which was consistent with the data of our study. Besides, the addition of palbociclib to fulvestrant was associated with an OS absolute benefit of 6.9 months in the PALOMA-3 trial.[24] However, these very encouraging data deriving from RCTs need to be confirmed in real-world practice, in less-selected patients. Currently, real-life data about palbociclib in Asia are still limited, which is the first available CDK4/6i in China. Our study provided insights into treatment efficiency and complete blood count monitoring patterns in China practice. Eventually, the present study recruited 54 eligible female patients from 7 hospitals in Hebei Province of North China. To our knowledge, this was one of the few reviews of China data reported in the literature thus far.

Table 2

Treatment characteristics and main toxicities of palbociclib plus ET (N = 54).

Characteristic	Patients, N (%)
ET combined with palbociclib	
Letrozole	23 (42.6%)
Fulvestrant	31 (57.4%)
Line of palbociclib + ET	
1 line	28 (51.9%)
2 lines	15 (27.8%)
≥3 lines	11 (20.4%)
Dosage of palbociclib	
Start at 125 mg/d	49 (90.7%)
Reduction from 125 to 100 mg/d	11 (20.4%)
Start at 100 mg/d	5 (9.3%)
AEs-Neutropenia	17 (31.5%)
Grade 1, n (%)	2 (11.8%)
Grade 2, n (%)	2 (11.8%)
Grade 3, n (%)	7 (41.2%)
Grade 4, n (%)	6 (35.3%)
Non-hemotological toxicity	
Fatigue	12 (22.2%)
Anemia	0
Elevated liver enzymes	0
Diarrhea	0
Rash	0
Headache	0
Dizziness	0
Discontinuation of palbociclib	3 (5.6%)
Due to AEs	1 (1.9%)
Due to financial issues	2 (3.7%)

AEs = adverse events, DFS = disease-free interval, ET = endocrine therapy.

As expected, the median PFS time of patients who had received palbociclib in combination with either letrozole or fulvestrant as a first-line treatment was longer than that of patients who received this as a second-line or beyond treatment in our cohort ($P < .001$). However, the CBR was achieved in 66.7% of patients, and the median PFS was 16.0 months in the first-line setting of palbociclib + AI in our study. This was lower than the results from the PALOMA-2 trial (85% and 24.8 months, respectively), which was possibly owing to the difference in the proportion of visceral metastasis (48.2% in PALOMA-2 vs 59.3% in our study).[16] Moreover, it should be noted that the median follow-up period was only 14.3 months in our study. The difference in treatment lines and patient heterogeneity also influenced the clinical outcome. Our study showed that previous treatment might lead to a lower sensitivity of palbociclib. This might be due to the increased burden and heterogeneity associated with tumor

Table 3

Responses to palbociclib according to different treatment lines (N = 54).

Drug combination	Line of therapy	N (%)	CR n (%)	PR n (%)	SD n (%)	ORR n (%)	CBR n (%)	PD n (%)	Median PFS
Palbociclib + Letrozole (N = 23)	1 line	9 (39.1)	1 (11.1)	2 (22.2)	3 (33.3)	3 (33.3)	6 (66.7)	3 (33.3)	16.0 ± 10.6
	2 lines	8 (34.8)	–	1 (12.5)	6 (75.0)	1 (12.5)	7 (87.5)	1 (12.5)	12.6 ± 8.3
	≥3 lines	6 (26.1)	–	–	2 (33.3)	–	2 (33.3)	4 (66.7)	8.3 ± 6.6
Palbociclib + Fulvestrant (N = 31)	1 line	19 (61.3)	–	4 (21.1)	10 (52.6)	4 (21.1)	14 (73.7)	5 (26.3)	17.6 ± 8.0
	2 lines	7 (22.6)	–	–	2 (28.6)	–	2 (28.6)	5 (71.4)	14.1 ± 7.4
	≥3 lines	5 (16.1)	–	–	–	–	–	5 (100)	5.0 ± 2.8

Best response	Real-world Palbociclib + Letrozole (1 line)	PALOMA-2 Palbociclib + Letrozole	Real-world Palbociclib + Fulvestrant	PALOMA-3 Palbociclib + Fulvestrant	Real-world Palbociclib + ET (all lines)
ORR (%)	3/9 (33.33%)	42.1%	4/31 (13.0%)	19.0%	8/54 (14.8%)
CBR (%)	6/9 (66.67%)	84.9%	16/31 (51.6%)	67.0%	31/54 (57.4%)
PFS, mo	16.0	24.8	14.8	9.5	13.9

CBR = clinical benefit rate, CR = complete response, ECOG PS = Eastern Cooperative Oncology Group Performance Status, ET = endocrine therapy, ORR = overall response rate, PFS = progression-free survival, PR = partial response, SD = stable disease.

Table 4

Univariate and multivariate analyses (Cox regression) for PFS.

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
DFS ≥5 years	1.459 (0.700–3.042)	.311	0.982 (0.450–2.141)	.963
Bone-only metastases	0.490 (0.170–1.416)	.179	0.481 (0.149–1.555)	.222
Single metastatic organ	1.233 (0.593–2.562)	.574	1.255 (0.556–2.831)	.585
Previous treatment for MBC	0.338 (0.155–0.734)	.006	0.336 (0.148–0.765)	.009
Line of therapy		.000		.001
Line of therapy (1 vs 2)	0.174 (0.069–0.437)	.025	0.298 (0.108–0.824)	.020
Line of therapy (1 vs 3)	0.348 (0.139–0.875)	.000	0.167 (0.064–0.437)	.000
Ki 67# <30%	1.958 (0.681–5.632)	.204	0.478 (0.161–1.420)	.184
PR# ≥20%	1.527 (0.724–3.221)	.263	1.350 (0.620–2.938)	.450
Ki 67* <30%	2.979 (1.073–8.268)	.036	3.174 (1.085–9.290)	.035
PR* ≥20%	2.857 (1.034–8.386)	.045	3.070 (0.984–9.579)	.053

DFS = disease-free interval, HR = hazard ratio, MBC = metastatic breast cancer, PFS = progression-free survival, PR = progesterone receptor. #: in primary tumor; *: in metastasis tumor.

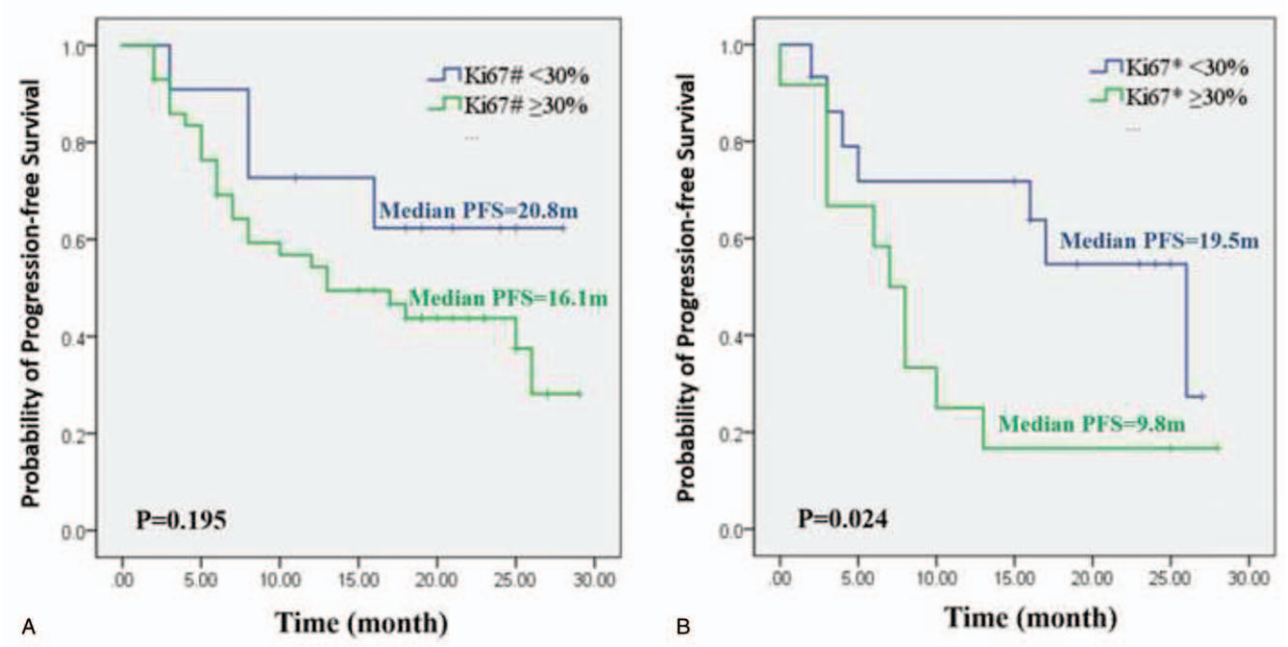

Figure 3. Progression-free survival for palbociclib plus endocrine therapy stratified by Ki67 expression. (A) Stratified by Ki67# expression in primary tumors in the total population (N = 54); (B) stratified by Ki67* expression in metastatic tumors in the population who underwent biopsy of metastatic tumors (N = 27).

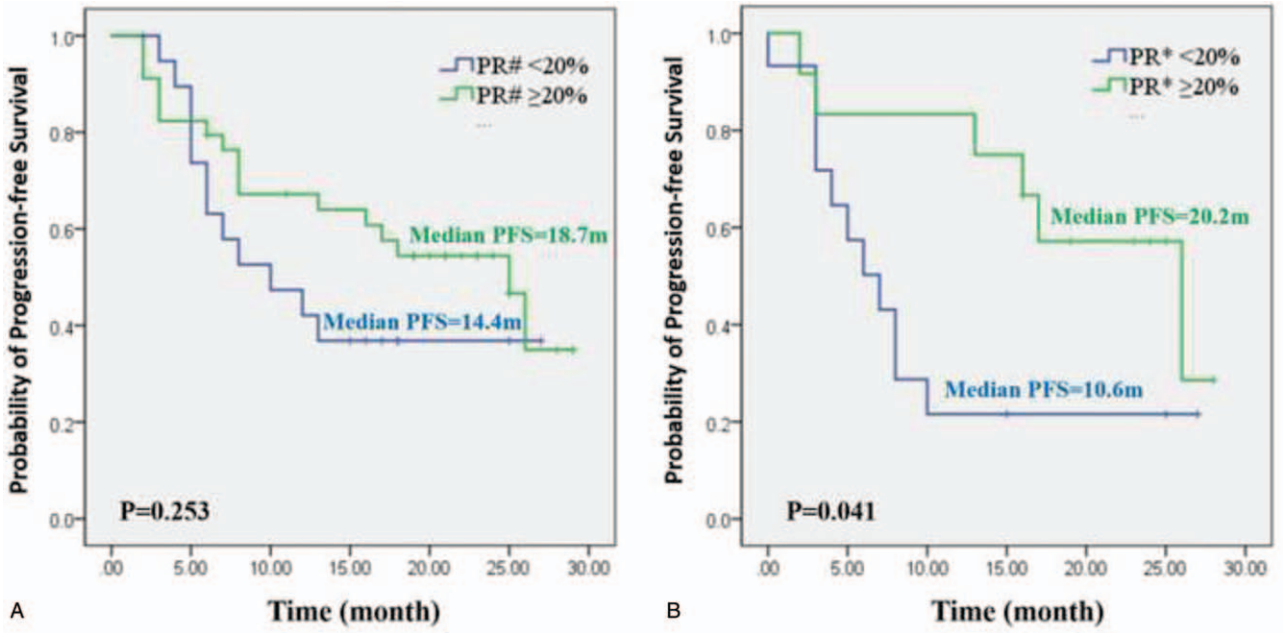

Figure 4. Progression-free survival for palbociclib plus endocrine therapy stratified by PR expression. (A) Stratified by PR# expression in primary tumors in the total population (N = 54); (B) stratified by PR* expression in metastatic tumors in the population who underwent biopsy of metastatic tumors (N = 27).

progression. Overall, our study results were satisfactory. Both in terms of the effectiveness and tolerability of palbociclib in real-world clinical practice and corresponded with those of the RCTs[9,14–16] and other clinical retrospective experiences in the Americas and Europe.[13,17–20,25]

In addition, our study demonstrated that the statuses of Ki67 <30% and PR ≥20% in metastatic tumors might be potential predictive biomarkers of palbociclib sensitivity in patients with HR+/HER2− MBC. Currently, no robust predictive or prognostic biomarkers that guide clinical medication have been explored in the randomized trials of palbociclib, other than ER expression in a large-pooled America FDA group analysis.[21] The predictive values of the statuses of Ki67 and HR status were controversial in previous studies. Palleschi et al[26] revealed that the PFS of patients with CDK4/6i plus ET was inversely related to Ki67 expression, but not to PR, which was similar to our findings. Another retrospective study also revealed that PFS seemed to be negatively influenced by elevated Ki67 expression. Moreover, the change in Ki67 from primary tissues to metastatic lesions was also related to PFS.[27] The PARSIFAL trial showed that Ki67 and PR levels had no impact on the clinical outcome of palbociclib + fulvestrant, but greatly affected the benefit of palbociclib + aromatase inhibitor.[23] These findings might provide insights into the optimal patient selection of palbociclib using Ki67 and PR values, with a relatively easily available, economical, and practical detection. However, the predictive value of Ki67 and PR needs further confirmation in a prospective study.

The toxicity profile of palbociclib in our study was more conservative than the published clinical literature with CDK4/6i in the James Cancer Hospital at the Ohio State University[19] and the PALOMA trials,[9,16] with a lower dose reduction rate due to toxicity (20.4% in our study vs 57% in James Cancer Hospital vs 36% in PLOMA-2 vs 34% in PLOMA-3). In PALOMA-3 and PALOMA-2 trials, grade 3/4 neutropenia occurred in 62.0% and 66.4% of patients, respectively.[9,16] However, in our study, the most common adverse event of neutropenia was occurred only in 31.5% of patients. In addition, we did not identify any episodes of febrile neutropenia (FN) within our cohort, and 51 patients were able to continue palbociclib with dose reductions in 11 cases. Only 3 patients had discontinuation of palbociclib due to adverse events (N = 1) or financial issues (N = 2). This difference could be due to differences in the follow-up period, the initial dosage, and the national variations.

Although our results were consistent with those from some RCTs and prior studies carried out in a real-word setting, our study had several limitations in our study. First, it had a relatively small sample size, which might have led to selection bias. Second, our follow-up was still particularly short, and further data evaluation was needed following longer observation. Third, some of the electronic records had missing information such as laboratory data and incomplete documentation on treatment toxicities. Besides, only 27 patients had a re-biopsy of the metastatic lesion due to metastasis accessibility and other real issues. The failure to perform re-biopsy in all metastatic tumors might be a defect in our study. Finally, the observational retrospective design deserves to be mentioned in light of the tendency toward confounding and biases, which characterize this type of studies. Based on the aforementioned issues, we need to expand the sample size of the study and continue the follow-up of these patients. Nonetheless, the present study provided valuable information on the real-world effectiveness and sensitivity of palbociclib plus ET in patients with HR+/HER2− MBC.

In conclusion, the development of CDK4/6 inhibitors and the introduction of palbociclib into clinical practice certainly represent an important addition to therapeutic treatment in HR+/HER2− MBC. In this retrospective study, we investigated the real-world clinical outcomes of palbociclib plus ET in patients with HR+/HER2− MBC. The study showed that palbociclib was well tolerated, with a manageable toxicity profile and low drug discontinuation rate. In addition, our study demonstrated that

the statuses of Ki67 <30% and PR ≥20% in metastatic tumors might be potential predictive biomarkers of palbociclib sensitivity in patients with HR+/HER2− MBC, thus helping to guide clinical medication in real-world practice. Overall, these findings need to be confirmed through prospective, adequately sized clinical trials.

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Author contributions

Jingping Li, Yunjiang Liu, and Xiangmei Zhang contributed to conception and design. Yalei Lv, Hua Yang, Xiangshun Kong, Meng Han, Zunyi Wang, Jie Ma, and Jianjun Han were involved in patient recruitment and sample and data collection. Jingping Li and Xiangmei Zhang performed sample analysis and statistical analyses. Jingping Li, Chao Yang, Yunjiang Liu, and Xiangmei Zhang performed data analysis and interpretation. Jingping Li drafted the manuscript. All the authors participated in the critical revision and validation of the final manuscript.

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