Original Article

Survival outcomes, multidimensional prediction and subsequent therapy in patients with hormone receptor-positive advanced breast cancer receiving palbociclib: a real-world analysis

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Background: To date, the overall survival (OS) of hormone receptor-positive advanced breast cancer (ABC) treated with palbociclib has not been reported in Chinese patients. It still remains unclear what kind of patients may benefit in OS from palbociclib treatment and what the optimal sequential antineoplastic regimen is for those progressing on palbociclib. Therefore, we aimed to investigate the OS outcome of ABC patients receiving palbociclib, establish a predictive model to identify the potential candidates who may benefit from palbociclib and explore the ideal subsequent treatment strategy after palbociclib.

Methods: This is a single-center ambispective real-world analysis of palbociclib in hormone receptor-positive ABC from April 2018 to August 2021. The patients were followed up via telephone or clinic visit. Progression-free survival (PFS), OS, overall response rate and time to second disease progression (PFS2) were evaluated as prognosis outcomes. Cyclin-dependent kinases 4/6 inhibitor (CDKI) score was established to predict OS benefit on the basis of tumor burden, line of palbociclib treatment and tumor marker.

Results: Fifty patients were included with the median PFS of 9.57 months and the median OS of 33.60 months. Age <65 years [hazard ratio (HR) 0.33, P=0.008], lung or liver involvement (HR 3.01, P=0.005) and > first line palbociclib therapy (HR 2.13, P=0.03) were independent unfavorable prognosticators for PFS. Positive estrogen receptor (ER) (HR 0.22, P=0.004), metastatic sites <3 (HR 3.59, P=0.02), absence of lung or liver involvement (HR 3.77, P=0.058) and PFS ≥12 months during palbociclib regimen (HR 0.14, P<0.001) could predict longer OS. CDKI score discriminated OS significantly (HR 4.41, P=0.009) and the CDKI score-based models were multidimensionally verified with satisfying performance, among which the area under the curve of receiver operating characteristic reached 0.835 and the C-index was 0.72. Moreover, chemo-free regimens saw improvement in time to second disease progression (HR 0.32, P=0.006) and OS (HR 0.32, P=0.049) for patients progressing on palbociclib compared with chemotherapy-based regimens.

Conclusions: CDKI score is a practical and comprehensive tool in predicting OS benefit for ABC patients treated with palbociclib, which deserves further validation. Patients who progressed on palbociclib seem to keep benefiting from chemo-free antineoplastic treatments. These findings may help identify the candidates for CDK4/6 inhibitor and optimize the strategies for hormone receptor-positive ABC.

Keywords: Advanced breast cancer (ABC); hormone receptor-positive; overall survival (OS); palbociclib; cyclin-dependent kinases 4/6 inhibitor score (CDKI score)

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Introduction

The hormone receptor-positive breast cancer subtype accounts for approximately 70% of all breast cancer cases. For decades, endocrine therapy (ET) has been the standard strategy for this large population. Unfortunately, approximately 20% of hormone receptor-positive patients exhibit primary or acquired resistance to aromatase inhibitor (AI) or tamoxifen treatment after 10 years in the adjuvant setting (1), suggesting a need for novel approaches to address endocrine resistance and improve the survival outcomes of these patients. Abnormalities in the cell cycle pathway are crucial causes of endocrine resistance, and cyclin-dependent kinases (CDKs) are key regulators of cell cycle progression (2,3). CDK4 and CDK6 interact with D-type cyclin, which plays an essential role in the transition from G1 to S phase (4). CDK4/6 inhibitors exert antitumor effects by downregulating the cyclin D-CDK4/6 pathway and eventually arresting the activity of cell cycle progression (5,6). Recent studies also found that CDK4/6 inhibitors could trigger osmotic and replication stress to promote senescence and cause cell death (7,8).

CDK4/6 inhibitors (CDK4/6i) combined with AI or fulvestrant are currently indicated as first-line therapy for hormone receptor-positive advanced breast cancer (ABC) (9,10). Palbociclib has shown favorable efficacy and safety profiles for hormone receptor-positive/human epidermal growth factor receptor 2 (HER2)-negative patients with advanced disease in a series of randomized controlled trials, PALOMAs (11,12), and in real-world studies (RWS) (13-16). However, data on palbociclib in Chinese breast cancer patients still need to be consolidated. The overall survival (OS) outcome of palbociclib was not mature in PALOMA-4 (17) and other Chinese real-world analysis (18,19). The recommended subsequent treatment regimen after progression on CDK4/6 inhibitors is not yet clear. Moreover, considering the financial burden (20) and the side effects, physicians still require effective predictive models to identify patients who are more likely to benefit from CDK4/6i therapy.

Accordingly, we aimed to accumulate real-world evidence concerning the long-term survival outcomes and adverse events (AEs) for palbociclib plus ET in Chinese patients with ABC and to establish a scoring system as a novel predictive instrument to stratify the prognosis of CDK4/6i treatment. We present this article in accordance with the TRIPOD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-362/rc) (21).

Highlight box

Key findings

- This study established a multidimensional model to discriminate the candidates who may benefit more from palbociclib therapy and revealed that chemo-free regimens after palbociclib progression might provide a better survival outcome than subsequent chemotherapy.

What is known and what is new?

- CDK4/6 inhibitors significantly improve the survival outcomes of hormone receptor-positive advanced breast cancer (ABC) patients.
- It still remains unclear what kind of patients may benefit in overall survival from palbociclib treatment and what the optimal sequential antineoplastic regimen is for those progressing on palbociclib.

What is the implication, and what should change now?

- The cyclin-dependent kinases 4/6 inhibitor (CDKI) score may provide reference for the construction of further predictive model for CDK4/6 inhibitors in ABC. Continuing chemo-free regimens as immediate subsequent treatments after palbociclib progression might be an effective strategy.

Methods

Patients

This study retrospectively collected records of patients who received palbociclib with AI or fulvestrant from April 2018 to August 2021 in Renji Hospital, School of Medicine, Shanghai Jiao Tong University, from electronic medical records and then prospectively followed-up until 29 November 2022. The study was approved by the Independent Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University (approval No. KY2022-097-B) and individual consent for this retrospective analysis was waived. This study was registered with ClinicalTrials.gov (NCT05795335). The study was

Table 1 Point assignments for the CDKI score

Factors	Point
Tumor marker	
ER-negative	1
Line of palbociclib	
>1st line	1
Tumor burden	
Presence of lung or liver involvement	1
Number of metastatic sites ≥3	1

CDKI, cyclin-dependent kinases 4/6 inhibitor; ER, estrogen receptor.

conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Prescriptions, laboratory assessments and instances of palbociclib dose reduction and interruption were obtained from electronic medical records and updated every 3 months prospectively. Primary or metastatic lesions were measured by computed tomography or magnetic resonance imaging every two to three months according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (22). Laboratory assessments were conducted regularly during palbociclib treatment. Treatment-emergent adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 (23).

Statistical analysis

Baseline characteristics were collected, including age at palbociclib initiation (<65 or ≥65 years), menstrual status (pre-/peri- or post-menopause), estrogen receptor (ER) status (negative or positive), lung or liver involvement (yes or no), *de novo* stage IV (yes or no), number of metastatic sites (<3 or ≥3), line of palbociclib therapy (first or >first), endocrine combination partner (AI or fulvestrant), previous chemotherapy for advanced disease (yes or no), and palbociclib dose reduction (yes or no).

Progression-free survival (PFS) was defined as the time from the first dose of palbociclib to the first occurrence of radiological disease progression per RECIST version 1.1 (22) or death for any reason. OS was defined as the time from the first dose of palbociclib to death due to any cause. The overall response rate (ORR) was defined as the rate of complete response or partial response, as assessed by physicians. Time to second disease progression (PFS2) was defined as the time from the starting date of immediate subsequent therapy after palbociclib progression to the earliest event of its corresponding disease progression or death due to any cause.

Median PFS (mPFS) and median OS (mOS) were estimated via a life table. Median follow-up time was analyzed by the reverse Kaplan-Meier method. The log-rank test and Cox proportional hazards regression analysis were performed for time-to-event variables. Age (<65 or ≥65 years), lung or liver involvement (yes or no), line of palbociclib treatment (first or >first) and *de novo* stage IV (yes or no) were included in the multivariate model. The hazard ratio (HR) and 95% confidence interval (CI) are presented.

The cyclin-dependent kinases 4/6 inhibitor (CDKI) scoring system was established to predict the OS after palbociclib treatment. Four indices combining tumor burden, line of palbociclib and tumor marker were selected. Points assigned for the CDKI score are displayed in *Table 1*. The cutoff value of the CDKI score was determined at the median value of 2. Patients with CDKI scores >2 and ≤2 were categorized into high-risk and low-risk groups, respectively. We constructed four models according to different combinations of CDKI score and important clinicopathological characteristics. ER status, line of palbociclib, presence of lung or liver involvement and number of metastatic sites composed Model 1. Model 2 consisted of the CDKI score alone. Model 3 included features in Model 1, menopausal status and *de novo* stage IV, and Model 4 incorporated CDKI score, menopausal status and *de novo* stage IV. A nomogram was constructed to display the predicted probabilities of OS. Receiver operating characteristic (ROC) curves, decision curve analysis (DCA), the Akaike information criterion (AIC), Harrell's concordance index (C-index) and calibration curves were used to evaluate the performance of the four models graphically and quantitatively using the R packages 'survival', 'rms', 'timeROC', 'ggDCA', 'MASS' and 'foreign'. Both an area under the curve (AUC) and a C-index =0.5 indicate a random chance, while 1.0 shows that the model is able to discriminate outcome. A lower AIC value indicates a better-fitting model.

Statistical analysis was conducted using STATA Statistics SE 16 (Stata Corp LP, College Station, TX, USA) and R software (version 4.2.2). The statistical tests were two-sided, and P values less than 0.05 were considered statistically significant.

Table 2 Clinicopathological characteristics

Characteristics	Number of patients [%]
Age of starting palbociclib (years)	
≥65	11 [22]
<65	39 [78]
Menopausal status	
Pre-/peri-menopause	13 [26]
Post-menopause	37 [74]
ER status	
Positive	46 [92]
Negative	4 [8]
Bone-only involvement	
Yes	13 [26]
No	37 [74]
Lung or liver involvement	
Yes	36 [72]
No	14 [28]
De novo stage IV	
Yes	11 [22]
No	39 [78]
Number of metastatic sites	
<3	44 [88]
≥3	6 [12]
Line of palbociclib treatment	
>1st	28 [56]
1st	22 [44]
Previous chemotherapy for advanced disease	
Yes	22 [44]
No	28 [56]
Endocrine combination partner	
AI	39 [78]
Fulvestrant	11 [22]
Palbociclib dose reduction	
Yes	15 [30]
No	11 [22]

ER, estrogen receptor; AI, aromatase inhibitor.

Results

Baseline clinicopathological characteristics

A total of 50 hormone receptor-positive ABC patients were included. Among these patients, 49 (98%) had HER2-negative breast cancer; 1 (2%) had HER2-positive disease and received anti-HER2 therapy concurrently with palbociclib. The median age at palbociclib initiation was 58 years (ranging from 31 to 82 years), and 37 patients (74%) were post-menopausal (*Table 2*). At baseline, 46 patients (92%) presented with ER-positive tumors, 4 patients (8%) were ER-negative, progesterone receptor (PR)-positive and 11 patients (22%) had *de novo* stage IV disease. Lung or liver involvement was seen in 36 patients (72%). Six patients (12%) had metastasis to three or more sites. Before the application of palbociclib, 28 patients (56%) had at least one line of ET for advanced disease, and 22 patients (44%) previously received chemotherapy in the advanced setting. Thirty-nine patients (78%) were administered palbociclib in combination with AI.

ORR and PFS

The median follow-up time was 25.63 months for the total population. Among the 50 patients, the ORR was 36%. Forty-one patients (82%) experienced progression on palbociclib, and the mPFS was 9.57 months (95% CI: 5.80–16.47). Univariate analysis revealed that patients aged ≥65 years were more likely to benefit from palbociclib than those aged <65 years (mPFS: 17.03 *vs.* 8.90 months, HR 0.46, 95% CI: 0.21–1.01, P=0.055; log-rank P=0.049; *Figure 1A*). For those with lung or liver metastasis, the PFS was significantly shorter than that for those without lung or liver metastasis (mPFS: 6.17 *vs.* 17.10 months, HR 2.52, 95% CI: 1.19–5.30, P=0.02; log-rank P=0.01; *Figure 1B*). No statistically significant difference in PFS was noted for endocrine combination partner (AI or fulvestrant), dose reduction of palbociclib or other clinicopathological characteristics (Table S1).

Multivariate analysis for all patients showed that elderly patients (≥65 years) had a longer PFS with palbociclib therapy (HR 0.33, 95% CI: 0.14–0.74, P=0.008). Lung or liver involvement (HR 3.01, 95% CI: 1.41–6.43, P=0.005) and > first line palbociclib therapy for advanced disease (HR 2.13, 95% CI: 1.10–4.14, P=0.03) were unfavorable prognosticators for PFS (*Table 3*).

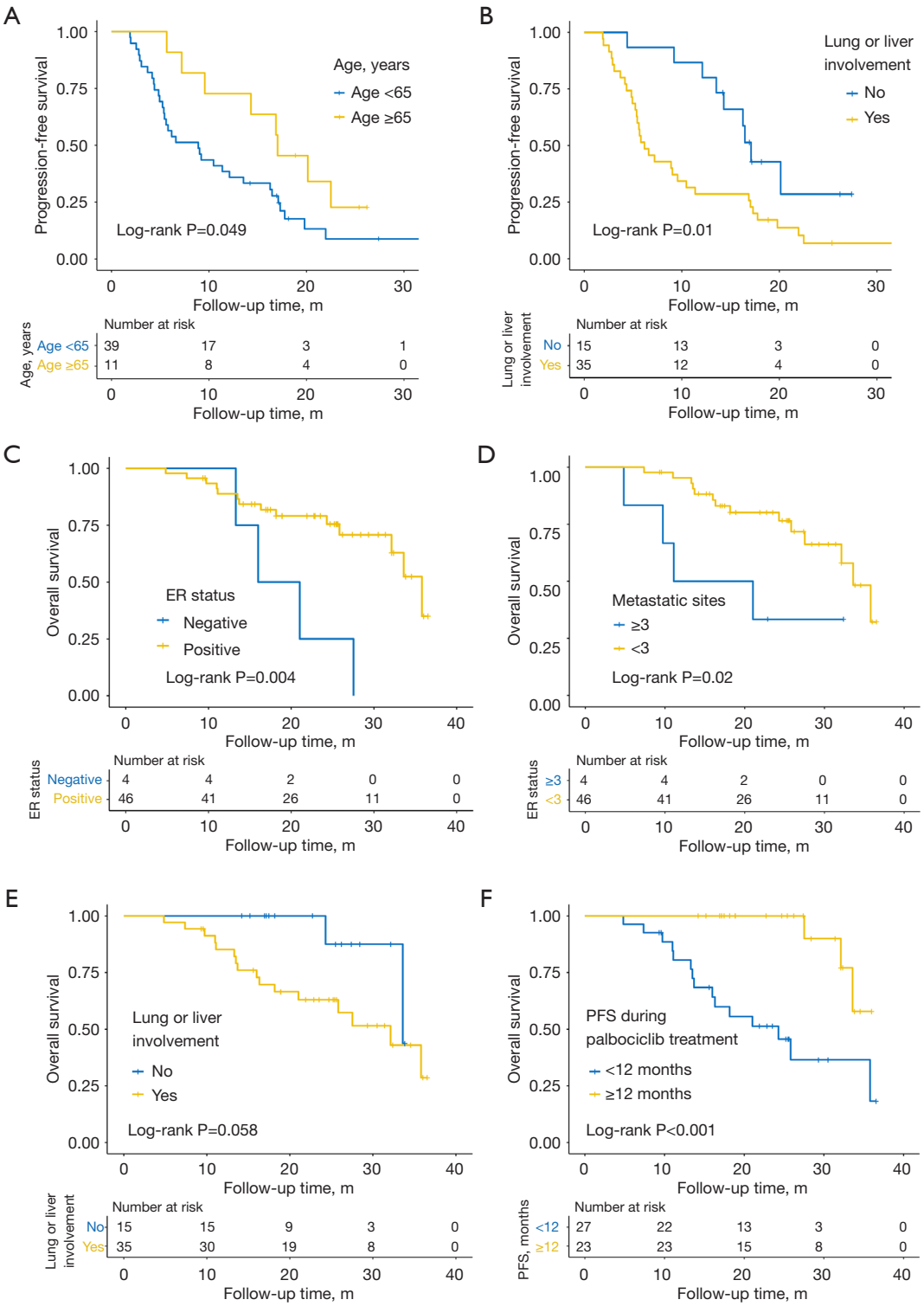

Figure 1 Kaplan-Maier analysis of progression-free survival by (A) age, (B) lung or liver involvement and overall survival by (C) ER status, (D) number of metastatic sites, (E) lung or liver involvement, (F) PFS during palbociclib treatment. ER, estrogen receptor; PFS, progression-free survival; m, month.

Table 3 Multivariate analysis of progression-free survival in 50 patients

Characteristics	HR	95% CI	P value
Age of starting palbociclib (≥65 *vs.* <65 years)	0.33	0.14–0.74	0.008
Lung or liver involvement (yes *vs.* no)	3.01	1.41–6.43	0.005
Line of palbociclib treatment (>1st *vs.* 1st)	2.13	1.10–4.14	0.03
De novo stage IV (yes *vs.* no)	1.12	0.48–2.62	0.79

HR, hazard ratio; CI, confidence interval.

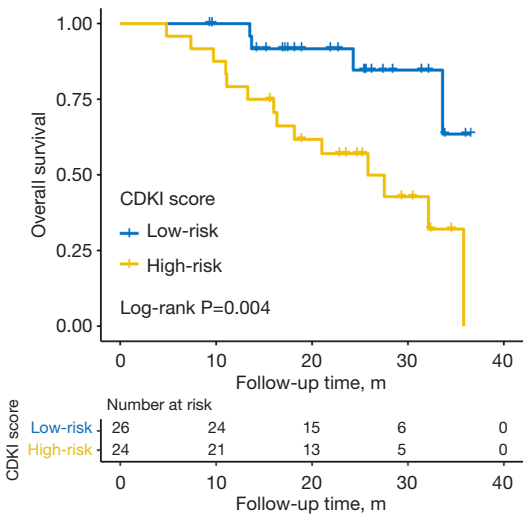

Figure 2 Kaplan-Maier analysis of overall survival in 50 patients by CDKI score (low-risk *vs.* high-risk). CDKI, cyclin-dependent kinases 4/6 inhibitor; m, month.

OS

Eighteen survival events (36%) occurred. The mOS was 33.60 months (95% CI: 25.83–not evaluable). In subgroup analysis, patients with ER-positive disease had a longer OS than ER-negative (PR-positive) counterparts (mOS: 35.80 *vs.* 16.00 months, HR 0.22, 95% CI: 0.07–0.69, P=0.009; log-rank P=0.004; *Figure 1C*). Patients with at least 3 metastatic sites had an inferior OS than those with one or two (mOS: 11.10 *vs.* 33.60 months, HR 3.59, 95% CI: 1.15–11.20, P=0.03; log-rank P=0.02; *Figure 1D*), though the difference in OS did not achieve statistical significance between patients with and without lung or liver metastasis (mOS: 32.13 *vs.* 33.60 months, HR 3.77, 95% CI: 0.86–16.49, P=0.08; log-rank P=0.058; *Figure 1E*). According to response to palbociclib therapy, we found that patients with PFS ≥12 months during palbociclib treatment had a much longer OS than those with PFS <12 months (mOS: not evaluable *vs.* 24.30 months, HR 0.14, 95% CI: 0.04–0.50, P=0.002; log-rank P<0.001; *Figure 1F*). No statistically significant difference was observed in other clinicopathological characteristics (Table S2).

Performance evaluation of the four predictive models

According to the CDKI score, 24 patients (48%) were classified as high-risk, and 26 patients (52%) were classified as low-risk. For all patients, OS was significantly shorter in the high-risk group compared to that in the low-risk group (HR 4.41, 95% CI: 1.45–13.46, P=0.009; log-rank P=0.004; *Figure 2*). The AUCs of the CDKI score-based models (Model 2, 0.768; Model 4, 0.835) were better than those of the clinicopathological models (Model 1, 0.763; Model 3 0.733; *Figure 3A*). Regarding AIC, the CDKI score-based models (Model 2, 108.88; Model 4, 108.50) presented better performance than the clinicopathological models (Model 1, 114.50; Model 3, 114.10). Similarly, in terms of the C-index, the CDKI score-based models (Model 2, 0.72; Model 4, 0.71) showed superior efficiency to the clinicopathological models (Model 1, 0.69; Model 3, 0.65). A nomogram was created for Model 4 (*Figure 3B*). The corresponding calibration curve showed that the observed survival outcomes agreed with the predicted probabilities (*Figure 3C*). In addition, DCA consistently displayed more benefit with the CDKI score-based models than with the clinicopathological models (*Figure 3D*).

Immediate subsequent therapy after palbociclib progression and its effect on prognosis

Among 41 patients who experienced progression on palbociclib, records of subsequent therapy were available for 34. In 14 cases, treatment was switched to chemotherapy. Among the 20 patients (58.82%) continuing with ET, 10 (29.41%) received palbociclib plus another ET agent. In

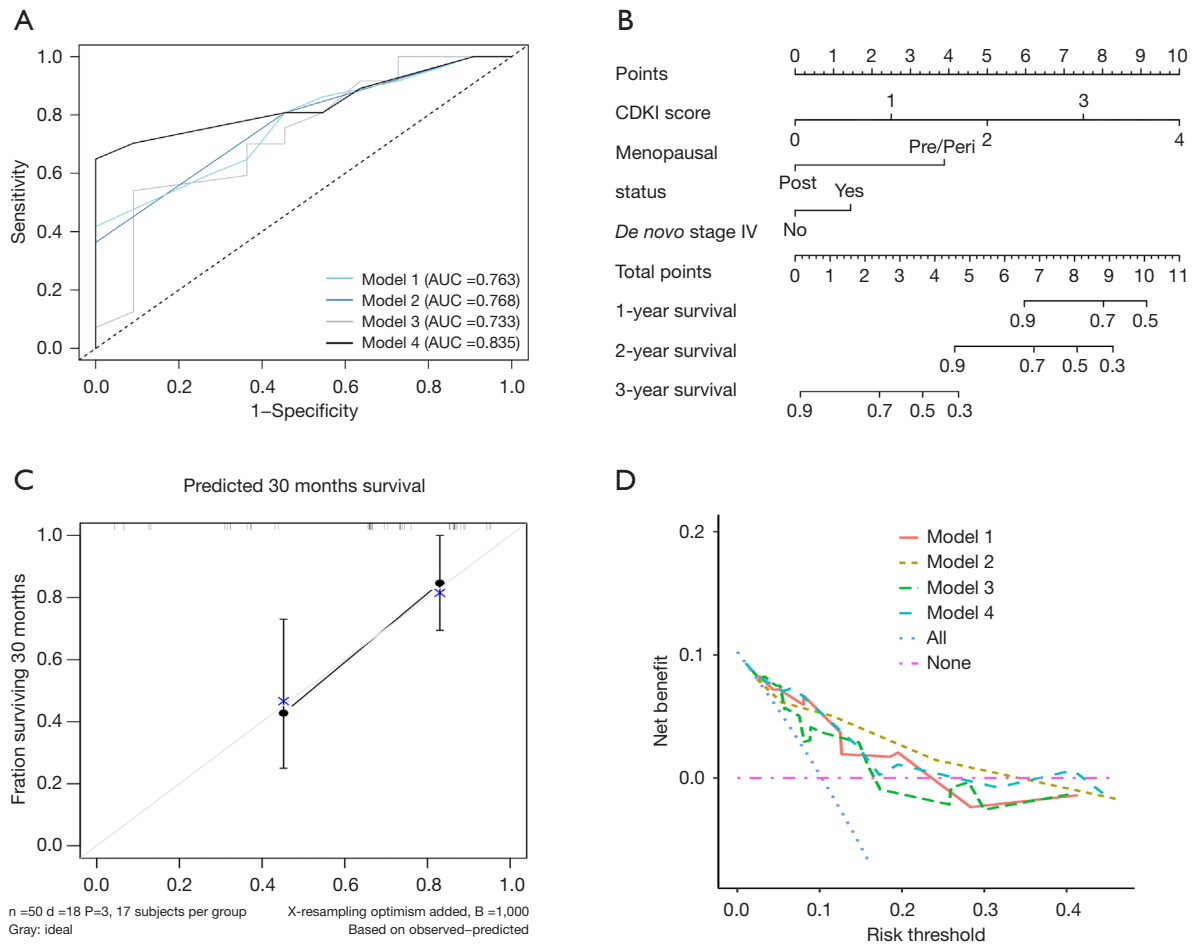

Figure 3 Performance evaluation of the four predictive models. (A) Receiver operating characteristic curves for Model 1 (lung or liver involvement + number of metastatic sites + ER status + line of palbociclib treatment), Model 2 (CDKI score alone), Model 3 (lung or liver involvement + number of metastatic sites + ER status + line of palbociclib treatment + menopausal status + *de novo* stage IV), Model 4 (CDKI score + menopausal status + *de novo* stage IV). The horizonal coordinate was the false positive rate and the vertical coordinate was the true positive rate. (B) Nomogram based on Model 4. (C) Calibration curve of Model 4. (D) DCA of Model 1 (red line), Model 2 (yellow line), Model 3 (green line) and Model 4 (blue line). ER, estrogen receptor; CDKI, cyclin-dependent kinases 4/6 inhibitor; DCA, decision curve analysis; AUC, area under the curve.

6 patients, other targeted treatments were implemented; 5 of these patients received another CDK4/6i, and the other was given chidamide plus another ET agent. Furthermore, 3 patients were treated with another ET agent alone, and one continued with the original regimen plus regional radiotherapy (Table S3). Chemotherapy alone (35.29%) was the most common immediate subsequent treatment after progression on palbociclib. Exploratory analysis revealed that patients with chemo-free regimens had a better survival outcome than those administered chemotherapy in terms of both PFS2 (mPFS2: 4.17 *vs.* 2.50 months, HR 0.32, 95% CI: 0.15–0.72, P=0.006; log-rank P=0.004; *Figure 4A*) and OS (mOS: 33.60 *vs.* 25.83 months, HR 0.32, 95% CI: 0.10–0.99, P=0.049; log-rank P=0.04; *Figure 4B*).

AEs and compliance

According to the available data, hematology tests for 36 patients and biochemistry tests for 35 patients were recorded. The most common AEs were hematologic AEs, including leukopenia (88.89%), neutropenia (88.89%), anemia (69.44%) and thrombocytopenia (33.33%). The

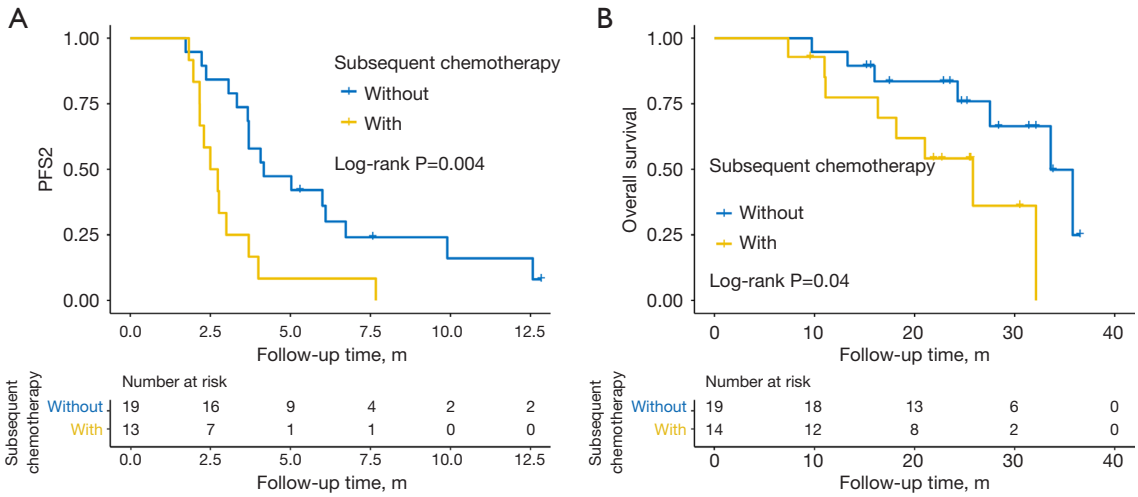

Figure 4 Kaplan-Maier analysis of (A) PFS2 in 32 patients and (B) overall survival in 33 patients by immediate subsequent regimen. PFS2, time to second disease progression; m, month.

most common grade 3 or 4 hematologic AEs included leukopenia (47.22%), neutropenia (47.22%), anemia (8.33%) and thrombocytopenia (8.33%). No grade 3 or 4 hepatic or renal AEs were reported (Table S4). Five thrombotic events occurred, including three cerebral infarction events, one pulmonary embolism event and one deep-vein thromboembolic (VTE) event in a patient with a history of pulmonary embolism before receiving palbociclib.

Among the 26 patients with palbociclib dose records, 25 were given an initial dose of 125 mg; the other received 100 mg. In addition, dose reduction in 15 patients due to AEs and early discontinuation of palbociclib in one patient due to lacuna infarction occurred.

Discussion

Our study corroborates a promising survival benefit and acceptable safety of palbociclib combined with ET for hormone receptor-positive ABC in Chinese patients. Of note, we first established the CDKI scoring system with satisfying performance to identify candidates for palbociclib treatment. Furthermore, we found that an immediate subsequent chemo-free regimen following palbociclib progression might be a reasonable option for a subset of patients.

The patients in our study had an mPFS of 9.57 months during palbociclib treatment, which was nearly identical to corresponding data of 9.5 months in the PALOMA-3 trial (24) and in other Chinese RWSs (19,25). In the case of elderly patients, subgroup analysis in PALOMAs showed that patients aged 65–74 years were likely to derive more benefit from palbociclib combined with fulvestrant than patients aged <65 years (HR 0.27 *vs.* 0.59) (12), consistent with the results in our study. Previous publications revealed that lung or liver metastasis was an independent inferior prognostic factor for PFS in hormone receptor-positive ABC, which supported our findings (26,27). Furthermore, as described in one observational study of 794 hormone receptor-positive metastatic breast cancer patients, the median survival time from the first diagnosis of metastatic disease to death due to cancer was 26.0 months for patients with lung metastasis, 13.0 months for women with liver metastasis, 33.0 months for those with bone metastasis, and 55.0 months for the counterparts with skin metastasis, respectively (28). On the other hand, the mOS was 33.60 months for all patients in our study. This is similar to the mOS of 34.8 months in the updated exploratory study of the PALOMA-3 trial (29), which was not yet reported in other Chinese RWSs (19,25). In subgroup analysis of OS, we first identified ER-positive status and metastatic sites <3 as favorable characteristics for OS. In addition, responders to palbociclib treatment, who had a longer PFS of at least 12 months, demonstrated the improvement in OS in our study.

In our study, we first created the CDKI scoring system to predict prognosis of palbociclib treatment for patients with hormone receptor-positive ABC. To date, few studies have focused on this topic. Kripa and colleagues found in 30

ER+/HER2– breast cancer patients treated with CDK4/6 inhibitors that sarcopenia and obesity evaluated through computed tomography could predict negative outcome (30); Emile and coworkers also identified low baseline lymphopenia as a single prognostic factor to predict poor outcome (31). Besides, the efficiency of nomogram using clinicopathological features was established in predicting the prognosis of hormone receptor-positive breast cancer patients with liver metastasis(32). So we integrated several clinicopathological variables as an innovative instrument and achieved a satisfying performance. Similar to our study, Kim and colleagues combined adjuvant ET, liver metastasis, initial CA-15-3, weak ER expression and BRCA2 mutation together, but different from our study, they applied the model to predict primary resistance to palbociclib with letrozole treatment for metastatic breast cancer rather than to predict OS, with no comparisons of the created model with other models (33). In our study, we compared the CDKI score-based models with other clinicopathological models multidimensionally, and proved that the CDKI score is practical and promising, with encouraging performance.

Standard systemic therapy after progression on palbociclib is not well established in current guidelines. Although multiple novel therapies according to the mutation of ESR1, PIK3CA and BRCA1/2 were recommended by increasing clinical trials (34), the availability and financial burden limited the application. Therefore, in the real-world setting, sequential regimens implemented were multiple. Our study categorized immediate subsequent treatment into chemo-free and chemotherapy-based regimens. We are the first to report a subset of patients among Chinese patients who could still derive benefit in both PFS2 and OS from a number of chemo-free regimens compared with chemotherapy-based regimens. In the US, a cohort of 87 patients presented an mPFS of 5.3 months with sequential abemaciclib after progression on palbociclib (35). Similarly, another RWS in the US reported that the continuation of CDK4/6i was associated with improvements in PFS (P<0.0001) and OS (P<0.0001) compared to chemotherapy after first-line CDK4/6i therapy (36). Furthermore, a multicenter observational study revealed that patients may continue to benefit from subsequent ET after progression on palbociclib (37). Therefore, sequential chemo-free therapy might be a rational strategy for those who experience progression on palbociclib. On the other hand, biomarkers might offer implications to physicians. PADA-1, a randomized, phase 3 trial, revealed that alteration of AI to fulvestrant may result in a longer PFS relative to no switch in ABC with newly emerging or increased ESR1 mutation during palbociclib and AI treatment (38). In the future, liquid biopsy and genetic testing might aid in guiding optimal regimens for selected patients after CDK4/6i progression.

The incidence of neutropenia was 88.89% in our study, which was lower than that in Asians in PALOMAs (95.4% in PALOMA-2 and 92% in PALOMA-3) (39,40). The percentage of grade 3–4 neutropenia (47.22%) in our study was much lower than that in PALOMAs (89.2% in PALOMA-2 and 92% in PALOMA-3) (39,40). Consistent with our study, two other Chinese RWSs also showed a lower rate (30.0% and 45.3%) (18,19), which indicates palbociclib plus ET is a relatively safe regimen in Chinese patients. In addition, thrombotic events occurred in 10% (5/50) of patients in our study. An increasing hazard of thrombotic events was observed in other RWSs (40,41). Watson *et al.* found that thrombotic events occurred in 11% of patients receiving palbociclib (42), and Gervaso *et al.* reported 6.3% of 424 patients (91.8% of whom used CDK4/6i) experiencing venous embolism caused by CDK4/6i in the first year of treatment (43). These findings suggest that great importance should be attached to the assessment of thrombosis risk before application of palbociclib as well as the prophylaxis and management of thrombotic events during palbociclib treatment in clinical practice (44,45).

The limitations of this analysis should be considered. First, this was an ambispective study. However, our study constituted an exploratory analysis based on a prospective follow-up database. A prospective study is currently being carried out, and validation is awaited. Second, the sample size was relatively small. Of note, the CDKI score was validated multidimensionally with consistent results, which suggests that the findings are enlightening. Last, only patients treated with palbociclib were included in our study, while those on other CDK4/6i regimens were absent due to the lag time for approval in China. Nevertheless, the predictive model for other CDK4/6i warrants additional verification and exploration.

Conclusions

In conclusion, our study supports palbociclib plus ET as an efficient regimen with satisfying tolerance for Chinese patients with hormone receptor-positive ABC. The CDKI scoring system may serve as a novel comprehensive tool for predicting prognosis. Continued efforts should be devoted

to prospective studies with larger sample sizes to validate the performance of the CDKI score and optimize strategies for patients with progression on palbociclib.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-362/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-362/dss

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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 approved by the Independent Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University (approval No. KY2022-097-B) and individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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