The CDK4/6 inhibitor in HR-positive advanced breast cancer

A systematic review and meta-analysis

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Abstract

Background: Recently, several high-quality clinical randomized controlled trials (RCTs) have identified that cyclin-dependent kinases (CDKs) 4/6 inhibitors obtained a great safety and efficacy, which can be consequently applied as a combination therapy with letrozole or fulvestrant for women who had advanced breast cancer and progressed while receiving endocrine therapy. In this systemic review, we performed a meta-analysis to explore whether CDK4/6 inhibitors had a significantly benefit to treating hormone receptor-positive (HR-positive)/human epidermal growth factor receptor 2 negative (HER2-negative) advanced breast cancer.

Methods: The data for meta-analysis were collected from MEDLINE, EMBASE, and Cochrane Library from January 1980 to December 2017, and eventually 3182 patients from 6 RCTs were included.

Results: The result showed the CDK4/6 inhibitor group had a longer progression-free survival (PFS) (hazard ratio=0.51; 95% confidence interval [CI], 0.46–0.57, $P < .00001$), a better objective response (risk rate=1.53; 95% CI, 1.35–1.74, $P < .00001$), as well as a better clinical benefit response (risk rate=1.29; 95% CI, 1.13–1.47, $P = .0001$). Besides, subgroup analyses of PFS according to stratification factors and other baseline characteristics confirmed a great performance of CDK4/6 inhibitors across the all subgroups. And sensitive analysis showed that all outcomes were stable except Finn 2014 trial.

Conclusion: CDK4/6 inhibitors can significantly prolong the PFS and improve the objective response and clinical benefit response among the patients with HR-positive/ HER2-negative advanced breast cancer.

Abbreviations: ALT = alanine transaminase, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, ER = estrogen receptor, FDA = Food and Drug Administration, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, HR-positive = hormone receptor positive, PFS = progression-free survival, PR = progesterone receptor, pRb = retinoblastoma protein, Rb = retinoblastoma, RCT = randomized controlled trial, RECIST = Evaluation Criteria in Solid Tumors, RR = risk rate, TNBC = triple-negative breast cancer; CDK4/6 = cyclin-dependent kinases 4/6.

Keywords: advanced breast cancer, CDK4/6 inhibitor, HR-positive, meta-analysis

1. Introduction

Breast cancer is a molecularly diverse disease, which can be mainly divided into 3 molecular subtypes. The first subtype is hormone receptor positive (HR-positive) breast cancer, whose tumors tend to be estrogen receptor positive (ER-positive) or progesterone receptor positive (PR-positive), or both, with a

normal expression of human epidermal growth factor receptor 2 (HER2-negative). The second subtype is HER2+ breast cancer, which is defined by HER2 gene amplification or overexpression. Interestingly, approximately 45% of this subtype breast cancer has variable expression levels of ER or PR, or both. And the third subtype is triple-negative breast cancer (TNBC), defined by the deficiency of ER, PR, and HER2.^[1] Furthermore, approximately 80% of breast cancer patients express hormone receptors (HRs). Endocrine therapy, also known as hormone therapy, is the standard treatment for these HR-positive breast cancer subtypes, significantly reducing the relapse rate after receiving treatment in an early stage.^[2] However, most patients have different resistance reactions to current endocrine therapy, which requires the development of alternative endocrine therapies.^[3–6]

Deregulation of cell cycle is one of the cancer hallmarks. In this regard, several genetic mutations in key proteins of cell cycle regulatory have been described to be responsible for breast cancer.^[7,8] The cyclin-dependent kinases (CDKs), a large family of serine threonine kinases, play an important role in regulating cell cycle progression. CDK4 and CDK6, activated by cyclin D, facilitate the hyperphosphorylation of retinoblastoma protein (pRb), which can lead to the cell cycle transition from G1 phase to S phase. Importantly, this critical Rb checkpoint has been demonstrated to be associated with endocrine resistance in breast cancer. At this point, the inhibition of this pathway including cyclin D, CDK4/6, and pRb can be considered as an effective

Editor: Jianxun Ding.

WD, ZL, and CW equally contributed to this work.

Data Availability: All data generated or analyzed during this project are presented in this article (and its Supplementary Information files).

The authors have no funding and conflicts of interest to disclose.

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Medicine (2018) 97:20(e10746)

Received: 30 January 2018 / Accepted: 24 April 2018

<http://dx.doi.org/10.1097/MD.00000000000010746>

treatment for HR-positive advanced breast cancer, not only as a first-line therapy,^[9–11] but also for patients with disease progress after receiving endocrine therapy.^[12,13]

Recently, a large number of CDK4/6 inhibitors, especially palbociclib, ribociclib, and abemaciclib, have been tested in clinical trials. In all, 165 postmenopausal women with HR-positive/HER2-negative advanced breast cancer were randomly selected in a phase-II trial (PALOMA-1) to receive letrozole with or without palbociclib. Median progression-free survival (PFS) with combination therapy was 20.2 months, whereas in the control group (letrozole only) was 10.2 months (hazard ratio [HR]=0.49; 95% confidence interval [CI], 0.319–0.748; $P = .0004$).^[9] Similar result was found in other 2 phase-III trials,^[10,13] supporting the conclusion that the combination therapy would contribute to a longer survival. Based on this research finding, the U.S. Food and Drug Administration (FDA) eventually approved palbociclib and letrozole as the treatment for postmenopausal patients with HR-positive/HER2-negative advanced breast cancer in 2015.

Besides palbociclib, ribociclib and abemaciclib have also been considered as the target inhibitors of CDK4/6 in several clinical trials.^[11,14,15] Here, we performed a meta-analysis to assess the safety and efficacy of these CDK4/6 inhibitors for treating HR-positive/HER2-negative advanced breast cancer.

2. Methods

2.1. Study protocol

At the beginning of this project, a research protocol was drafted following the Cochrane Collaboration format. The ethics committee of Shaoxing Second Hospital approved the study.

2.2. Eligibility criteria

Eligibility criteria were designed as follows: research type—randomized controlled trial (RCT); language restriction—English only; participants—patients with HR-positive/HER2-negative advanced breast cancer; intervention—CDK4/6 inhibitors; outcomes—progression-free survival, response, and adverse events.

On the contrary, eligibility criteria did not include the conditions as follows: control—positive control; withdraw rate > 20%.

2.3. Search strategy and information sources

MEDLINE, EMBASE, and *Cochrane Library* were used for information search by 2 independent authors (WD and ZL). They collected all available researches published up to December 2017. The search strategy for the MEDLINE was mainly the combination of variable keywords: “cyclin dependent kinase 4 and 6 inhibitors” or “palbociclib” or “abemaciclib” or “ribociclib” AND “breast cancer.” A limited number of clinical trials were found from MEDLINE, which then would be double-checked by the correlation between titles and abstracts. The search strategy for EMBASE and *Cochrane Library* was similar to the one for MEDLINE. Besides the electronic databases, articles from RCT reference lists and systematic reviews were checked after a manually screening, to ensure that all the relevant researches had been included in this systematic review. As for unpublished or ongoing trials, we searched the website of ClinicalTrials.gov and contacted authors for the relevant data.

2.4. Study selection and data collection

All records from this systematic review in electronic databases, reference lists of RCTs, and systematic reviews were independently evaluated by 2 authors (WD and ZL), in accordance with the eligibility criteria as mentioned above. After strict selection and evaluation, the data were extracted from these RCT records with the basic information, including clinical trials, criteria, study design, patient demographic characteristics, and outcome assessments.

After data collection, we performed a meta-analysis and obtained 2 outcomes. The primary outcome was PFS. And the secondary outcome included objective response (complete response or partial response) and clinical benefit response (complete response + partial response + stable disease for ≥ 24 weeks).

2.5. Risk of bias and quality assessment

In this review, WD and CW independently assessed the risk of bias in individual studies using Review Manager 5.3 software. For evaluating the risk of bias of RCTs, we applied uniform criteria recommended by the Cochrane Collaboration, which included 6 items: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential bias as previously used in our meta-analysis.

2.6. Summary measures and synthesis of results

Review Manager 5.3 from the Cochrane Collaboration was used to assess the risk of bias in individual studies. After that subgroup analyses were performed to detect the influence of stratification factors and other baseline characteristics. Sensitivity analysis was used to detect the stability of the consolidated results except the only phase-II clinical trial. Statistical heterogeneity was estimated by the I^2 statistic as follows: $I^2 < 30\%$ means “low heterogeneity”; I^2 between 30% and 50% denotes “moderate heterogeneity”; $I^2 > 50\%$ represents “substantial heterogeneity.” Dichotomous outcomes were analyzed as HR (95% CI) by using the Mantel–Haenszel test. A fixed-effects model was used if the heterogeneity was low or moderate. Otherwise, the random-effect model was reported after exploring the cause of heterogeneity. All tests mentioned were 2-tailed and a P value of $< .05$ was considered to be statistically significant for all analyses.

3. Results

According to the search strategy established by us, 1182 records were retrieved totally from MEDLINE, EMBASE, and *Cochrane Library*. After removing the duplicates and irrelevant records, 17 full-text articles were eligible for the meta-analysis. Furthermore, 11 records were excluded due to the following reasons: 8 conference abstracts, 2 meta-analyses, and 1 note. Ultimately, 6 RCT records containing 3182 patients were included in qualitative synthesis (Fig. 1). The main characteristics of these included studies are listed in Table 1.

3.1. Primary outcome analysis

All 6 RCTs enrolling 3182 patients were available for the analysis of PFS at the end of the observation period. The fixed-effects model was used because there were no heterogeneities ($I^2 = 0\%$, $P = 0.64$) between these data. The pooled data showed that the

Figure 1. The flowchart of data search, collection and selection. Ultimately, 5 RCTs containing 3182 patients were selected to undergo meta-analysis.

CDK4/6 inhibitor group had a longer PFS than the control group (HR=0.52; 95% CI, 0.46–0.57, $P < .00001$; Fig. 2).

3.2. Secondary outcome analysis

For the analysis of overall response among 3182 patients enrolled from 6 RCTs, 2422 patients can be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.^[16]

3.3. Objective response

Because the heterogeneity of these data was apparent ($I^2 = 58\%$, $P = .03$), the random-effects model was used. All the patients who were treated with CDK4/6 inhibitors (palbociclib, ribociclib, or abemaciclib) had a trend to get an increasing probability of objective response (complete response or partial response), compared with the nontreated patients (risk rate [RR]=1.51; 95% CI, 1.26–1.82, $P < .00001$; Fig. 3). For another subgroup whose patient disease could be evaluated according to the RECIST version 1.1, there were also apparent heterogeneities ($I^2 = 65\%$, $P = .01$). And the CDK4/6 inhibitor group had a higher rate of objective response compared with the control group (RR=1.53; 95% CI, 1.27–1.85, $P < .00001$; Fig. 3). Thus, the results showed that CDK4/6 inhibitors could significantly increase the rate of objective response.

3.4. Clinical benefit response

Because the data heterogeneity of clinical benefit response (complete response + partial response + stable disease for ≥ 24 weeks) was apparent ($I^2 = 78\%$, $P = .0003$), the random-effects model was used. And the results of meta-analysis showed that the CDK4/6 inhibitor group had a higher rate of clinical benefit response compared with the control group (RR=1.25; 95% CI, 1.12–1.39, $P < .0001$; Fig. 4). Moreover, in patients with measurable disease, the data of clinical benefit response also presented an apparent heterogeneity ($I^2 = 63\%$, $P = .002$). And the CDK4/6 inhibitor group had a higher rate of clinical benefit response compared with the control group (RR=1.20; 95% CI, 1.10–1.31, $P < .0001$; Fig. 4). Thus, the results showed that

Table 1
Characteristics of included studies and outcome events.

Trials	Finn 2014 ^[9]	Finn 2016 ^[10]	Hortobagyi 2016 ^[11]	Cristofanilli 2016 ^[13]	Sledge 2017 ^[14]	Goetz 2017 ^[15]
Information of the included trials						
Regions	50 sites in 12 countries	186 sites in 17 countries	223 sites in 29 countries	144 sites in 17 countries	142 sites in 19 countries	158 sites in 22 countries
Phases	II	III	III	III	III	III
Accrual dates	December 22, 2009, and May 12, 2012	February 2013 and July 2014	January 24, 2014, and March 24, 2015	October 7, 2013, and August 26, 2014	August 7, 2014, and December 29, 2015	November 18, 2014, and November 11, 2015
Inclusion criteria and study design						
Inclusion criteria	Postmenopausal; HR+, HER2– ABC; first-line	Postmenopausal; HR+, HER2– ABC; first-line	Postmenopausal; HR+, HER2– ABC; first-line	Any menopausal status; HR+, HER2– ABC; second-line	Any menopausal status; HR+, HER2– ABC; second-line	Postmenopausal; HR+, HER2– ABC; first-line
Study design	Palbociclib (125 mg daily for 21 d every 28 d) + letrozole (2.5 mg daily) vs placebo + letrozole (2.5 mg daily)	Palbociclib (125 mg daily for 21 d every 28 d) + letrozole (2.5 mg daily) vs placebo + letrozole (2.5 mg daily)	Ribociclib (600 mg daily for 21 d every 28 d) + letrozole (2.5 mg daily) vs placebo + letrozole (2.5 mg daily)	Palbociclib (125 mg daily for 21 d every 28 d) + fulvestrant (500 mg every 28 d) vs placebo + fulvestrant (500 mg every 28 d)	Abemaciclib (150 mg twice daily every 28 d) + fulvestrant (500 mg every 28 d) vs placebo + fulvestrant (500 mg every 28 d)	Abemaciclib (150 mg twice daily every 28 d) + anastrozole (1 mg daily) or letrozole (2.5 mg daily) vs placebo + anastrozole (1 mg daily) or letrozole (2.5 mg daily)
Patient demographic characteristic						
Age, y	T: 63 (54–71) C: 64 (56–70)	T: 62 (30–89) C: 61 (28–88)	T: 62 (23–91) C: 63 (29–88)	T: 57 (30–88) C: 56 (29–80)	T: 59 (32–91) C: 63 (29–88)	T: 63 (38–87) C: 63 (32–88)
No. of patients	T: 84 C: 81	T: 444 C: 222	T: 334 C: 334	T: 347 C: 174	T: 446 C: 223	T: 328 C: 165
Outcomes assessment						
Primary end point	Progression-free survival	Progression-free survival	Progression-free survival	Progression-free survival	Progression-free survival	Progression-free survival
Secondary end point	Objective response, the clinical benefit response	Objective response, the clinical benefit response	Objective response, the clinical benefit response	Objective response, the clinical benefit response	Objective response rate, the clinical benefit response	Objective response rate, the clinical benefit response

ABC = advanced breast cancer, C = control group, HER2– = human epidermal growth factor receptor 2 negative, HR+ = hormone receptor positive, T = treatment group (also known as CDK4/6 inhibitor group).

Figure 2. Forest plot of comparison: progression-free survival.

CDK4/6 inhibitors could significantly increase the rate of clinical benefit response.

3.5. Subgroup analysis and sensitive analysis

Subgroup analyses of PFS, according to stratification factors and other baseline characteristics, confirmed a consistent conclusion across all subgroups that CDK4/6 inhibitors could decrease the incidence of disease progression or death (Table 2). For patients with age <65 years, the CDK4/6 inhibitor group had a significant decrease in the incidence of disease progression or death ($HR = 0.50$; 95% CI, 0.44–0.57); similar result was observed in patients with age ≥ 65 years ($HR = 0.56$; 95% CI, 0.47–0.67). For patients with visceral disease, the CDK4/6 inhibitor group had a significant decrease in the incidence of disease progression or death ($HR = 0.57$; 95% CI, 0.47–0.62); patients with nonvisceral disease had a similar result ($HR = 0.50$; 95% CI, 0.42–0.59). For patients with bone-only disease at baseline, the CDK4/6 inhibitor group had a significant decrease in the incidence of disease progression or death ($HR = 0.47$; 95% CI, 0.34–0.65); patients with other sites of metastasis had a similar result ($HR = 0.56$;

95% CI, 0.47–0.66). For race, not only Asian but also non-Asian patients had a significant decrease in the incidence of disease progression or death with the treatment of CDK4/6 inhibitors ($HR = 0.46$; 95% CI, 0.36–0.59 vs $HR = 0.56$; 95% CI, 0.49–0.64). In addition, with respect to disease-free interval, the risk of disease progression or death in the CDK4/6 inhibitor group was also lower than that in the control group, where all the patients had a disease-free interval of 12 months or less ($HR = 0.51$; 95% CI, 0.38–0.68) or had a disease-free interval of >12 months ($HR = 0.48$; 95% CI, 0.37–0.61). In the subgroup of patients with newly metastatic disease, patients in the CDK4/6 inhibitor group also had a significantly lower risk of disease progression or death than those in the control group ($HR = 0.58$; 95% CI, 0.43–0.79). Besides, for patients who had received prior hormonal therapy, the incidence of disease progression or death was significantly decreased in the CDK4/6 inhibitor group ($HR = 0.48$; 95% CI, 0.40–0.56); similar result was shown in the patients who had not received prior hormonal therapy ($HR = 0.56$; 95% CI, 0.48–0.66). Therefore, receiving previous chemotherapy did not reduce the therapeutic effect of CDK4/6 inhibitors for advanced breast cancer patients ($HR = 0.51$; 95%

Figure 3. Forest plot of comparison: objective response.

Figure 4. Forest plot of comparison: clinical benefit response.

CI, 0.43–0.61 vs HR=0.51; 95% CI, 0.41–0.62). Furthermore, Eastern Cooperative Oncology Group (ECOG) performance status also did not weaken the therapeutic effect of CDK4/6 inhibitors, which was verified by the data that the risk of disease progression or death was lower in the CDK4/6 inhibitor group than that in the control group, among patients who had ECOG performance status of 0 (HR=0.55; 95% CI, 0.45–0.65) and among those who had ECOG performance status of 1 or 2 (HR=0.55; 95% CI, 0.46–0.67). The status of PR would not weaken the curative effect of CDK4/6 inhibitors. The CDK4/6 inhibitors could reduce the risk of disease progression or death in patients with PR-positive (HR=0.55; 95% CI, 0.45–0.67), and the similar result was presented in the patients with PR-negative (HR=0.48; 95% CI, 0.36–0.64). In addition, different kind of CDK4/6 inhibitors (palbociclib or ribociclib or abemacicli) had a similar effect which could decrease the incidence of disease progression or death (HR=0.51; 95% CI, 0.43–0.60 vs HR=0.56; 95% CI, 0.43–0.72 vs HR=0.49; 95% CI=0.41–0.59). And no matter whether the patients received previous systemic therapy for advanced disease or not, CDK4/6 inhibitors could decrease the incidence of disease progression or death (first-line therapy vs second-line therapy: HR=0.56; 95% CI, 0.48–0.65 vs HR=0.46; 95% CI, 0.39–0.55). Sensitive analysis showed that all outcomes were stable except Finn 2014^[9] (Table 2).

3.6. Adverse events

As for neutropenia, all grades of it were substantially more frequent in the CDK4/6 inhibitor group (65%), compared with the control group (5%). Interestingly, grade 3 or 4 neutropenia was found among 43% of patients in the CDK4/6 inhibitor group and among 1% of patients in the control group.

Meanwhile, leucopenia with all grades also appeared much more common in the CDK4/6 inhibitor group than in the control group (35% and 3% respectively), especially grade 3 or 4 leucopenia. Furthermore, infection, fatigue, nausea, anemia,

thrombocytopenia, alopecia, nausea, rash, constipation, vomiting, and stomatitis were also more common in the CDK4/6 inhibitor group. Serious adverse events from any cause were occurred among 308 (19%) persons of 1974 patients in the CDK4/6 inhibitor group, and among 121 people (12%) of 1185 patients in the control group (Table 3).

3.7. Risk of bias in included RCT studies

Full details about the risk of bias of RCT studies are shown in Figure 5. For allocation concealment, the risk of bias was unclear in 3 RCTs with an allocation scheme which was not mentioned in the trials. For random sequence generation, the risk of bias was unclear in 2 RCT studies. For the performance bias and detection bias, the risk was high in one study and unclear in another one. Except these 3 outliers, no high or unclear risk of bias was observed in any other studies.

4. Discussion

As we mentioned above, HR-positive breast cancer is the most common subtype of breast cancer, with the fact that approximately 80% of breast cancer patients express HRs. And endocrine therapy is a preferred approach for patients with advanced or metastatic disease due to its treatment effectiveness and preferable toxicity profile. To date, improvements have been made in clinical outcomes with both new endocrine agents and new endocrine combinations. Recently, several clinical trial data have suggested that the orally highly selective inhibitors of CDK4/6, such as palbociclib, ribociclib, and abemaciclib, would significantly improve the clinical outcomes when combined with letrozole or fulvestrant.

Based on the data from 6 published RCTs, the current meta-analysis we performed achieved higher testing efficiency, and the results showed that the CDK4/6 inhibitors were associated with significant improvement in objective response, clinical benefit,

Table 2
Subgroup sensitivity and analysis for progression-free survival.

	HR (95% CI)	P	P, %
1. Subgroup analysis			
Age			
<65 y	0.50 (0.44–0.57)	<.00001	11
≥65 y	0.56 (0.47–0.67)	<.00001	0
Visceral metastasis			
Yes	0.57 (0.47–0.62)	<.00001	0
No	0.50 (0.42–0.59)	<.00001	23
Bone-only metastasis			
Yes	0.47 (0.34–0.65)	<.0001	17
No	0.56 (0.47–0.66)	<.00001	35
Race			
Asian	0.46 (0.36–0.59)	<.00001	0
Non-Asian	0.56 (0.49–0.64)	<.00001	24
Disease-free interval			
<12 mo	0.51 (0.38–0.68)	<.00001	20
≥12 mo	0.48 (0.37–0.61)	<.00001	0
Newly metastatic disease			
Yes	0.58 (0.43–0.79)	.0005	33
No	0.55 (0.45–0.67)	<.00001	0
Previous hormonal therapy			
Yes	0.48 (0.40–0.56)	<.00001	0
No	0.56 (0.48,0.66)	<.00001	0
Previous chemotherapy			
Yes	0.51 (0.43–0.61)	<.00001	0
No	0.51 (0.41–0.62)	<.00001	47
ECOG performance status			
0	0.55 (0.45–0.65)	<.00001	0
1 or 2	0.55 (0.46,0.67)	<.00001	0
Hormone-receptor status			
ER and PR-positive	0.55 (0.45–0.67)	<.0001	0%
Other	0.48 (0.36–0.64)	<.00001	0%
Palbociclib vs ribociclib vs abemaciclib			
Palbociclib	0.51 (0.43–0.60)	<.00001	37
Ribociclib	0.56 (0.43–0.72)	<.00001	—
Abemaciclib	0.49 (0.41,0.59)	<.00001	0
First-line vs second-line			
First-line	0.56 (0.48–0.65)	<.00001	0
Second-line	0.46 (0.39–0.55)	<.00001	—
2. Sensitivity analysis			
Excluding Finn 2014 trial	0.51 (0.46–0.58)	<.00001	3

CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, ER = estrogen receptor, HR = hazard ratio, PR = progesterone receptor.

and PFS in patients with HR-positive advanced breast cancer. Furthermore, these results were not influenced by age, race, performance status, disease site, prior chemotherapy, prior endocrine therapy, disease-free interval after adjuvant treatment, the kind of CDK4/6 inhibitors, or biomarkers that affect sensitivity to endocrine therapy, such as the expression level of estrogen and progesterone receptors (Table 2).

In the patients who received the combination treatment with CDK4/6 inhibitors, a higher incidence of hematologic adverse events would occur. The most common hematologic adverse events with grade 3 or 4 were neutropenia (43% vs 1%), leucopenia (20% vs 0.4%), anemia (5% vs 1%), and thrombocytopenia (2% vs 0.1%). Although the incidence of neutropenia with any grade in the CDK4/6 inhibitor group was 65% in the current meta-analysis, it did not go along with the significantly increasing rate of febrile neutropenia; the incidence of febrile neutropenia was 1.3%. In contrast to other CDK4/6 inhibitors, the most common adverse event of abemaciclib was low-grade diarrhea, which was readily managed in most

instances with conventional antidiarrheal medications and dose adjustments.^[15]

Given the increasing risk of toxicity, how to identify the patients who might preferentially benefit from CDK4/6 inhibitors is important. Many predictive biomarkers have been evaluated for this purpose, such as the changed levels of protein RB, cyclin D1 amplification, or p16 loss.^[17] Recently, a number of researches have focused on the loss of Rb function, the over expression/amplification of cyclin E, and CDK6 amplification, trying to figure out the possible resistance mechanisms.^[18–20] But most of these results remained speculative and have not been validated in clinical specimens. Therefore, these putative biomarkers, however, have not yet been demonstrated to be clinically useful because of the lack of their sufficiently predictive ability or reproducibility.

However, the main reason for permanent treatment discontinuation in both subgroups of meta-analysis was disease progression.^[9,10] The rate of discontinuation due to adverse events was lower than other therapies applied for this population. The majority of adverse events with grade 1 or 2 and grade 3 or 4 were reversible and controlled by dose interruptions and reductions, which allowed most patients to go on with the treatment with light adverse events.

Palbociclib is an orally available pyridopyrimidine compound, which can inhibit CDK4 and CDK6. Previous researches have demonstrated that palbociclib have the ability to inhibit pRb phosphorylation as well and cause growth inhibition of tumors, in particular for the ER-positive subtype of breast cancer.^[18] PALOMA-1^[9] and PALOMA-2^[10] trials were designed to assess the safety and efficacy of the combination of palbociclib and letrozole as a first-line therapy for postmenopausal women with HR-positive/HER2-negative advanced breast cancer. The result showed that the patients in the palbociclib–letrozole group (i.e., CDK4/6 inhibitor group) had a longer median PFS (>10 months) than those in the letrozole group (i.e., control group). And PALOMA-3^[13] studied the combination of palbociclib and fulvestrant as a second-line treatment for premenopausal and postmenopausal patients with HR-positive/HER2-negative metastatic breast cancer and progression after prior endocrine therapy. Adding palbociclib to endocrine therapy with fulvestrant clinically led to a significant improvement in median PFS from 3.8 months (95% CI, 3.5–5.5) to 9.2 months (95% CI, 7.5 to not estimable). The difference in PFS rates between PALOMA-2 and PALOMA-3 might be caused of the fact that different studies recruited different patient populations (endocrine-sensitive disease vs endocrine-resistant disease, first-line therapy vs second-line therapy). Besides, the PARSIFAL phase-II trial compared the efficacy of palbociclib–fulvestrant to palbociclib–letrozole as a first-line treatment.^[21] The trial enrolled patients with HR-positive/HER2-negative advanced breast cancer, and the primary endpoint was 1-year PFS. To date, this trial, started from August 2015, has still been in progress and planned to end in July 2017. Subgroup analyses revealed that the PFS was similar in both pre/perimenopausal and postmenopausal patients. And the overall global quality of life scores of palbociclib-treated patients was significantly higher than that in the control group (66.1, 95% CI, 64.5–67.7 vs 63.0, 95% CI, 60.6–65.3; $P = .0313$).^[22]

In addition to palbociclib, 2 other highly selective inhibitors of CDK4/6, ribociclib and abemaciclib, have currently been in early clinical development. Ribociclib, a oral molecule CDK4/6 inhibitor molecule, has been tested as a first-line therapy in the MONALEESA-2^[11] trial and an initial therapy with letrozole in

Table 3**Adverse events from any cause that occurred in at least 10% of the patients in either study group.**

Adverse event	CDK4/6 inhibitor group		Control group	
	All grades % (n)	Grade 3 or 4% (n)	All grades % (n)	Grade 3 or 4% (n)
Any adverse event	91 (1793)	73 (1450)	61 (724)	35 (419)
Neutropenia	65 (1280)	43 (847)	5 (54)	1 (14)
Leucopenia	35 (683)	20 (355)	3 (37)	0 (5)
Fatigue	39 (766)	2 (46)	29 (349)	1 (8)
Anaemia	26 (515)	5 (94)	7 (78)	1 (16)
Alopecia	25 (489)	0 (0)	10 (120)	0 (0)
Thrombocytopenia	14 (225)	2 (32)	18 (182)	0 (1)
Vomiting	22 (444)	1 (23)	14 (158)	1 (15)
Nausea	40 (786)	1 (26)	25 (293)	1 (12)
Diarrhoea	49 (971)	5 (103)	24 (280)	1 (10)
Constipation	18 (357)	1 (11)	15 (181)	0 (2)
Arthralgia	22 (358)	1 (9)	24 (241)	1 (7)
Hot flush	17 (279)	0 (1)	20 (206)	0 (1)
Back pain	16 (267)	1 (21)	17 (175)	1 (7)
Cough	18 (296)	0 (0)	15 (156)	0 (0)
Decreased appetite	20 (390)	1 (21)	11 (133)	0 (4)
Headache	20 (401)	0 (9)	19 (220)	0 (6)
Pain in extremity	14 (119)	0 (1)	14 (66)	1 (6)
Upper respiratory tract infection	11 (144)	0 (3)	8 (56)	0 (2)
Stomatitis	14 (188)	0 (5)	6 (42)	0 (0)
Nasopharyngitis	14 (75)	0 (0)	10 (30)	0 (0)
Dizziness	13 (112)	1 (6)	11 (52)	0 (0)
Asthenia	16 (86)	2 (12)	10 (29)	0 (0)
Dyspnoea	13 (167)	2 (20)	11 (75)	1 (9)
Rash	15 (237)	1 (13)	7 (71)	0 (1)
Increased ALT	13 (181)	5 (75)	5 (42)	1 (11)
Infections	44 (440)	4 (37)	37 (243)	2 (18)
Abdominal pain	21 (328)	1 (21)	10 (76)	1 (5)
Insomnia	13 (99)	0 (1)	10 (38)	0 (0)
Pyrexia	11 (141)	0 (4)	7 (41)	0 (1)

ALT = alanine transaminase, CDK = cyclin-dependent kinase.

patients with HR-positive/HER2-negative advanced breast cancer. And this large RCT also supported the results found in our meta-analysis, that adding ribociclib could prolong the duration of PFS and improve the rate of overall response and clinical benefit. Besides ribociclib, abemaciclib is another highly specific oral CDK4/6 inhibitor molecule. Preclinical data verified that abemaciclib can effectively inhibit tumor growth and prolong survival time of patients.^[23] MONARCH-1 is a phase-II single-arm study designed to evaluate safety and efficacy of abemaciclib monotherapy in women with HR-positive/HER2-negative advanced breast cancer whose disease progressed on or after endocrine therapy and chemotherapy.^[24] In MONARCH-2, patients with similar conditions were given abemaciclib and fulvestrant. The result showed that the rate of objective response was 35.2% (95% CI, 30.8%–39.6%), the clinical benefit rate was 72.2% (95% CI, 68.0%–76.4%), and median PFS was 16.4 months, which significantly improved PFS and overall response rate compared with placebo plus fulvestrant.^[14]

The CDK4/6 inhibitors are efficacious and low toxic when applied in combination with various hormonal compounds in the treatment for HR-positive/HER2-negative advanced breast cancer. However, how to combine it with chemotherapy or other targeted drugs is still a significantly clinical problem to be solved. Clinical data showed that CDK4/6 inhibitors could suppress the proliferation of breast cancer cells, which would not only be a great benefit to patients with advanced breast cancer, but also to patients with early breast cancer.^[25] Besides, related preclinical researches have shown that HER2+ breast cancer cell

lines remain to be sensitive to CDK4/6 inhibitors, indicating that HER2+ breast cancer patients may also benefit from the treatment of CDK4/6 inhibitors.^[26] In contrast to ER-positive and HER2-positive disease, one preclinical research has revealed that there was no relevant effect of CDK4/6 inhibitors on triple-negative subtype of breast cancer.^[18] In addition, animal experiments showed that CDK4/6 inhibitors may have the ability to cross the blood–brain barrier, which can be the potential target for treating brain metastases in patients with breast cancer.^[27] Based on this data, a phase-II trial, designed to investigate the potential role of abemaciclib in patients with newly diagnosed brain metastases or brain metastases progressing after prior local therapy who had original HR-positive or HER2-positive breast cancer, has been currently under way (NCT02308020). Nevertheless, there is still doubt whether the CDK4/6 inhibitors have the ability to antagonize the antitumor effects of cytotoxic chemotherapy and targeted therapy that have the function of killing cancer cells in cell cycle.^[28]

This meta-analysis improved the result credibility that CDK4/6 inhibitors could prolong the PFS, compared with the placebo-treated group from 5 RCTs. Importantly, several limitations should be noted in our analysis. First, the present meta-analysis only included 6 published RCTs with 3182 patients, which might cause publication bias. The Finn 2014 trial was a rater-blinded RCT. Although the randomization codes were only released at the time of interim and final analyses without any crossover, and the sensitivity analysis showed that all the outcomes were stable after excluding the Finn 2014 trial, it should still be cautious

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cristofanilli 2016	+	+	+	+	+	+	+
Finn 2014	+	+	-	-	+	+	+
Finn 2016	?	?	+	+	+	+	+
Goetz 2017	+	+	+	+	+	+	+
Hortobagyi 2016	?	?	+	+	+	+	+
Sledge 2017	+	?	?	+	+	+	+

Figure 5. Risk of bias: a summary table for each risk of bias item for each study.

when applying these results to the clinical practice. Second, overall survival results are not mature and available today. Thus, the finding that this prolonged PFS can result in longer overall survival will not be proved until the further follow-up is completed. However, this result of clinically relevant potential PFS prolongation can already be used in the individual patients to delay the time of cytotoxic chemotherapy, and reduce the associated toxicity, side effects, and psychological pressure.

5. Conclusion

CDK4/6 inhibitors can significantly prolong the PFS and improve the objective response or clinical benefit response, which was confirmed in every subgroup of the meta-analysis we performed. Adverse events are reversible, and the rate of discontinuation due to adverse events is low. Further studies should focus on whether treating with CDK4/6 inhibitors can significantly prolong the overall survival of patients with advanced breast cancer.

Author contributions

C.J. Tu designed the study and developed the analysis plan. W. Ding and Z.A. Li collected the data and performed the meta-analysis. C.Y. Wang and W. Ding assessed the risk of bias. W.

Ding was responsible for writing the article. G.D. Ruan and L.P. Chen revised the manuscript with helpful comments.
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Acknowledgments

We thank LiGen Shi and Zhenwei Li for their support and guidance throughout the project.

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