SYSTEMATIC REVIEW AND META-ANALYSIS

Adjuvant and neoadjuvant therapy with cyclin-dependent kinase 4 and 6 inhibitors in hormone receptor-positive, human epidermal growth factor receptor 2-negative early breast cancer: a systematic review and meta-analysis

Meilin Zhang[1], Jian Song[2], Shigang Guo[3], Feng Jin[2] and **Ang Zheng[2]**

[1]Department of Burn and Plastic Surgery, Chaoyang Central Hospital, Chaoyang, Liaoning Province, China
[2]Department of Breast Surgery, the First Hospital of China Medical University, Shenyang, Liaoning Province, China
[3]Department of General Surgery, Chaoyang Central Hospital, Chaoyang, Liaoning Province, China

Correspondence should be addressed to A Zheng: azheng@cmu.edu.cn

Abstract

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have shown advantages in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer. This study aimed to evaluate the efficacy and safety of CDK4/6 inhibitors combined with endocrine therapy (ET) in patients with HR+, HER2− early breast cancer. The PubMed, Embase, Cochrane Library, and Web of Science databases were searched for randomized controlled trials (RCTs) related to CDK4/6 inhibitors combined with ET. Literature conforming to the research content was identified according to the inclusion and exclusion criteria. The efficacy endpoints included invasive disease-free survival (IDFS), distant relapse-free survival (DRFS), and overall survival (OS) with adjuvant therapy. The efficacy endpoint of neoadjuvant therapy was complete cell cycle arrest (CCCA). The safety outcomes included the incidence of adverse events (AEs) and grade 3–4 hematological and non-hematological AEs. Data analysis was performed using Review Manager software (version 5.3). A statistical model (fixed-effects model or random-effects model) was selected based on the level of heterogeneity, and a sensitivity analysis was performed if strong heterogeneity existed. Subgroup analyses were performed based on the baseline patient characteristics. Nine articles (including six RCTs) were included in the study. In adjuvant therapy, compared with the control group, CDK4/6 inhibitors combined with ET showed no statistically significant difference in IDFS (hazard ratio = 0.83, 95% confidence interval (CI) = 0.64–1.08, $P = 0.17$) and DRFS (hazard ratio = 0.83, 95% CI = 0.52–1.31, $P = 0.42$). In neoadjuvant therapy, CDK4/6 inhibitors combined with ET significantly improved CCCA compared with the control group (odds ratio = 9.00, 95% CI = 5.42–14.96, $P < 0.00001$). In terms of safety, the combination treatment group had a significantly increased incidence of grade 3–4 hematological AEs in patients, especially grade 3–4 neutropenia (risk ratio (RR) = 63.90, 95% CI = 15.44–264.41, $P < 0.00001$) and grade 3–4 leukopenia (RR = 85.89, 95% CI = 19.12–385.77, $P < 0.00001$), with statistically significant differences. In patients with HR+, HER2− early breast cancer, the addition of

Key Words

- early breast cancer
- CDK4/6 inhibitors
- endocrine therapy
- randomized controlled trial

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CDK4/6 inhibitors may prolong IDFS and DRFS in adjuvant therapy, especially in high-risk patients. Further follow-up is needed to establish whether OS can be improved with CDK4/6 inhibitors plus ET. CDK4/6 inhibitors also showed effective anti-tumor proliferation activity in neoadjuvant therapy. Regular monitoring of routine blood tests in patients using CDK4/6 inhibitors is essential.

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Introduction

Breast cancer is the most common malignancy in women, with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) breast cancer occurring in approximately 70% of cases (Serra *et al.* 2019). In recent years, with the continuous innovation of therapies, the emergence of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors has brought new therapeutic directions for HR+, HER2− breast cancer. Globally marketed CDK4/6 inhibitors include palbociclib, ribociclib, and abemaciclib. Palbociclib, the first CDK4/6 inhibitor, was approved by the Food and Drug Administration in 2015 and approved for marketing in China in 2018 (Finn *et al.* 2015).

CDK4/6 is an important regulator of the cell cycle, which can form a complex with cyclin D1, phosphorylate retinoblastoma protein (RB), and complete the process of cell proliferation. As molecular targeted drugs, CDK4/6 inhibitors can efficiently and accurately inhibit the activity of CDK4 and CDK6 kinase in tumor cells and block RB phosphorylation; thus, blocking the cell cycle process from G1 to S phase of tumor cells and preventing tumor cell proliferation. Meanwhile, CDK4/6 inhibitors hinder the expression of the upstream estrogen receptor signaling pathway and achieve synergistic effects between them and endocrine therapy (ET), which can delay and reverse endocrine drug resistance (Roberts *et al.* 2012, Spring *et al.* 2020).

In patients with HR+, HER2− advanced breast cancer, multiple clinical studies have demonstrated that CDK4/6 inhibitors combined with aromatase inhibitors or fulvestrant can significantly delay disease progression and reduce the risk of death and that most adverse events (AEs) are controllable (Finn *et al.* 2015, Slamon *et al.* 2020). Obviously, the application of CDK4/6 inhibitors has improved the clinical treatment of patients with advanced breast cancer, raising our interest as to whether we can benefit patients with HR+, HER2− early breast cancer. The goal of treatment for advanced and early breast cancer is different, with advanced breast cancer aimed at prolonging survival and early breast cancer usually aimed at a cure. The tumor burden, tumor microenvironment, and host body state differ between the two stages. Therefore, the application of drugs that demonstrate therapeutic value in advanced breast cancer in early stage patients needs to be further explored. The reported efficacy of CDK4/6 inhibitor combinations and ET in HR+, HER2− early breast cancer is controversial, with varying results across major clinical trials (Harbeck *et al.* 2021, Gnant *et al.* 2022). Therefore, this meta-analysis included all available randomized controlled trials (RCTs) with the aim of exploring the efficacy and safety of CDK4/6 inhibitors plus ET in patients with HR+, HER2− early breast cancer receiving adjuvant or neoadjuvant therapy. Accurate prediction of breast cancer populations that can benefit from CDK4/6 inhibitor therapy will provide new evidence for clinical diagnosis and treatment.

Materials and methods

Data sources and search strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement and registered with INPLASY (registration number: 2022110008) (Moher *et al.* 2009). The PubMed, Embase, Cochrane Library, and Web of Science databases were searched in October 2022 using a combination of subject words and free words: 'breast neoplasms' and free words, 'cyclin dependent kinase 4/6 inhibitors', and the specific names of CDK4/6 inhibitors ('abemaciclib', 'palbociclib', and 'ribociclib') were searched simultaneously. Moreover, 'Endocrine therapy' and drug names ('aromatase inhibitors', 'letrozole', and 'fulvestrant') were searched. Based on McMaster University's search formula, the search filters used in retrieving specific types of studies included 'randomized controlled trial', 'randomized', 'placebo', 'randomized', or 'clinical trial'. During the search, the conjunction 'or' was inserted between the subject words and free words; 'and' was used to connect the subject words. Moreover, we screened references to identify additional reviews and meta-analyses related to CDK4/6

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inhibitors to ensure the inclusion of all currently available RCTs. A literature search was independently performed by two investigators (Meilin Zhang and Ang Zheng). In case of disagreement, a third researcher (Feng Jin) was consulted to reach a consensus.

Inclusion and exclusion criteria

This study included (i) studies conducted among patients who were pathologically diagnosed with HR+, HER2− early breast cancer (early breast cancer is defined as breast cancer patients without distant metastasis and inflammatory breast cancer); (ii) phase II/III studies; (iii) studies that comprised an experimental group (consisting of patients who received CDK4/6 inhibitors in combination with ET) and a control group (consisting of patients who received ET with or without placebo); (iv) studies whose endpoints were invasive disease-free survival (IDFS), distant relapse-free survival (DRFS), overall survival (OS), complete cell-cycle arrest (CCCA), or AEs; and (v) studies that directly extracted or calculated hazard ratios, odds ratios (ORs), risk ratios (RRs), and 95% confidence intervals (CIs).

Meanwhile, (i) phase I and single-arm tests; (ii) non-RCTs; (iii) systematic review, case reports, comments, and animal studies; (iv) studies with unavailable data and relevant outcomes; and (v) incomplete or ongoing studies were excluded.

Endpoints

The endpoints of this meta-analysis were efficacy and safety. The primary efficacy endpoint in adjuvant therapy was IDFS (defined as the time from randomization to the date of the first event: local or regional invasive ipsilateral recurrence, contralateral invasive breast cancer, distant recurrence, second primary invasive cancer of non-breast origin, or death from any cause). Secondary endpoints were DRFS (defined as the time from randomization to the date of the first event, distant recurrence or death from any cause) and OS (defined as time from randomization to the date of death due to any cause). The efficacy endpoint in neoadjuvant therapy was CCCA (defined as Ki-67 less than or equal to 2.7%). AEs were defined according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute (Chung *et al.* 2019).

Data extraction

First, general information about the study was extracted from the included RCTs, including the trial name, phase, number of experimental and control groups, and treatment. Second, we extracted data on outcome indicators, such as IDFS, DRFS, OS, and AEs. Data extraction was performed independently by two investigators (Meilin Zhang and Ang Zheng). Disagreements were resolved by a third researcher (Feng Jin).

Literature quality evaluation

The RCT quality was evaluated using the Cochrane Collaboration tool (Higgins *et al.* 2011). The process was completed using the Review Manager, version 5.3. The criteria used to assess the quality of the literature were as follows: (i) random sequence, (ii) allocation concealment, (iii) blinding of participants and personnel, (iv) blinding of outcomes, (v) incomplete outcome data, (vi) selective reporting, and (vii) other biases: 'low-risk', 'high-risk', and 'unclear'. Two researchers (Meilin Zhang and Ang Zheng) independently assessed the quality of the literature and resolved differences through discussion until a consensus was reached.

Statistical analysis

This study was carried out using the Review Manager software (version 5.3). IDFS, DRFS, and OS were analyzed using hazard ratio and 95% CI, and subgroup analyses were performed based on the baseline characteristics of the patients. CCCA and AEs were analyzed using OR and RRs. Statistical significance was set at $P < 0.05$. Heterogeneity was assessed according to the results of Cochran's Q and I^2 tests. A Cochran's Q statistic of $P < 0.1$ or an I^2 of ≥50% indicated heterogeneity among the included studies, using the random-effects model and sensitivity analysis, if necessary. The fixed-effects model was used when Cochran's Q statistic was >0.1 and I^2 was <50%.

Results

Study characteristics and quality assessment

A flowchart of the literature screening process is shown in Fig. 1. We identified 9 articles (Johnston *et al.* 2019*b*, 2023, Hurvitz *et al.* 2020, Johnston *et al.* 2020, Khan *et al.* 2020, Harbeck *et al.* 2021, Loibl *et al.* 2021, Mayer *et al.* 2021, Gnant *et al.* 2022) (six RCTs) from 577 records. The characteristics of the six studies are listed in Table 1. In total, 13,299 patients with early breast cancer were included. Adjuvant and neoadjuvant therapy were

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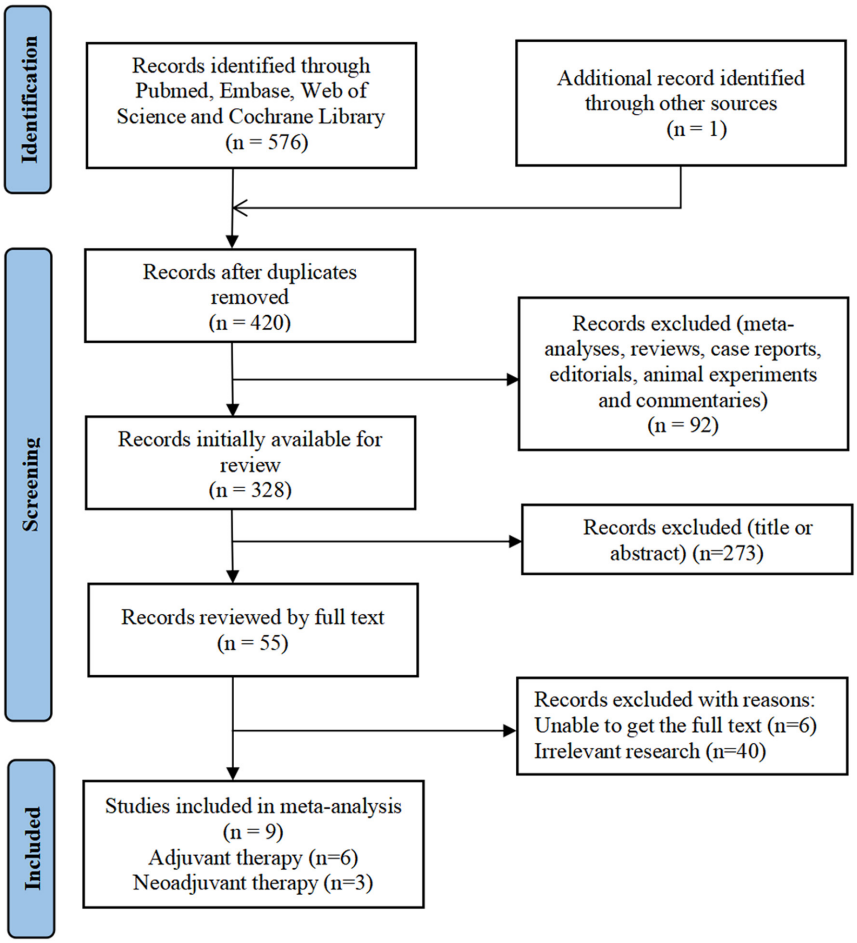

Figure 1
Flowchart of review design.

included in three studies respectively. All the participants included in the neoadjuvant studies were post-menopausal women. All studies were of high quality; the results of these studies are presented in Supplementary Fig. 1 (supplementary files, see section on supplementary materials given at the end of this article).

Efficacy of adjuvant therapy: IDFS

Six articles (Johnston *et al.* 2020, 2023, Harbeck *et al.* 2021, Loibl *et al.* 2021, Mayer *et al.* 2021, Gnant *et al.* 2022) reported the IDFS of the CDK4/6 inhibitors vs the ET group, which showed an obvious heterogeneity ($I^2 = 85\%$, $P = 0.002$); therefore, the random-effects model was selected for analysis. There was no statistically significant difference in IDFS between the CDK4/6 inhibitor group and the control group (hazard ratio = 0.83, 95% CI 0.64–1.08, $P = 0.17$) (Fig. 2A). We also performed a subgroup analysis based on the baseline characteristics of the patients, and the results suggested a trend toward prolonged IDFS in all subgroup analyses, but only a significant difference in a geographical region (Asian), T stage (T2), and tumor stage (stage IIA) (Table 2).

Efficacy of adjuvant therapy: DRFS

Two RCTs (Johnston *et al.* 2020, 2023, Harbeck *et al.* 2021, Mayer *et al.* 2021, Gnant *et al.* 2022) studied the DRFS and found a significant heterogeneity ($I^2 = 93\%$, $P = 0.0002$); therefore, the random-effects model was selected for the analysis. The results showed that the combination group might have suggested an improvement in DRFS compared with the ET group, but the difference was not statistically significant (hazard ratio = 0.83, 95% CI = 0.52–1.31, $P = 0.42$) (Fig. 2B).

Efficacy of adjuvant therapy: OS

Three RCTs (Johnston *et al.* 2020, 2023, Harbeck *et al.* 2021, Loibl *et al.* 2021, Mayer *et al.* 2021, Gnant *et al.* 2022) studied OS and found slight heterogeneity ($I^2 = 54\%$, $P = 0.11$). The results indicated that OS was not prolonged in the combination treatment group, and the significance

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Table 1 Characteristics of included studies.

Study	NCT number	Study design	Phase	Eligible patients	Treatment	Patients, *n* (experimental /control)	Median follow-up (months)	Endpoints
Adjuvant therapy								
MonarchE	NCT03155997	RCT	III	Female (any menopausal status) and male patients with HR+, HER2−, high-risk[a] EBC	Abemaciclib + AI/tamoxifen vs AI/tamoxifen	5637 (2808/2829)	42	IDFS, DRFS, OS, AEs
PENELOPE-B	NCT01864746	RCT	III	Women with HR+, HER2− EBC without pCR after NACT and at high risk[b] of relapse	Palbociclib + AI/amoxifen, +/−LHRH analog vs Placebo + AI/amoxifen, +/−LHRH analog	1250 (631/619)	42.8	IDFS, OS, AEs
PALLAS	NCT02513394	RCT	III	Patients with stage II–III histologically confirmed HR+ and HER2−	Palbociclib + AI/tamoxifen, +/−LHRH analog vs AI/ tamoxifen, +/−LHRH analog	5761 (2884/2877)	31	IDFS, DRFS, OS, AEs
Neoadjuvant therapy							**The change in Ki67**	
FELINE	NCT02712723	RCT	II	Postmenopausal women with >2 cm or node+ ER+ HER2− breast cancer	Ribociclib + Letrozole vs Placebo + Letrozole	120 (82/38)	Baseline, day 14 cycle 1 (D14C1), and surgery	CCCA
PALLET	NCT02296801	RCT	II	Postmenopausal women with ER+ HER2− EBC and tumors ≥ 2 cm	Palbociclib + Letrozole vs Letrozole alone	307 (204/103)	Baseline, 2 weeks and 14 weeks	CCCA, pCR
neoMONARCH	NCT02441946	RCT	II	Postmenopausal women with stage I–IIIB HR+ HER2−	Abemaciclib + Anastrozole vs Anastrozole	224 (74/74)	Baseline, 2 weeks, and the end of treatment (16 weeks)	CCCA

[a]High risk was defined as patients with four or more positive pathologic axillary lymph nodes or one to three positive axillary lymph nodes and at least one of the following: tumor size ≥ 5 cm, histologic grade 3, or centrally assessed Ki-67 ≥ 20%.
[b]Clinical pathological staging-estrogen receptor grading score ≥ 3 or 2 and ypN1.
AEs, adverse events; AI, aromatase inhibitors; CCCA, complete cell-cycle arrest; DRFS, distant relapse-free survival; EBC, early breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; LHRH, luteinizing hormone-releasing hormone; LRFS, locoregional recurrence-free survival; OS, overall survival; pCR, pathological complete response; RCT, randomized controlled trial.

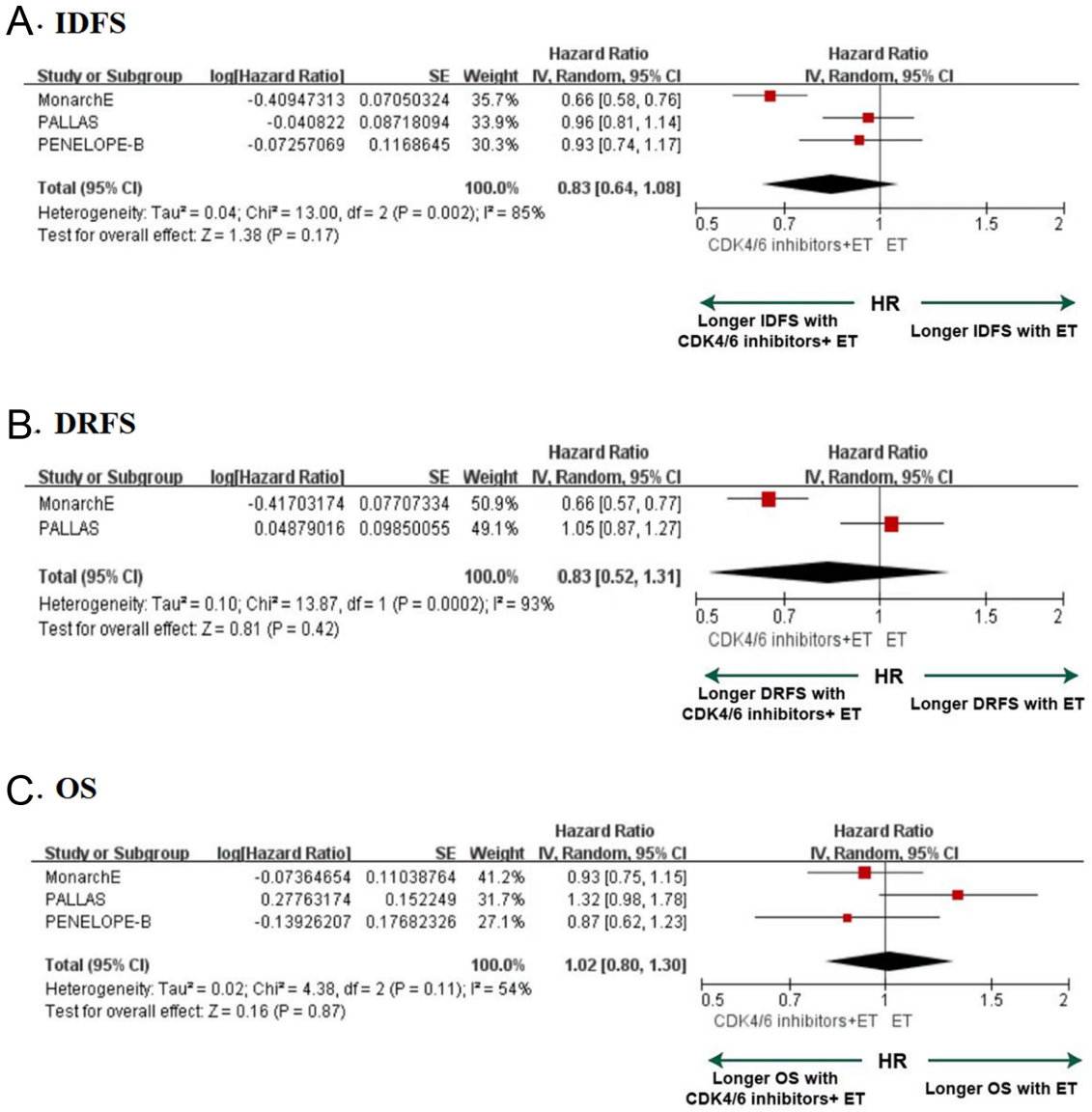

Figure 2
Forest plots of pooled hazard ratios in adjuvant therapy. (A) IDFS of adjuvant therapy. (B) DRFS of adjuvant therapy. (C) OS of adjuvant therapy. A full color version of this figure is available at https://doi.org/10.1530/ERC-22-0365.

between the groups was not reached (hazard ratio = 1.02, 95% CI = 0.80–1.30, $P = 0.87$) (Fig. 2C).

Efficacy of neoadjuvant therapy: CCCA

Three RCTs (Johnston *et al.* 2019*b*, Khan *et al.* 2020, Hurvitz *et al.* 2020) that studied CCCA suggested that there was no significant heterogeneity ($I^2 = 0\%$, $P = 0.58$); therefore, the fixed-effects model was selected. The results suggested that the combination treatment group could significantly improve CCCA (OR = 9.00, 95% CI = 5.42–14.96, $P < 0.00001$) (Fig. 3).

Safety of adjuvant therapy: AEs

Regarding adjuvant therapy, three RCTs (Harbeck *et al.* 2021, Gnant *et al.* 2022, Loibl *et al.* 2021, Johnston *et al.* 2023) reported the safety of CDK4/6 inhibitors. The results showed that compared with the ET group, the combined treatment group showed a significant increase in the incidence of grade 3–4 any AEs, serious AEs and grade 3–4 hematological AEs, and there were significant statistical differences except for grade 3–4 alanine aminotransferase increase ($P < 0.05$). Second, in non-hematological AEs, grade 3–4 nausea (RR = 2.89, 95% CI = 1.30–6.47, $P = 0.01$) and grade 3–4 fatigue (RR = 5.94, 95% CI = 1.66–21.31,

Table 2 Subgroup analysis of IDFS.

Subgroup	Studies	Hazard ratio (95% CI)	Test for overall effect (*P*)	Test for subgroup differences (*P*)
Age (years)				0.42
≤50	2	1.01 (0.83–1.23)	0.94	
>50	2	0.90 (0.74–1.09)	0.28	
Geographical region				0.26
Asian	2	0.61 (0.43–0.88)	0.008	
Non-Asian	2	0.80 (0.59–1.11)	0.18	
T stage				0.92
T0/1	2	0.71 (0.32–1.60)	0.41	
T2	2	0.80 (0.69–0.93)	0.003	
T3/4	2	0.86 (0.56–1.32)	0.48	
N stage				0.99
N0-1	3	0.78 (0.61–1.00)	0.05	
N2-3	3	0.78 (0.60–1.02)	0.07	
Tumor stage				0.05
Stage IIA	2	0.62 (0.41–0.93)	0.02	
Stage IIB–III	2	0.96 (0.82–1.12)	0.61	
Histological grade				0.72
G1/2	2	0.76 (0.56–1.03)	0.07	
G3	2	0.82 (0.60–1.13)	0.22	

CI, confidence interval; IDFS, invasive disease-free survival.

P=0.006) improved in the combined treatment group. In addition, no statistical differences were found between the two groups in any of the other AEs that were included (Table 3).

Discussion

CDK4/6 inhibitors combined with ET for HR+, HER2− advanced breast cancer have been recognized by experts worldwide. It has been reported that in 2018, 48.7% of advanced breast cancer patients in the United States received first-line CDK4/6 inhibitors combined with ET (Brufsky *et al.* 2020). Therefore, the application of CDK4/6 inhibitor molecular targeted drugs in early breast cancer has attracted increasing attention. Therefore, this study targeted HR+, HER2− patients with early breast cancer and divided them into two groups (adjuvant therapy and neoadjuvant therapy) to explore the efficacy and safety of CDK4/6 inhibitors combined with ET, respectively.

For adjuvant therapy, we included three RCTs. In the original studies, IDFS was the primary endpoint, and DRFS and OS were the secondary endpoints. Recurrence and distant metastasis of breast cancer are serious adverse events affecting patient survival, so monitoring patients with local or regional recurrence and distant metastasis during follow-up can significantly improve patient survival and quality of life. This is also the reason why IDFS and DRFS were chosen as the important endpoints in this meta-analysis. In terms of efficacy, the combined treatment group might have suggested an improvement in IDFS and DRFS, but the difference is not statistically

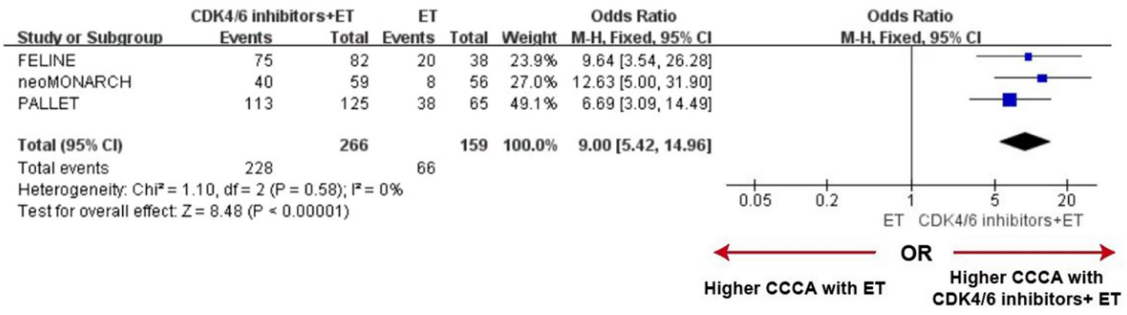

Figure 3
Forest plot of CCCA in neoadjuvant therapy. CCCA, complete: cell-cycle arrest; ET, endocrine therapy. A full color version of this figure is available at https://doi.org/10.1530/ERC-22-0365.

Table 3 Pooled risk ratio of adverse events in adjuvant therapy.

AEs	No. of studies	Experimental		Control		RR (95% CI)	*P*	Heterogeneity	
		Events	Total	Events	Total			I^2 (%)	*P*
Grade 3–4 any AEs	2	3457	5632	902	5702	3.80 (2.38–6.06)	<0.00001	98	<0.00001
Serious AEs	3	804	6263	491	6321	1.66 (1.49–1.84)	<0.00001	51	0.13
Grade 3–4 Hematologic AEs									
Neutropenia	3	2750	6263	41	6321	63.90 (15.44–264.41)	<0.00001	94	<0.00001
Lymphopenia	2	254	5632	23	5702	11.16 (7.29–17.07)	<0.00001	0	0.86
Leukopenia	3	1537	6263	18	6321	85.89 (19.12–385.77)	<0.00001	88	0.0002
Thrombocytopenia	3	66	6263	7	6321	9.47 (4.35–20.58)	<0.00001	44	0.17
Anemia	3	74	6263	17	6321	4.38 (2.59–7.41)	<0.00001	0	0.72
ALAT increased	2	80	3422	23	3419	2.01 (0.39–10.47)	0.41	78	0.03
ASAT increased	2	56	3422	16	3419	3.51 (2.02–6.10)	<0.00001	0	0.88
Grade 3–4 non-hematologic AEs									
Diarrhea	3	240	6263	14	6321	4.57 (0.46–45.17)	0.19	91	<0.0001
Nausea	3	23	6263	8	6321	2.89 (1.30–6.47)	0.01	36	0.21
Constipation	3	2	6263	2	6321	1.01 (0.17–5.85)	0.99	0	0.38
Headache	3	19	6263	15	6321	1.28 (0.65–2.51)	0.48	0	0.86
Arthralgia	3	46	6263	73	6321	0.57 (0.27–1.19)	0.13	67	0.05
Back pain	3	24	6263	13	6321	1.86 (0.95–3.64)	0.07	21	0.28
Pain in extremity	2	6	3422	6	3419	0.99 (0.32–3.08)	0.99	0	0.57
Rash	2	16	5632	3	5702	4.92 (0.3–79.47)	0.26	69	0.07
Lymphedema	2	9	5632	2	5702	4.55 (0.98–21.07)	0.05	0	0.90
Cough	3	2	6263	0	6321	3.04 (0.32–29.19)	0.34	0	0.99
Hot flush	3	16	6263	23	6321	0.7 (0.37–1.32)	0.27	0	0.48
Fatigue	3	157	6263	23	6321	5.94 (1.66–21.31)	0.006	86	0.0006
Upper respiratory tract infection	3	58	6263	28	6321	3.61 (0.47–27.49)	0.21	89	0.0001

AEs, adverse events; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CI, confidence interval; RR, risk ratio.

significant. Moreover, there was strong heterogeneity between the groups, which may be due to the relatively small number of included studies. According to the results, the data on OS are still immature, and longer follow-up is needed to verify the effect of CDK4/6 inhibitors on OS in patients with early breast cancer. In addition, larger clinical trials are warranted. The MonarchE trial (Johnston *et al.* 2020, 2023, Harbeck *et al.* 2021) enrolled patients with HR+, HER2−, and high-risk early breast cancer who were randomly assigned to receive abemaciclib plus ET or ET monotherapy. The results showed that the combination group had significantly improved IDFS (hazard ratio = 0.664, 95% CI = 0.578–0.762, $P < 0.0001$) and DRFS (hazard ratio = 0.659, 95% CI = 0.567–0.767, $P < 0.0001$). However, we did not observe a positive result in another RCT. The PALLAS trial (Mayer *et al.* 2021, Gnant *et al.* 2022) enrolled patients with early breast cancer who had completed adjuvant or neoadjuvant therapy and had undergone surgery. Patients were randomized to palbociclib combined with ET or ET monotherapy. At an updated follow-up, the addition of palbociclib to standard ET did not improve IDFS (IDFS at 4 years: 84.2 vs 84.5%; hazard ratio = 0.96, 95% CI = 0.81–1.14, $P = 0.65$). Similar to the results of the PALLAS study, the PENELOPE-B trial (Loibl *et al.* 2021) showed that palbociclib combined with ET did not significantly improve IDFS (IDFS at 3 years: 81.2 vs 77.7%; hazard ratio = 0.93, 95% CI = 0.74–1.17, $P = 0.525$), even after 42.8 months of follow-up. Thus, CDK4/6 inhibitors have shown different results in adjuvant therapies, which could be due to the following three points. First, there were differences in the study design and baseline characteristics of the enrolled patients among the three RCTs. Among them, the MonarchE and PALLAS trials had large sample sizes, whereas the PENELOPE-B trial included a relatively small number of patients. Moreover, patients enrolled in the MonarchE trial had a relatively higher risk and were more likely to have a higher risk of early recurrence. Second, abemaciclib and palbociclib have different mechanisms of action. Abemaciclib had a more significant inhibitory effect on CDK4, while palbociclib was more inclined to inhibit CDK6. It is worth noting that CDK4 plays a more important role in the pathogenesis of breast cancer. This may be an important reason for the positive results in the MonarchE trial. Some studies have shown that abemaciclib can also act on CDK9, and palbociclib and ribociclib did not show similar effects. Moreover, abemaciclib inhibited both CDK14 and CDKs16–18 to varying degrees. Due to the

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more targets of abemaciclib, it may be a potential basis for improved efficacy (Gelbert *et al.* 2014, Wells *et al.* 2020). Third, compared with the MonarchE trial, the PALLAS trial has a higher rate of early drug discontinuation, and each study has different control methods for AEs, which leads to significantly different treatment compliance in patients. In conclusion, abemaciclib can be used as a new adjuvant therapy option for patients with early breast cancer. The MonarchE trial suggested that patients with high-risk HR+, HER2− early breast cancer might benefit from abemaciclib. At the same time, we also look forward to more clinical trials to further determine the status of CDK4/6 inhibitors in the treatment of early breast cancer and accurately select the population with the greatest clinical benefit.

Currently, CDK4/6 inhibitors are still in their infancy in the field of neoadjuvant therapy. A smaller proportion of patients with HR+, HER2− breast cancer achieve pathological complete response with neoadjuvant therapy, and therefore, current clinical trials of neoadjuvant endocrine therapy prefer CCCA as the study endpoint. In the three RCTs included in this study, CCCA was an important endpoint (Johnston *et al.* 2019*b*, Hurvitz *et al.* 2020, Khan *et al.* 2020). CCCA was defined as Ki67 ≤ 2.7%. As a biomarker of persistent change, Ki67 can predict the prognosis of breast cancer patients and can be used as a dynamic monitoring indicator of the efficacy of neoadjuvant therapy. Low Ki67 may indicate that patients have a better survival and a lower risk of recurrence (Dowsett *et al.* 2022). Therefore, CCCA has important clinical significance in neoadjuvant endocrine therapy. Three RCTs were included in our study, and the results suggested that CDK4/6 inhibitors combined with ET could significantly improve CCCA, supporting the importance of CDK4/6 inhibitors in the antitumor activity in early breast cancer. The PALLET trial (Johnston *et al.* 2019*b*) also conducted an analysis of pathological complete response, and the results showed that there was no statistically significant difference between the combination treatment group (6/180) and the control group (1/89) ($P = 0.43$). The NeoPalAna trial (Ma *et al.* 2017), a single-arm study evaluating the efficacy of palbociclib plus anastrozole as neoadjuvant therapy, found that CCCA was more pronounced with the addition of palbociclib. These results suggest that palbociclib is an effective antiproliferative agent for the treatment of early breast cancer resistant to anastrozole. In addition, some researchers have compared the efficacy of CDK4/6 inhibitors combined with ET vs chemotherapy in neoadjuvant therapy. The CORALLEEN trial (Prat *et al.* 2020) enrolled patients with stage I–IIIA, luminal B early breast cancer. The results indicated that patients with early and high-risk breast cancer could achieve molecular downstaging of the disease from ribociclib and letrozole. The feasibility of CDK4/6 inhibitors in neoadjuvant therapy was demonstrated again. However, whether this combination therapy can replace neoadjuvant chemotherapy remains to be proven in definitive clinical trials. The population selection for CDK4/6 inhibitors in combination with ET instead of chemotherapy is a future research direction.

While focusing on efficacy, any drug-related AEs are always important to consider for patients, clinicians, and triallists. This study investigated the incidence of AEs in patients with breast cancer receiving adjuvant therapy. The results showed that, compared with the control group, the combined treatment group had an increased incidence of hematological AEs, especially grade 3–4 leukopenia and neutropenia. Among the non-hematological AEs, the combination therapy group had an increased incidence of grade 3–4 fatigue and nausea. In addition, the combined treatment group also increased the incidence of serious AEs. But from our data, deaths due to AEs of CDK4/6 inhibitors are rare. MonarchE trial showed that there were only two treatment-related deaths in the abemaciclib plus endocrine therapy group (diarrhoea and pneumonitis) (Johnston *et al.* 2023). None of the 176 deaths in the PALLAS trial was considered related to treatment (Gnant *et al.* 2022). In the PENELOPE-B trial, eight patients were fatal, two in the combined treatment group (cardiogenic shock and influenza, both not related to the study drug) (Loibl *et al.* 2021). Some studies have shown that neutropenia is the most common AEs of CDK4/6 inhibitors, among which palbociclib and ribociclib have the highest proportion of neutropenia (Finn *et al.* 2016, Hortobagyi *et al.* 2018, Tripathy *et al.* 2018, Johnston *et al.* 2019*a*, Rugo *et al.* 2019). However, the mechanism of myelosuppression induced by CDK4/6 inhibitors differs from that induced by chemotherapy. CDK4/6 inhibitors cause cell cycle arrest but do not cause cell apoptosis (Hu *et al.* 2016, Rugo *et al.* 2018). The study showed that the incidence of febrile neutropenia is only 1% to 2% (Ge *et al.* 2022). Regular routine blood monitoring during treatment is also recommended in patients receiving CDK4/6 inhibitors, especially in patients who have received multiple chemotherapies or are elderly. In addition, diarrhea is the most common AEs of abemaciclib, with a 9% incidence of grade 3 diarrhea. Severe diarrhea can cause electrolyte disturbances that greatly reduce the quality of life of patients (Johnston *et al.* 2019*a*, Goetz *et al.* 2020). Therefore, patients are advised to

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eat soft and easily digestible food during treatment and to use anti-diarrheal drugs or adjust the dosage, if necessary.

Limitations

This study had several limitations. First, because of the limited number of available RCTs, some results were statistically inevitably heterogeneous. Second, we were unable to do a pooled analysis on progression-free survival due to the deficiency in original studies, despite the fact that it has also been widely used to assess the impact of adjuvant therapy. Third, due to the short follow-up, the OS data were immature and failed to reach the expected statistical results. Finally, owing to the limited number of included studies, the incidence of AEs during neoadjuvant therapy was not analyzed in this study.

Conclusion

In conclusion, CDK4/6 inhibitors may improve the efficacy of adjuvant and neoadjuvant therapy in patients with HR+, HER2− early breast cancer. Data with a longer follow-up time and more clinical trial results are highly expected. In the era of classified breast cancer treatment, the role of CDK4/6 inhibitors in HER2-positive and triple-negative breast cancers is also a direction for future research. Identifying effective biomarkers for the predominant population of CDK4/6 inhibitors is a goal we all aspire to.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/ERC-22-0365.

Declaration of interest
The authors declare that they have no conflict of interest.

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Availability of data and materials
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FJ and AZ were the directors of the fund and conceived the study. MLZ collected the medical records and drafted the manuscript. JS and SGG assisted in the revision of the manuscript. All authors have contributed to the manuscript and approved the submitted version.

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