ORIGINAL PAPER

Submitted: 24.09.2022
Accepted: 21.11.2022
Early publication date: 18.01.2023

Endokrynologia Polska
DOI: 10.5603/EP.a2023.0007
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 74; Number/Numer 1/2023

The effect and safety of CDK4/6 inhibitors combined endocrine therapy on HR+, HER2-breast cancer: a meta-analysis of randomized controlled trials

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Abstract

Introduction: The purpose of this meta-analysis is to evaluate the efficacy and safety of cyclin-dependent kinase4/6 inhibitors (CDK4/6i) combined with endocrine therapy (ET) on hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) breast cancer (BC).

Material and methods: A search was conducted in the PubMed, Embase, Web of Science, and Cochrane Library databases before July 2022.

Results: A total of 19 studies comprising 19,004 patients were eligible for this meta-analysis. This meta-analysis found that for unresectable locally advanced or metastatic HR+, HER2– BC, CDK4/6i combined with ET can significantly improve the progression-free survival (PFS) (hazard ratio = 0.59, $p < 0.001$), overall survival (OS) (hazard ratio = 0.77, $p < 0.001$), objective response rate (ORR) [risk ratio (RR) = 1.32, $p = 0.001$)], disease control rate (DCR) (RR = 1.10, $p < 0.001$), and clinical benefit response (CBR) (RR = 1.15, $p = 0.001$). For early HR+, HER2- BC, CDK4/6i combined with ET improved ORR (RR = 1.14, $p = 0.05$) and invasive disease free survival (iDFS) (hazard ratio = 0.87, $p = 0.045$) but had no effect on pathologic complete response (pCR) (RR = 1.75, $p = 0.33$), distant recurrence free survival (DRFS) (hazard ratio = 0.83, $p = 0.311$), and OS (hazard ratio = 1.08, $p = 0.705$).

Conclusion: CDK4/6i combined with ET can improve the prognosis of patients with unresectable locally advanced or metastatic HR+, HER2– BC, but it has no obvious effect on patients with early HR+, HER2– BC. It is generally safe and manageable. **(Endokrynol Pol 2023; 74 (1): 89–105)**

Key words: *hormone receptor-positive; human epidermal growth factor receptor 2-negative; breast cancer; cyclin-dependent kinase4/6 inhibitors; endocrine therapy; meta-analysis*

Introduction

Breast cancer (BC) is the most common malignant disease among women worldwide [1, 2]. The most common subtype is hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) BCs, which account for approximately 60–70% of all BCs [3, 4]. According to international guidelines, endocrine therapy (ET) is the treatment of choice for patients with HR+ and HER2– BC [5, 6]. Aromatase inhibitors (AIs) [7], selective oestrogen receptor degraders (SERDs), and selective oestrogen receptor modulators (SERMs) [8, 9] play an important role in this regard [10]. Initial single-agent ET is optional with letrozole, fulvestrant, and tamoxifen [11]. Studies have demonstrated 5-year specific survival of 94% in stage I HR+, HER2– BC and up to 4–5 years in metastatic HR+, HER2– BC patients after treatment [12, 13].

Despite favourable improvements in overall survival in HR+, HER2– BC after ET, 20% of patients will develop recurrent metastases, and patients with high-risk clinical or pathologic features are at higher risk of recurrence [14–16]. Moreover, patients may develop intrinsic or acquired endocrine resistance and thereby resistance during first-line or multiple lines of ET [17, 18]. Researchers have found a variety of resistance pathways [21–23], based on their investigation of the potential endocrine resistance mechanisms of HR+, HER2– BC [19, 20]. Among them, cyclin-dependent kinase4/6 (CDK4/6) promotes retinoblastoma (Rb) protein hyperphosphorylation [24, 25], which leads to the transition of the cell cycle from the G1 to S phase [26, 27]. This critical Rb checkpoint is involved in endocrine resistance in BC [28]. Therefore, researchers developed a series of CDK4/6 inhibitors (CDK4/6i): palbociclib, ribociclib, and abemaciclib [29–31].

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Due to inconsistent results from clinical trials [32, 33] and concerns about adverse effects [34, 35], scientists still have many opinions and disagreements about these newly proposed therapeutic regimens involving CDK4/6i [36]. For example, results of the MONALEESA-3 trial [37] showed that ribociclib could significantly promote the overall survival (OS) of patients with HR+, HER2- BC [hazard ratio = 0.72, 95% confidence interval (CI) = 0.57–0.92]. The results of the MONALEESA-2 trial [38] showed that ribociclib had no effect on OS, compared with placebo (hazard ratio = 0.75, 95% CI = 0.52–1.08). The aim of this review paper is to provide a relatively comprehensive and reliable data analysis for clinical treatment by evaluating the efficacy and safety of CDK4/6i combined with ET on HR+, HER2– BC, including unresectable, locally advanced or metastatic tumours and early tumours.

Material and methods

Search strategy

A search of relevant studies that investigated the efficacy and safety of CDK4/6i in HR+, HER2- BC patients published before July 2022 was conducted in the PubMed, Embase, Web of Science, and Cochrane Library databases. The complete retrieval formula used to identify the number of studies was as follows: ("breast cancer" OR "breast neoplasms" OR "BC") AND ("cyclin-dependent kinase 4/6 Inhibitors" OR "CDK4/6 inhibitors" OR "Palbociclib" OR "ribociclib" OR "abemaciclib"). Moreover, the references of the included articles were manually checked for additional sources. This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2009 Checklist [39]. This meta-analysis's Prospero registration number was CRD42022350244.

Selection criteria

A qualifying standard has been established. The specific criteria are as follows:

Inclusion criteria: 1 — All included studies were randomized controlled trials (RCTs), limited to clinical studies; 2 — The study included only patients diagnosed with HR+, HER2- BC, whether unresectable, locally advanced, metastatic, or early stage; 3 — The experimental group in the RCTs was treated with CDK4/6i combined with ET, while the control group could be treated with other treatments; 4 — All studies included full-text articles.

Exclusion criteria: 1 — The study neither reported relevant survival outcomes nor prognostic indicators; 2 — The study is a preclinical or phase I clinical trial; 3 — The study was published repeatedly. When referring to duplicate literature, only the most recent or comprehensive articles are included; 4 — The study was not published in English.

Two researchers used an independent search strategy to select studies from the database and independently reviewed the titles and abstracts of these articles for inclusion. When in doubt, the full text was searched for further selection. When necessary, authors were contacted for more information about their research. In case of disagreement, discussions were held with a third researcher, and when consensus could not be reached, the study was excluded.

Quality assessment and data extraction

For data collection, a jointly agreed-upon data collection form was used. The following information was extracted: the author's name, year of publication, trial duration, NCT number, country, patient age, therapeutic regimen, trial phase, follow-up time, patient number, primary outcomes, and secondary outcomes. Two researchers independently extracted the data from each study. Disagreements were arbitrated by a third researcher. The Cochrane risk bias assessment tool was used to assess the methodological quality of each included RCT.

Objectives and endpoints

For unresectable locally advanced or metastatic HR+, HER2– BC patients, the primary objectives were progression-free survival (PFS), which was defined as the proportion of cancer patients who did not experience the progression of disease or death for any reason in the 5 years since the treatment began, and overall survival (OS), which was defined as the proportion of tumour patients who survived more than 5 years after a variety of comprehensive treatments. The secondary objectives were objective response rate (ORR), which refers to the proportion of patients whose tumour shrank to a certain amount and remained stable for a certain period of time, and disease control rate (DCR), which is defined as ORR plus stable disease (SD) rate, clinical benefit response (CBR) (defined as ORR plus SD ≥ 24 weeks rate), and safety.

For early HR+, HER2– BC patients, the primary goal was a complete pathological response (pCR), defined as ypT0/is ypN0, which means no invasive or non-invasive residuals in the breast and axilla. The secondary objectives were invasive disease-free survival (iDFS), which was defined as the time in months between random assignment and first event (ipsilateral invasive in-breast or locoregional recurrence, distant recurrence, invasive contralateral BC, second primary invasive cancer [non-breast], or death because from any cause) for CDK4/6i versus placebo, distant recurrence-free survival (DRFS), which was defined as the time from randomization to the date of the first event (distant recurrence or death from any cause), OS, ORR, and safety.

Statistical analysis

RevMan 5.3.5 software for Windows® and the Stata software version 12 (StataCrop, College Station, Texas, USA) were used to analyse the data. Heterogeneity across included studies was tested by Q statistics and the I^2 statistic. The values I^2 of 25–50%, 50–75%, and > 75% were considered low, moderate, and high heterogeneity, respectively [40]. The confidence interval (CI) of the hazard ratio and risk ratio (RR) was set at 95%. Hazard ratios were used to evaluate continuous variables, and RRs were used to assess enumeration data. p-values less than 0.05 were considered statistically significant. A random-effects model was used to incorporate data due to the variety of treatment regimens to increase the credibility of the results. When more than 10 studies [41, 42] were included, sensitivity analysis and publication bias tests were performed to evaluate the stability and reliability of the results. Begg's test was used to test publication bias.

Results

Literature search

A total of 4694 relevant articles were identified through preliminary searches in the PubMed, Embase, Web of Science, and Cochrane Library databases. No other records were identified from other sources. A total of 2243 duplicate articles were deleted, and 1748 articles were excluded according to the title or abstract. The remaining 703 articles were reviewed through full-text reading. Among them, 684 articles were eliminated because of non-RCTs (n = 423), non-CDK4/6i versus other treatments (n = 119), duplicate reports (n = 85), not containing relevant results (n = 49), and not published in

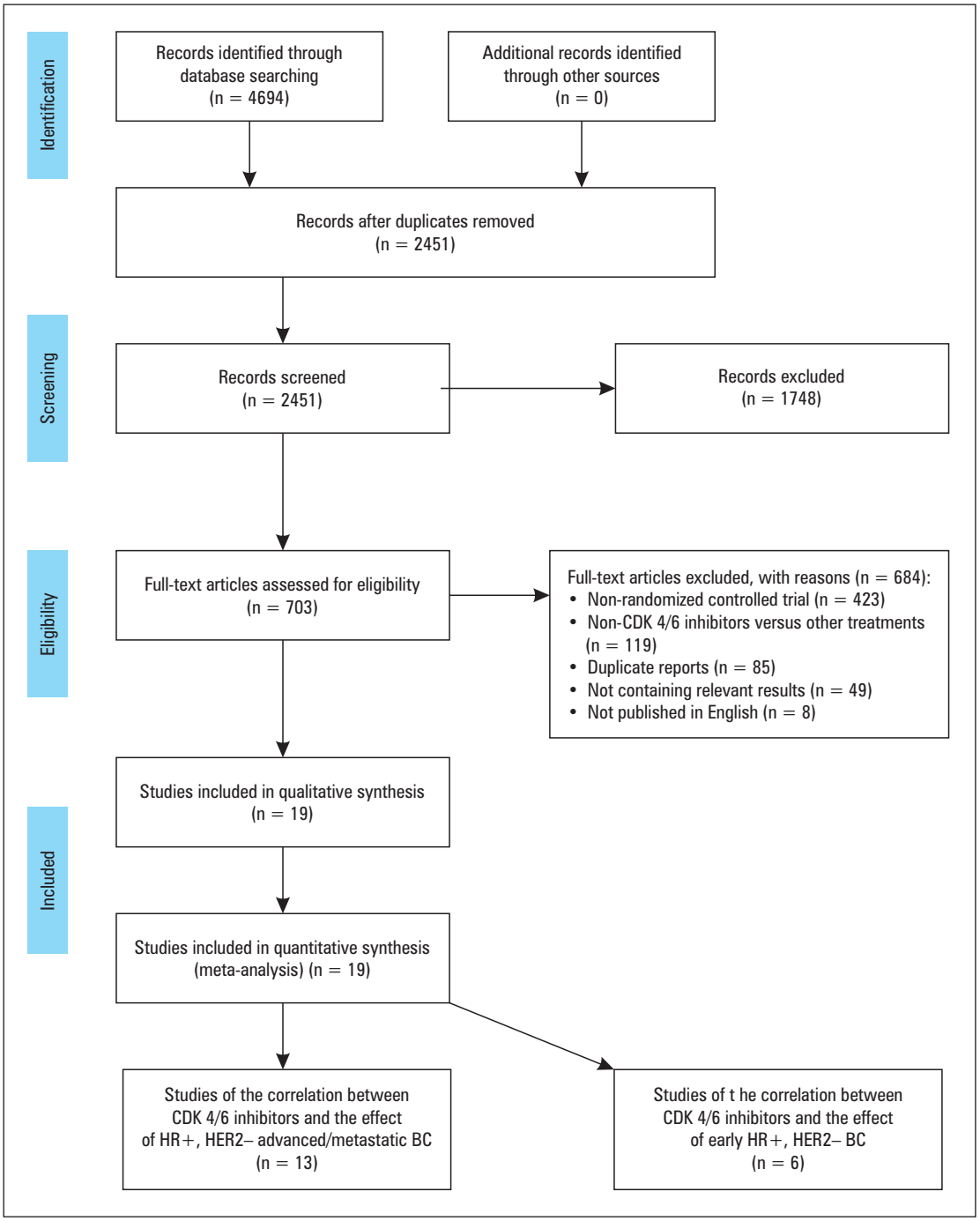

Figure 1. *A schematic flow for the selection of articles included in this meta-analysis. HR+ — hormone receptor positive; HER2– — human epidermal growth factor receptor 2 negative; BC — breast cancer*

English (n = 8). Eventually, 19 studies comprising 19,004 patients were eligible for this meta-analysis, of which 13 studies were on HR+, HER2– advanced/metastatic BC [43–55] and 6 [56–61] were on early HR+, HER2– BC. The detailed search and study selection process is shown in Figure 1.

Study characteristics

Among the 19,004 patients, 5838 were unresectable locally advanced or metastatic HR+, HER2– BC (3426 experimental patients and 2412 control patients) and 13,166 were early HR+, HER2– BC (6563 experimental patients and 6603 control patients). The experimental group in trials were all treated with CDK4/6i (palbociclib, ribociclib, or abemaciclib) combined with ET, while the control group was treated with other treatments, such as ET (anastrozole, letrozole, exemestane, fulvestrant, etc.), chemotherapy, or neoadjuvant therapy (5-fluorouracil, epirubicin, cyclophosphamide, docetaxel, etc.). All the studies

were published between 2015 and 2022, with a median follow-up time of 9.9 to 47.7 months. These were carried out in the United States, the United Kingdom, South Korea, Spain, Italy, Germany, and France. There were 9 studies on postmenopausal women and 2 on premenopausal women.

For unresectable, locally advanced or metastatic HR+, HER2– BC, 7 trials were in phase III and 6 were in phase II. Seven trials are still ongoing and will not complete the study. Seven studies administered palbociclib, 3 studies administered ribociclib, and 3 studies administered abemaciclib. The detailed characteristics of the included clinical trials are described in Table 1 and Supplementary File — Table S1. For early HR+, and HER2– BC, 3 trials were in phase III and 3 were in phase II. Also, 3 trials are still ongoing and will not complete the study. Four studies administered palbociclib, one study administered ribociclib, and one study administered abemaciclib. The detailed characteristics of included clinical trials are described in Table 2 and Supplementary File — Table S2.

Quality assessment

The Cochrane Collaboration tool was adopted to evaluate the quality of RCTs included in this study. The tool employed 6 targets, and every risk of bias was assessed by either "low risk", "high risk", or "unclear risk". According to the quality evaluation results of the investigators, all included studies were of higher quality. Detailed information on the quality assessment of studies related to unresectable locally advanced or metastatic HR+, HER2– BC is shown in Supplementary File — Figures 1 and 2. Similarly, detailed information on the quality assessment of studies related to early HR+, and HER2– BC, is shown in Supplementary File — Figures 3 and 4.

Unresectable, locally advanced or metastatic HR+, HER2-BC

Analysis of PFS and OS

Thirteen studies (3426 experimental and 2406 control patients) reported PFS to evaluate the efficacy of CDK4/6i combined with ET. The results showed that patients receiving CDK4/6i combined with ET had longer PFS compared to the control group (hazard ratio = 0.59, 95% CI = 0.53–0.66, $p < 0.001$) ($I^2 = 57.9\%$) (Fig. 2). Five studies (1695 experimental patients and 1054 control patients) investigated OS to evaluate the efficacy of CDK4/6i on unresectable locally advanced or metastatic HR+, HER2– BC. It was found that the patients receiving CDK4/6i combined with ET had longer OS in comparison with the control group (hazard ratio=0.77, 95% CI = 0.69–0.87, $p < 0.001$) ($I^2 = 0\%$) (Fig. 3).

Analysis of ORR, DCR, and CBR

Among the included studies, 13 (3426 experimental patients and 2406 control patients) mentioned ORR and CBR, and 12 studies mentioned DCR (2982 experimental patients and 2184 control patients). The results highlighted that the group receiving the CDK4/6i combined with ET achieved a higher proportion of ORR (RR = 1.32, 95% CI = 1.11–1.56, $p = 0.001$) (Fig. 4A). Patients receiving CDK4/6i combined with ET had higher DCR compared to controls, and the difference was statistically significant (RR = 1.10, 95 % CI = 1.04–1.16, $p < 0.001$) (Fig. 4B). In terms of CBR, the incidence of CBR in the group using CDK4/6i combined with ET was significantly higher than that in the control group (RR = 1.15, 95% CI = 1.06–1.26, $p = 0.001$) (Fig. 4C).

Safety analysis

The incidence of adverse events (AEs) was used to assess the safety of CDK4/6i combined with ET. The CDK4/6i joint with the ET group had a higher rate of AEs compared with the control group, whether all grade (RR = 1.04, 95% CI = 1.02–1.7, $p = 0.001$) (Tab. 3) or grade more than 3 (RR = 2.67, 95% CI = 2.67–3.15, $p < 0.001$) (Tab. 4). The CDK4/6i combined with the ET group had an increased event rate for neutropaenia, leukopaenia, fatigue, anaemia, thrombocytopaenia, decreased appetite, and rash, regardless of grade 3 or all grades. For nausea, alopecia, constipation, cough, infection, and pyrexia, the CDK4/6i with the ET group increased the rate of events of all grades but did not affect the rate of events above grade 3, compared to the control group. Similarly, there was no difference in the frequency of other AEs (such as diarrhoea, arthralgia, vomiting, headache, back pain, abdominal pain, and dyspnoea) ($p > 0.05$). Detailed analysis of the AEs is described in Tables 3 and 4.

Early HR+, HER2– BC

Analysis of pCR and ORR

Two studies reported pCR, and 3 studies reported ORR (225 experimental patients and 142 control patients). The experimental group reported data on 169 individuals, 6 of whom achieved pCR. Likewise, the control group reported data on 199 individuals, 4 of whom achieved pCR. There was no significant difference in the incidence of pCR between the group receiving CDK4/6i combined with ET and the control group (RR = 1.75, 95% CI = 0.57–5.32, $p = 0.33$) (Fig. 5A). However, in terms of ORR, the proportion of patients achieving ORR was higher in the experimental group than in the control group (RR = 1.14, 95% CI = 1.00–1.29, $p = 0.05$) (Fig. 5B).

Table 1. *Characteristics of included randomized controlled trials (RCTs) about cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors on hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced/metastatic breast cancer (BC) in the meta-analysis*

Author, year	Country	Clinical trial	Trial phase	Therapeutic regimen		Medication grade	Number of inclusions		Primary outcome measures	Secondary outcome measures
				Treatment	Control		Treatment	Control		
Finn, 2015	USA	PALOMA-1	II	Palbociclib + letrozole	Letrozole	First-line	84	81	PFS	CBR, ORR, AEs, DR, PR, CR
Finn, 2016	USA	PALOMA-2	III	Palbociclib + letrozole	Placebo + letrozole	first-line	444	222	PFS	ORR, DR, DC/CRB, OS, AEs, PROs
Turner, 2015	UK	PALOMA-3	III	Palbociclib + fulvestrant	Placebo + fulvestrant	First-line, second-line, third-line or greater	347	174	PFS	ORR, DR, CBR, OS, PROs, AEs
Park, 2019	South Korea	Young PEARL	II	Palbociclib + combination endocrine therapy (exemestane + palbociclib + GnRH agonist)	Chemotherapy (capecitabine)	First-line	92	92	PFS	CBR, ORR, DR, OS, AEs, PROs
Martin, 2021	Spain	PEARL	III	cohort 1: Palbociclib + exemestane	Cohort 1: capecitabine	First-line, second-line	153	154	PFS, OS	ORR, CBR, DR, AEs
				cohort 2: Palbociclib + fulvestrant	Cohort 2: capecitabine		149	156		
Malorni, 2018	Italy	TREnd	II	Palbociclib + endocrine therapy (oral anastrozole + letrozole + exemestane + intramuscular fulvestrant)	Endocrine therapy (oral anastrozole + letrozole + exemestane + intramuscular fulvestrant)	First-line, second-line	57	58	CBR	PFS, CR, PR, SD, ORR, TTP, DR
Albanell, 2022	Spain	FLIPPER	II	Palbociclib/fulvestrant	Placebo/fulvestrant	First-line	94	95	PFS	ORR, CBR, OS
Hortobagyi, 2016	USA	MONALEESA-2	III	Ribociclib + letrozole	Placebo + letrozole	First-line	334	334	PFS	ORR, CBR, AEs
Slamon, 2018	USA	MONALEESA-3	III	Ribociclib (LEE011) + fulvestrant	Placebo + fulvestrant	First-line, second-line	484	242	PFS	OS, ORR, CBR, TTR, DR, AEs
Tripathy, 2018	USA	MONALEESA-7	III	Ribociclib + tamoxifen/non-steroidal aromatase inhibitor + goserelin	Placebo + tamoxifen/non-steroidal aromatase inhibitor + goserelin	First-line	335	337	PFS	ORR, CBR, TTR, CR, PR, OS
Sledge, 2017	USA	MONARCH-2	II	Abemaciclib + fulvestrant	Placebo + fulvestrant	First-line	446	223	PFS	OS, CR, PR, ORR, SD, CPR, DC
Goetz, 2017	USA	MONARCH-3	III	Abemaciclib + anastrozole/letrozole	Placebo + anastrozole/letrozole	First-line	328	165	PFS	OS, CR, PR, DR, ORR, DC
Tolaney, 2020	USA	MONARCH-ER	II	Abemaciclib + trastuzumab + fulvestrant	Chemotherapy + trastuzumab	NA	79	79	PFS	OS, CR, PR, DR, ORR, DC

CDK4/6 — cyclin-dependent kinase 4 and 6; HR — hormone receptor; BC — breast cancer; PFS — progression-free survival; OS — overall survival; CBR — clinical benefit response; ORR — objective response rate; AEs — adverse events; DR — duration of response; DC — disease control; CR: complete response; PR — partial response; SD — stable disease; TTP — time to progression; TTR — time to response; PROs — patient-reported outcomes; GnRH — gonadotropin-releasing hormone; NA — not available

Table 2. *Characteristics of included randomized controlled trials (RCTs) about cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors on early hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) breast cancer (BC) in the meta-analysis*

Author, year	Country	Clinical trial	Trial phase	Therapeutic regimen		Medication grade	Number of inclusions		Primary outcome measures	Secondary outcome measures
				Treatment	Control		Treatment	Control		
Mayer, 2021	USA	PALLAS	III	Palbociclib + endocrine therapy	Endocrine therapy alone	Neoadjuvant therapy	2883	2877	OS, iDFS	DRFS, LRRFS, AEs
Johnston, 2019	UK	PALLET	II	C: palbociclib to week 2 + palbociclib + letrozole to week 14	B: letrozole to week 2 + palbociclib + letrozole to week 14	Neoadjuvant therapy	69	68	pCR	CRR, PEPI, the proliferation marker Ki-67, AEs
				D: palbociclib + letrozole to week 14	A: letrozole alone	Neoadjuvant therapy	67	103		
				B + C + D: palbociclib + letrozole	A: letrozole alone	Neoadjuvant therapy	204	103		
Loibl, 2021	Germany	PENELOPE-B	III	Palbociclib + endocrine therapy	Placebo + endocrine therapy alone	Neoadjuvant therapy	631	619	iDFS, DDFS, OS	QALY, AEs
Cottu, 2018	France	NeoPAL	II	Palbociclib + letrozole	5FU + epirubicin + cyclophosphamide + docetaxel	Neoadjuvant therapy	53	53	RCB	CRR, ROR, RCB, AEs, BCS
Prat, 2020	Spain	CORALLEEN	II	Ribociclib + letrozole	Multiagent chemotherapy	Neoadjuvant therapy	52	54	pCR	ORR, PEPI, RCB, BCS, AEs, decrease in Ki-67
Johnston, 2020	UK	MONARCH-E	III	Abemaciclib + endocrine therapy	Endocrine therapy alone	Neoadjuvant therapy	2808	2829	iDFS, OS	DRFS, FACT-B/ES/F, AEs

HR — hormone receptor; iDFS — invasive disease-free survival; OS — overall survival; pCR — pathological complete response; DDFS — distant disease-free survival; RCB — residual cancer burden; DRFS — distant recurrence-free survival; LRRFS — locoregional recurrence-free survival; CRR — clinical response rate; PEPI — preoperative endocrine prognostic index; QALY — quality-adjusted life years; ROR — risk of recurrence; RCB — residual cancer burden; AEs — adverse events; ORR — overall response rate; BCS — rate of breast conserving surgery; FACT-B/ES/F — change from baseline on the functional assessment of cancer therapy-breast/endocrine symptoms/fatigue

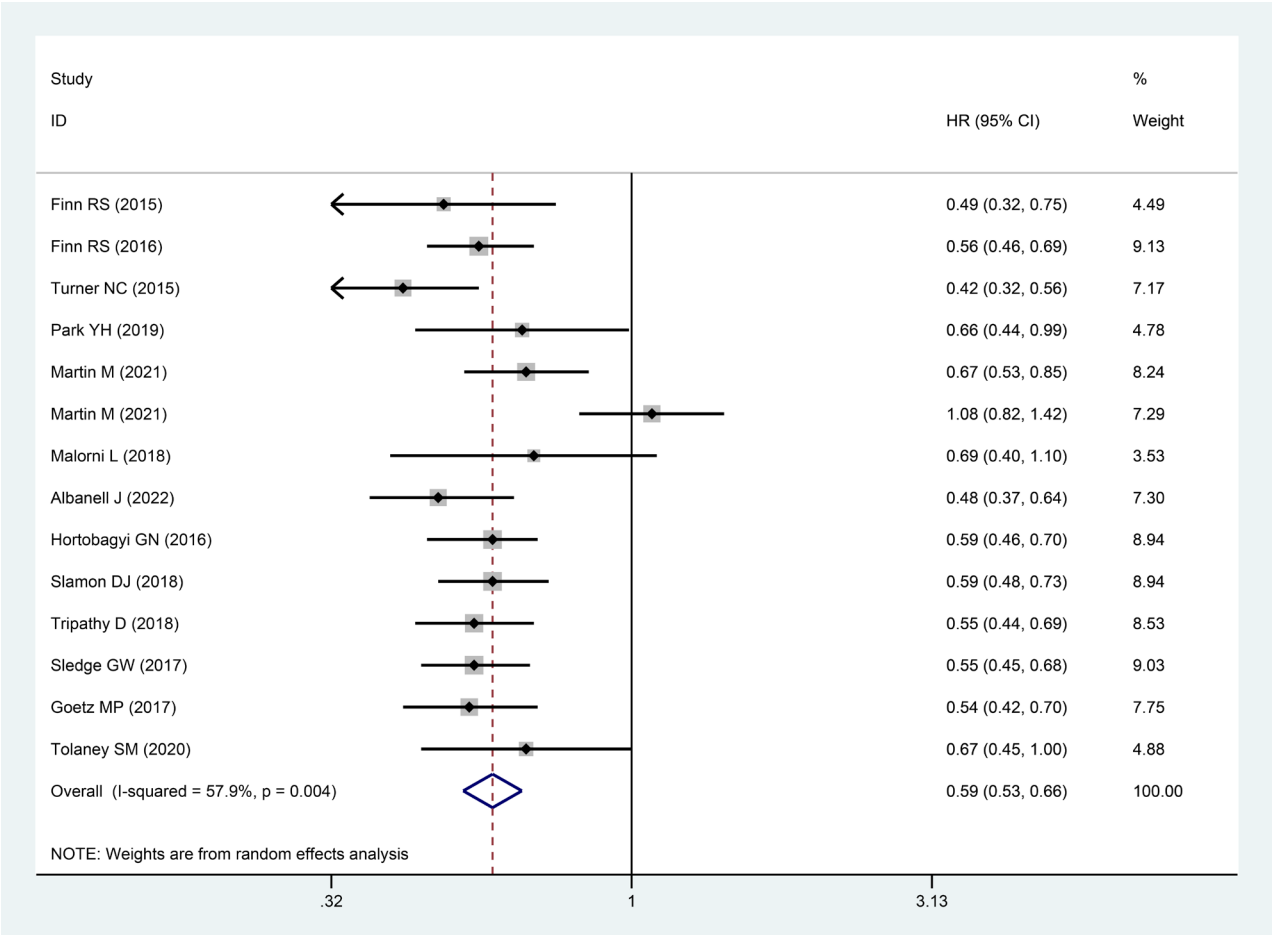

Figure 2. *Forest plot of the progression-free survival (PFS) of patients with unresectable locally advanced or metastatic hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) breast cancer (BC) on cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors combined with endocrine therapy (ET)*

Analysis of iDFS, DRFS, and OS

A total of 3 studies reported the iDFS of 6322 patients in the experimental group and 6325 patients in the control group. The CDK4/6i combined ET group had longer iDFS (hazard ratio = 0.87, 95% CI = 0.75–1.00, p = 0.045) (I^2 = 19.4%) than the control group (Fig. 6A). To assess the efficacy of CDK4/6i combined with ET, 2 studies reported DRFS (5691 experimental patients and 5706 control patients) and OS (3514 experimental patients and 3496 control patients). The findings revealed that in early HR+, HER2– BC patients, DRFS (hazard ratio = 0.83, 95% CI = 0.58–1.19, p = 0.311) (I^2 = 79.9%) (Fig. 6B) and OS (hazard ratio = 1.08, 95% CI = 0.72–1.63, p = 0.705) (I^2 = 68.7%) (Fig. 6C) did not reach statistical significance between the CDK4/6i combined with ET group and the control group.

Safety analysis

The incidence of AEs was used to evaluate the safety of CDK4/6i combined with ET. There were no significant differences in the rate of events of all grades between the CDK4/6i and ET groups (RR = 1.20, 95% CI = 0.84–1.24, p = 0.84) (Tab. 5), but the rate of events above grade 3 was increased (RR = 2.29, 95% CI = 1.47–3.57, p < 0.001) (Tab. 6) compared to the control group. For neutropaenia, leukopaenia, fatigue, anaemia, and thrombocytopaenia, the CDK4/6i combined with ET group had an increased event rate, either grade 3 or higher or all grades. For diarrhoea, arthralgia, hot flashes, and nausea, the CDK4/6i combined with ET increased the rate of AEs of all grades but did not affect the rate of AEs above grade 3. Detailed analysis of the AEs is described in Table 5 and Table 6.

Sensitivity analysis and publication bias

Sensitivity analysis and publication bias test were carried out for PFS of unresectable locally advanced or metastatic HR+, HER2- BC. Individual studies had little impact on the results (Supplementary File — Fig. 5), indicating that the analysis was relatively stable and reliable. Begg's test showed no publication bias (p > 0.05) (Supplementary File — Fig. 6).

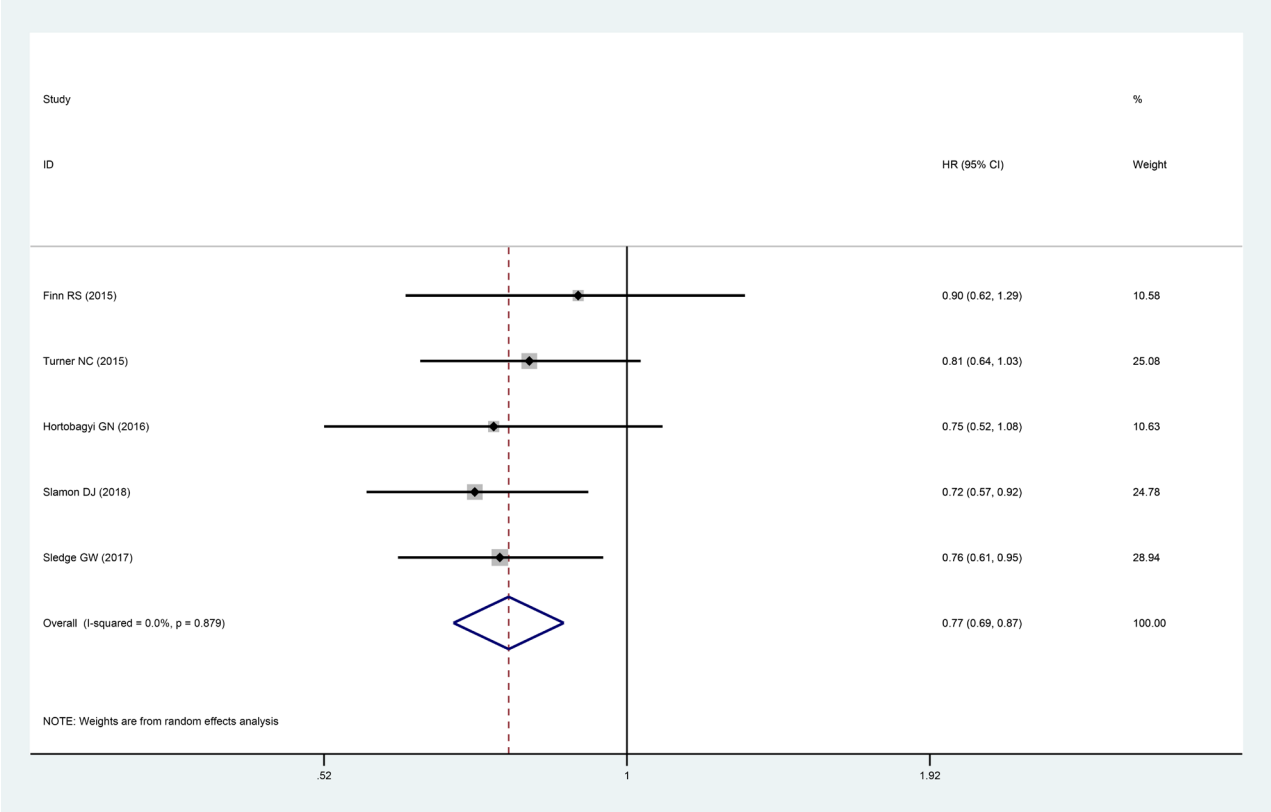

Figure 3. *Forest plot of the overall survival (OS) of patients with unresectable locally advanced or metastatic hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) breast cancer (BC) on cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors combined with endocrine therapy (ET)*

Discussion

This study revealed that CDK4/6i combined with ET could significantly prolong PFS and OS in patients with unresectable locally advanced or metastatic HR+, HER2– BC when compared to other treatments. Patients receiving CDK4/6i combined with ET had higher rates of ORR, DCR, and CBR. For early HR+, HER2– BC, it was found that CDK4/6i combined with ET could improve ORR and iDFS but had no effect on pCR, DRFS, and OS. In comparison, safety analysis showed that the combination of CDK4/6i with ET increased the incidence of AEs. In addition, regardless of unresectable locally advanced or metastatic HR+, HER2– BC patients or early HR+, HER2– BC patients, after receiving CDK4/6i combined with ET, AEs of any grade and above grade 3 were mainly manifested as neutropaenia, leukopaenia, anaemia, thrombocytopaenia, and fatigue.

Currently, researchers agree that dysregulation of the cell cycle plays a vital role in BC progression and endocrine resistance [72]. The mitotic cell cycle of eukaryotic cells is a well-conserved process that is tightly controlled [73]. In this process, CDKs are key regulatory enzymes that drive all cell cycle transitions [74]. The study found that the development process of the cell cycle is mainly driven by cyclin [75] and CDK complexes (both are positively driven) [76]. CDK is the core of the regulatory network, which dominates the initiation, progress, and outcome of the cycle [77]. The CDK4/6 pathway is one of many pathways that regulate the cell cycle [78]. Usually, CDK4/6 are common downstream targets of multiple signalling pathways, including oestrogen receptors (ER), and can form complexes with cyclin D during the G1 phase of the cell cycle [79]. The CDK4/6-cyclin D complex induces the inactivation and phosphorylation of Rb protein (a tumour suppressor protein) [80] and promotes the release of E2F transcription factors [81], stimulating cells from the G1 phase to the S phase [82], generating DNA replication/synthesis, and thereby completing cell proliferation [83, 84]. This process is genetically regulated and is a prerequisite for S phase entry and cell division [27].

Cyclin D1 is a direct transcriptional target of the ER [85]. In HR+ BC, activated ER after oestrogen signalling overexpresses cyclin D1, increases the activity of the HR-D1-CDK4/6 pathway, leads to hyperphosphorylation of Rb, and a large number of cells enter the S phase uncontrollably; eventually, it leads to excessive cell proliferation and promotes tumourigenesis [86–88]. Moreover, hyperphosphorylated Rb is also linked with

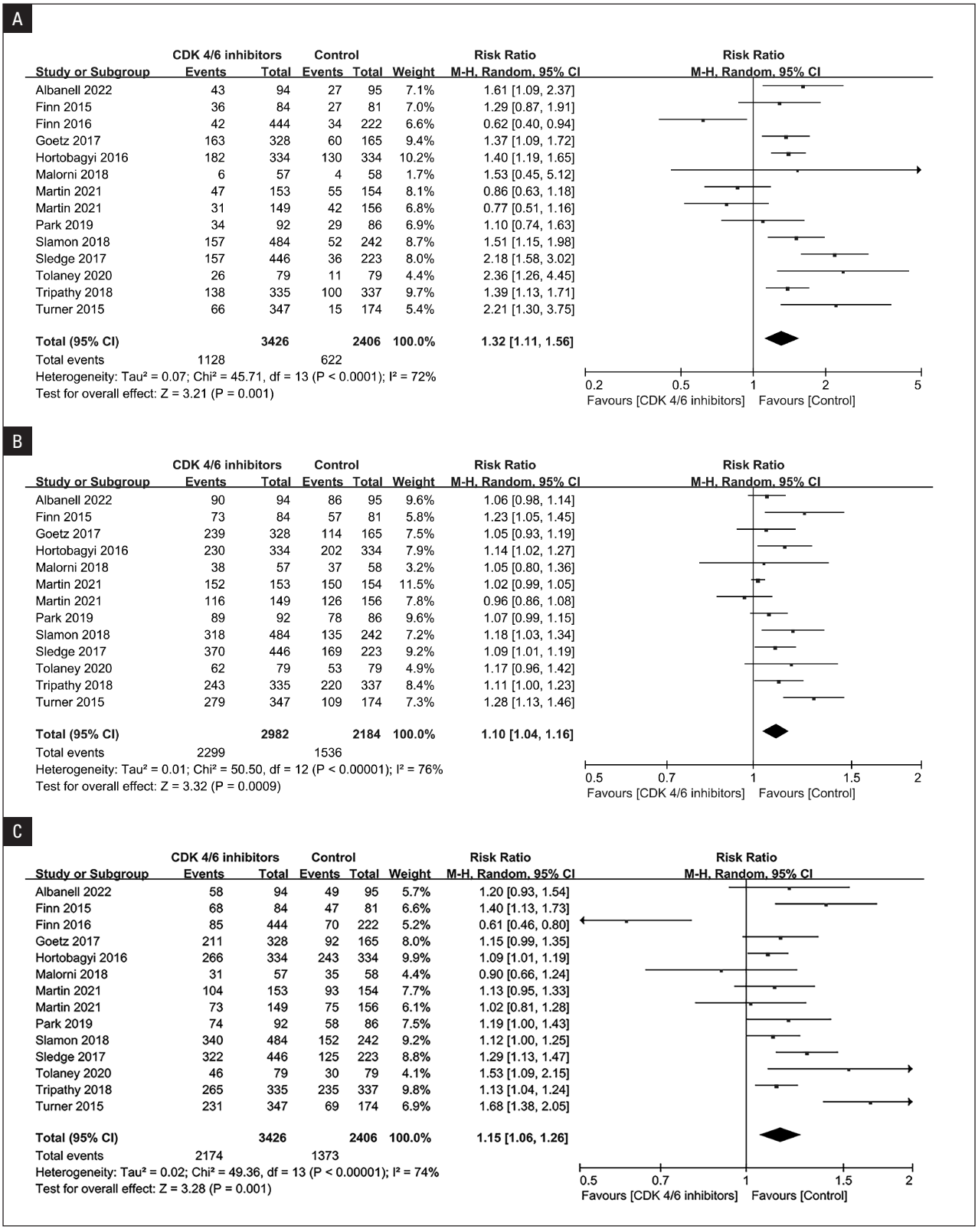

Figure 4. *Forest plot of the objective response rate (ORR), disease control rate (DCR), and clinical benefit response (CBR) of patients with unresectable locally advanced or metastatic hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) breast cancer (BC) on cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors combined with endocrine therapy (ET).* **A.** *ORR, p = 0.001;* **B.** *DCR, p < 0.001;* **C.** *CBR, p = 0.001; CI — confidence interval*

endocrine resistance [89, 90]. In vitro experiments revealed that ER+ BC cells can continue to grow in the presence of anti-oestrogens despite cyclin D1 overexpression [91, 92]. In other words, even if ER+

Table 3. *Subgroup analysis of the adverse events (AEs) (any grade) of cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors and control group in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced/metastatic breast cancer (BC)*

	No. of studies	Patients in the experimental group	Patients in the control group	RR	95% CI	p	Heterogeneity (I^2) (%)
Any AEs	12	3263	2508	1.04	1.02–1.07	0.001	85
Neutropaenia	13	3412	2652	6.47	2.79–15.02	< 0.001	99
Leukopaenia	13	3412	2652	5.26	2.98–9.30	< 0.001	98
Fatigue	13	3412	2652	1.19	1.06–1.34	0.002	62
Anaemia	13	3412	2652	2.26	1.67–3.05	< 0.001	92
Nausea	13	3412	2652	1.26	1.00–1.58	0.05	86
Arthralgia	13	3412	2652	1.08	0.91–1.28	0.37	58
Diarrhoea	12	3355	2594	1.17	0.76–1.81	0.47	95
Vomiting	11	3263	2508	1.36	0.99–1.88	0.06	85
Headache	11	3010	2422	1.12	0.97–1.29	0.13	31
Alopecia	10	3185	2436	2.55	2.02–3.23	< 0.001	50
Back pain	10	3185	2436	1.09	0.90–1.31	0.38	57
Constipation	10	3185	2436	1.24	1.05–1.45	0.009	35
Cough	10	2936	2347	1.27	1.12–1.45	< 0.001	0
Decreased appetite	9	2870	1835	1.62	1.31–1.99	<0.001	43
Hot flush	9	2858	2275	1.05	0.81–1.35	0.72	73
Thrombocytopaenia	9	1933	1583	5.35	2.40–11.94	< 0.001	93
Infection	8	1735	1611	1.26	1.08–1.47	0.003	0
Rash	7	2709	1686	2.23	1.73–2.86	< 0.001	37
Abdominal pain	7	2269	1765	1.33	0.87–2.04	0.19	80
Pain in extremity	7	2083	1722	0.91	0.76–1.09	0.30	0
Dizziness	7	2041	1704	1.14	0.80–1.62	0.47	61
Pyrexia	7	2036	1699	1.50	1.19–1.89	< 0.001	14
Dyspnoea	7	1820	1198	1.13	0.92–1.40	0.25	0

HR — hormone receptor; RR — risk ratio; CI — confidence interval

BCs develop resistance to ET, cyclin D1 and CDK4/6 are still indispensable for driving cell proliferation [93]. For the disorders of the CDK4/6 path, CDK4/6i differs from targeted antitumour drugs that previously acted on the upstream molecules of signal conduction [94]. It can regulate the cell cycle from the source position and block the proliferation to the G1 stage, thereby inhibiting tumour proliferation [95, 96]. Simultaneously, CDK4/6i can inhibit the expression of the upstream ER signalling pathway [97] and has a synergistic effect with ET to delay and reverse endocrine drug resistance [28]. This biological evidence supports the findings in this study that CDK4/6i combined with ET can significantly improve survival outcomes in patients with advanced HR+, HER2– BC, and ORR and iDFS in early HR+, HER2– BC compared with ET.

For early HR+, HER2– BC, this study found that CDK4/6i combined with ET could improve patients' ORR and iDFS but had no effect on pCR, DRFS, and OS. The following 3 points may explain this phenomenon. First, the number of studies reporting relevant data is small, with only 2 studies reporting pCR [57, 61] and OS [59, 60]. In addition, a low sample size limits this study to finding the effect of CDK4/6i combined with ET on pCR, DRFS, and OS. Second, the follow-up time was short. Early HR+, and HER2– BC have good sensitivity to therapy, and tumour resection after neoadjuvant therapy can often remove most cancer cells [98, 99]. Therefore, HR+, HER2– BC has a longer survival period [100], and it takes a long time from diagnosis and treatment to axillary invasion/metastasis/recurrence/death [101]. However, the longest follow-up time of studies targeting early HR+, HER2– BC was less than 4 years [59]. As a result, the short follow-up period could not determine whether the improvement in patient survival was caused by CDK4/6i combined with ET or by

Table 4. *Subgroup analysis of the adverse effects (AEs) (grade ≥ 3) of cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors and control group in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced/metastatic breast cancer (BC)*

	No. of studies	Patients in the experimental group	Patients in the control group	RR	95% CI	p	Heterogeneity (I^2) (%)
Any AEs	10	2964	1930	2.67	2.26–3.15	< 0.001	73
Neutropaenia	13	3412	2652	16.46	5.41–50.04	< 0.001	97
Leukopaenia	13	3412	2652	13.56	5.28–34.86	< 0.001	88
Fatigue	13	3412	2652	2.35	1.03–5.32	0.04	53
Anaemia	13	3412	2652	2.13	1.45–3.13	< 0.001	13
Nausea	12	3355	2594	1.30	0.70–2.41	0.41	7
Diarrhoea	11	3021	2264	1.48	0.52–4.17	0.46	73
Arthralgia	11	2993	2405	0.79	0.39–1.61	0.52	0
Back pain	10	3036	2147	1.66	0.91–3.01	0.10	0
Vomiting	10	2824	2241	1.09	0.57–2.08	0.79	22
Headache	9	3086	2336	0.70	0.31–1.58	0.39	0
Decreased appetite	9	2870	1835	2.35	1.00–5.52	0.05	0
Thrombocytopaenia	9	2211	1862	3.28	1.79–6.03	< 0.001	0
Rash	7	2709	1686	3.44	1.18–10.00	0.02	0
Abdominal pain	7	2269	1765	1.88	0.85–4.16	0.12	0
Infection	7	1562	1534	1.39	0.61–3.20	0.43	9
Pain in extremity	6	2000	1645	0.34	0.13–0.89	0.03	0
Dyspnoea	6	1726	1103	1.72	0.84–3.51	0.13	0

HR — hormone receptor; BC — breast cancer; RR — risk ratio; CI — confidence interval

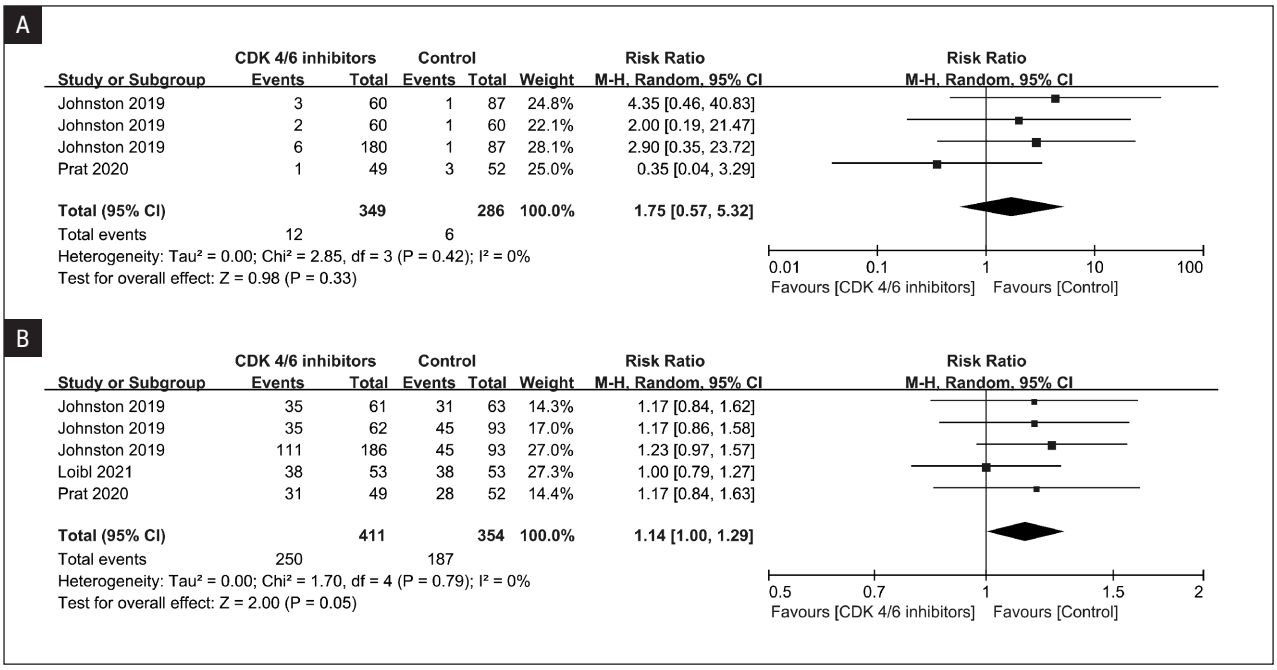

Figure 5. *Forest plot of the pathological complete response (pCR) and objective response rate (ORR) of patients with early hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) breast cancer (BC) on cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors combined with endocrine therapy (ET).* **A.** *pCR, p = 0.33;* **B.** *ORR, p = 0.05; CI — confidence interval*

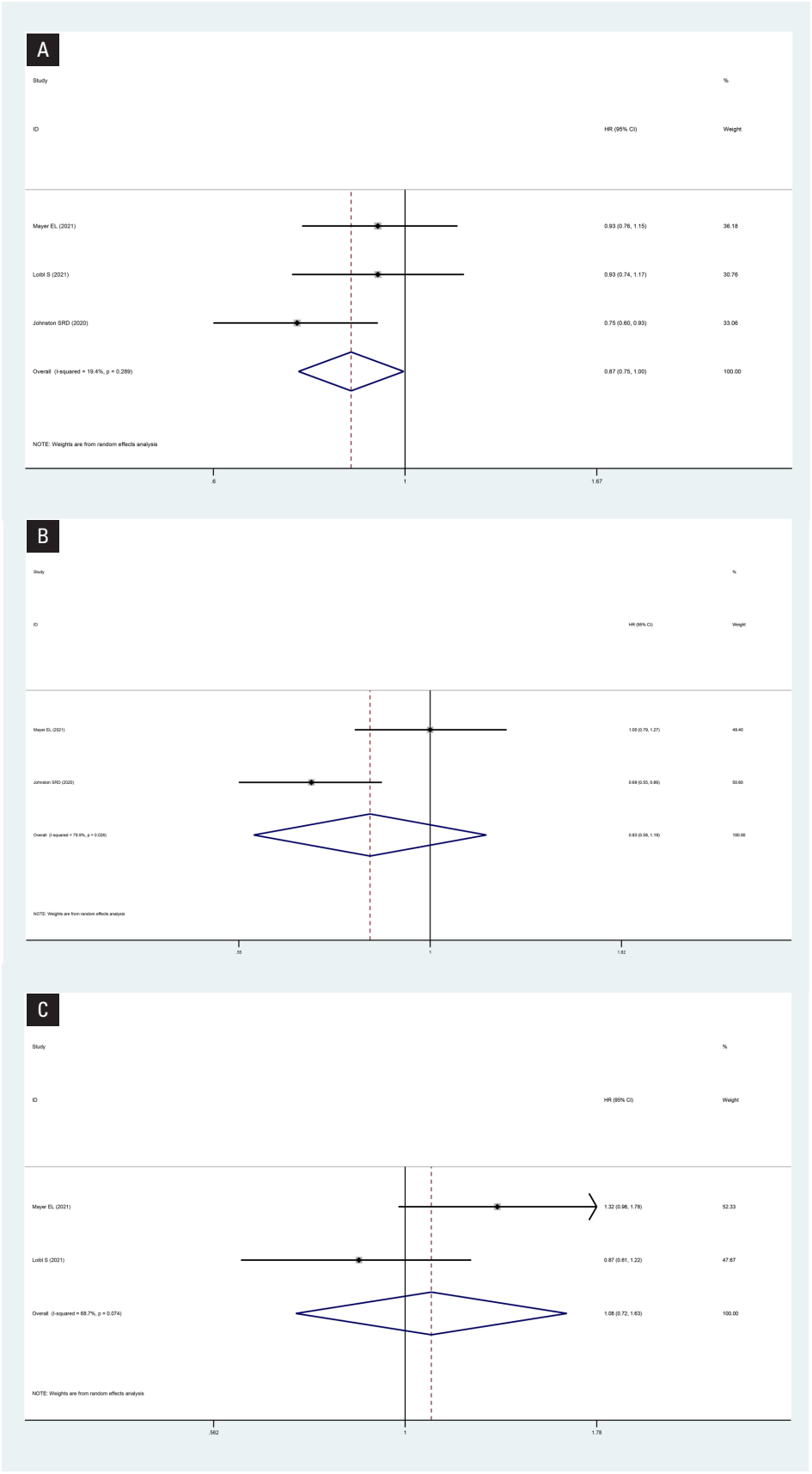

Figure 6. *Forest plot of the invasive disease-free survival (iDFS), distant recurrence-free survival (DRFS), and overall survival (OS) of patients with early hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) breast cancer (BC) on cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors combined with endocrine therapy (ET).* **A.** *iDFS, p = 0.045;* **B.** *DRFS, p = 0.311;* **C.** *OS, p = 0.705*

Table 5. *Subgroup analysis of the adverse events (AEs) (any grade) of cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors and control group in early hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) breast cancer (BC)*

	No. of studies	Patients in the experimental group	Patients in the control group	RR	95% CI	p	Heterogeneity (I^2) (%)
Any AEs	6	6569	6519	1.20	0.84–1.24	0.84	100
Neutropaenia	6	6569	6519	5.97	2.64–13.47	< 0.001	99
Leucopaenia	6	6569	6519	5.71	1.58–20.55	0.008	100
Fatigue	6	6569	6519	1.98	1.44–2.74	< 0.001	96
Arthralgia	6	6569	6519	0.90	0.74–1.10	0.31	89
Hot flush	6	6569	6519	0.79	0.66–0.95	0.01	80
Anaemia	6	6569	6519	3.66	2.26–5.93	< 0.001	95
Thrombocytopaenia	6	6569	6519	7.04	3.44–14.39	< 0.001	93
Nausea	6	6569	6519	2.27	1.45–3.55	< 0.001	95
Alopecia	6	6569	6519	3.64	2.52–5.24	< 0.001	81
Diarrhoea	6	6569	6519	2.96	1.15–7.64	0.02	99
Headache	6	6569	6519	1.26	0.92–1.71	0.15	86
Constipation	6	6569	6519	2.02	1.65–2.47	< 0.001	53
Cough	5	6518	6467	1.59	1.31–1.93	< 0.001	55
Infection	5	6368	6419	1.66	1.28–2.15	< 0.001	91
Lymphopaenia	4	6317	6367	2.06	1.12–3.80	0.02	95
Lymphoedema	3	5684	5756	1.36	1.13–1.63	0.001	44
Insomnia	3	3524	3566	1.05	0.91–1.21	0.47	11
Hypertension	3	3094	3056	0.90	0.75–1.08	0.24	0
Rash	3	2944	3008	1.89	0.89–4.02	0.10	74
Vomiting	3	2895	2905	3.95	3.25–4.79	< 0.001	0

HR — hormone receptor; RR — risk ratio; CI — confidence interval

Table 6. *Subgroup analysis of the adverse events (AEs) (grade ≥ 3) of cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors and control group in early hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) breast cancer (BC)*

	No. of studies	Patients in the experimental group	Patients in the control group	RR	95% CI	p	Heterogeneity (I^2) (%)
Any AEs	6	6569	6519	2.29	1.47–3.57	< 0.001	98
Neutropenia	6	6569	6519	21.58	3.67–126.79	< 0.001	98
Leucopaenia	5	6518	6467	43.21	11.70–159.50	< 0.001	82
Diarrhoea	5	6516	6466	2.46	0.25–23.90	0.44	89
Fatigue	4	6465	6414	5.68	1.82–17.70	0.003	80
Arthralgia	4	6465	6414	0.66	0.36–1.21	0.18	36
Anaemia	4	6315	6366	3.83	2.17–6.76	< 0.001	1
Hot flush	3	6264	6314	0.73	0.37–1.43	0.36	0
Thrombocytopaenia	3	6264	6314	8.26	2.33–29.34	0.001	49
Nausea	3	6264	6314	2.73	0.70–10.68	0.15	49
Headache	3	6264	6314	1.22	0.58–2.56	0.59	0

HR — hormone receptor; RR — risk ratio; CI — confidence interval

the characteristics of early HR+, HER2– BC patients. Third, the degree of different outcomes varies. ORR was defined as the proportion of patients whose tumours shrunk to a certain amount and maintained for a certain period of time [102] and was assessed according to the long diameter of the tumour [103]. pCR, defined as the absence of invasive and non-invasive residues in the breast and axilla, [104] was assessed by tumour biopsy and sentinel lymph node biopsy [105]. Many patients can achieve ORR after drug treatment, but residual cancer cells can still be found in pathological sections, indicating that pCR is not achieved [106]. The difference in the degree of ORR and pCR determines that pCR is a more accurate reference index for evaluating the efficacy of preoperative chemotherapy or ET and postoperative recurrence [104]. This study may be because CDK4/6i combined with ET did not shrink the tumour to the pCR standard.

Safety analysis showed that patients (unresectable locally advanced or metastatic HR +, HER2– BC patients, and early HR+, HER2– BC patients) receiving CDK4/6i combined with ET would increase the incidence of neutropaenia, leukopaenia, anaemia, thrombocytopaenia, and fatigue, regardless of any grade or grade above 3 AEs. Because CDK4/6i can stop the cell cycle and inhibit cell mitosis [76] but have no target specificity [86, 107], cells of the myeloid/haematological system with rapid metabolic turnover in humans would be significantly affected by the inhibition [108], showing symptoms of myelosuppression and various blood cell production and function disorders [109]. Among them, leukocytes represented by neutrophils were most obviously inhibited [110], which was the primary adverse reaction of CDK4/6i combined with ET [111]. The analysis showed that CDK4/6i combined with ET treatment of HR+, HER2– BC produced AEs that were generally safe and acceptable.

Review of published meta-analyses. Two studies investigated the efficacy and safety of adding CDK4/6i to adjuvant ET for early HR+, HER2– BC [112, 113]. They found that ET adjuvant CDK4/6i prolonged iDFS in HR+ and HER2–EBC patients while increasing the risk of treatment discontinuation. However, 2 of the 3 included studies did not have complete data published, and the benefit of iDFS was driven mainly by the results of one of the trials [59], which corresponded to an inadequate median follow-up of 19 months. Some meta-analyses concluded that CDK4/6i combined with ET could improve the long-term survival of patients with metastatic HR+, HER2– BC, which is consistent with the conclusions of this study, but further updates are needed [114–116]

Based on the above knowledge, this study is a meta-analysis to comprehensively and systematically explore the efficacy and safety of CDK4/6i combined with ET on HR+, HER2– BC. First, this meta-analysis examined unresectable locally advanced or metastatic HR+, HER2– BC, and early HR+, HER2– BC. Second, the included studies in this study are all high-quality RCT studies, which are more convincing and credible. In addition, this study selected palbociclib, ribociclib, and abemaciclib to comprehensively explore the efficacy and safety of CDK4/6i combined with ET.

Likewise, the limitations of this study should also be emphasized. First, the number of studies included in this meta-analysis was limited, and the long-term survival results of some trials were not published or updated. Second, subgroup analysis according to Ki-67, age, lymph node status, etc. could not be performed in this study due to limited data. Third, different eligibility criteria and different definitions of high-risk patients in the studies limit the possibility of direct comparisons between studies. Fourth, the inclusion of multiple treatment regimens in this meta-analysis, including different CDK4/6i and dosing regimens, prevented us from determining which was optimal. Therefore, large-scale RCTs are still needed to verify the relevant results. Overall, this meta-analysis has reported some meaningful conclusions that may provide new references for CD4/6i combined ET therapy in HR+ and HER2– BC populations.

Conclusion

This meta-analysis found that for unresectable locally advanced or metastatic HR+, HER2– BC, CDK4/6i combined with ET can significantly prolong PFS and OS and increase the incidence of ORR, DCR, and CBR when compared with other treatments. For early HR+, HER2– BC, CDK4/6i combined with ET improved ORR and iDFS but did not affect pCR, DRFS, and OS. Safety analysis showed that AEs of any grade and grade 3 or above caused by CDK4/6i combined with ET were mainly manifested in neutropaenia, leukopaenia, anaemia, thrombocytopaenia, and fatigue and were generally safe and manageable.

Ethical approval and consent to participate
Not applicable.

Consent to publish
Not applicable.

Availability of data and materials
Data supporting findings reported in this study are available in the supplementary materials.

Conflict of interests
The authors declare no conflict of interest.

Funding
The authors received no financial support in conducting this meta-analysis.

Acknowledgments
Not applicable.

Authors' contributions
Y.S. designed the research process. T.H. searched the database for corresponding articles and drafted the meta-analysis. Y.H. extracted useful information from the articles above. C.Y. used statistical software for analysis. FM polished this article. All authors contributed to manuscript revision, read, and approved the submitted version.

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