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CDK4/6 inhibitors plus endocrine therapy vs. placebo plus endocrine therapy for HR+/HER2- advanced breast cancer: a phase III RCTs based meta-analysis

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Abstract

Background Does incorporating Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors into endocrine therapy (ET) effectively enhance survival outcomes, notably overall survival (OS), among individuals with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer? This remains a clinical controversy. We compared the antitumor efficacy and adverse effects (AEs) between CDK4/6 inhibitors + ET (CET) and placebo + ET (PET) by conducting a phase III randomized controlled trials (RCTs) based meta-analysis.

Methods Seven databases were searched to identify eligible studies, comprising Phase III RCTs comparing CET to PET. The primary endpoints were OS and progression-free survival (PFS), with secondary endpoints including responses and adverse events (AEs).

Results Seven RCTs (DAWNA-2, MONALEESA-2, MONALEESA-3, MONALEESA-7, MONARCH-3, PALOMA-2, and PALOMA-4) were included. The CET group exhibited significantly improved OS (HR: 0.81 [0.74, 0.88]), PFS (HR: 0.57 [0.52, 0.63]), objective response rate (RR: 1.31 [1.20, 1.43]), and clinical benefit rate (RR: 1.11 [1.07, 1.15]). These benefits were consistent across almost all subgroups. Additionally, the CET group showed better overall survival rates (OSR) from 24 to 60 months (OSR 24–60 m) and progression-free survival rates (PFSR) from 6 to 60 months (PFSR 6–60 m). However, more total AEs, grade 3–5 AEs, and serious AEs were found in CET group. The top 5 grade 3–5 AEs in the CET group were neutropenia (59.39%), leukopenia (24.11%), decreased white blood cell count (12.99%), hypertension (7.03%), and increased alanine aminotransferase (5.91%).

Conclusions The superiority of CET over PET in HR+/HER2- advanced breast cancer is evident, showing improved survival and responses. Nonetheless, the higher incidence of AEs, specifically hematologic AEs, requires cautious attention.

Keywords CDK4/6 inhibitors, Endocrine therapy, Breast Cancer, Meta-analysis, Randomized controlled trials

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Introduction

For decades, breast cancer has been the most prevalent cancer worldwide, with approximately 2.26 million new cases diagnosed annually [1]. However, the five-year survival rate for hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer patients still remains below 30% [2, 3]. These tumors predominantly rely on hormonal signaling for cell survival and proliferation, representing over 70% of breast cancer cases in clinical settings. This underscores the importance of endocrine therapy (ET) for these patients [4]. However, research indicates that approximately one-third of HR+patients experience a relapse within 15 years following ET. Additionally, initial ET fails to benefit 50% of HR+breast cancer patients [5]. Consequently, the exploration of new therapeutic strategies in conjunction with ET is imperative.

Recently, Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors have become a focal point for breast cancer [6]. CDKs are essential regulators of the tumor cell cycle, controlling cell proliferation through a series of enzymatic reactions [7]. One key mechanism underlying resistance to ET in HR+patients is the cyclin D-CDK4/6 signaling pathway activated by the estrogen pathway [8]. Consequently, the combination of CDK4/6 inhibitors with ET has emerged as a new treatment method for patients with HR+/HER2- breast cancer. Commonly used CDK4/6 inhibitors in clinical practice (Dalpiciclib, Palbociclib, Ribociclib, and Abemaciclib) have been proven effective, although results (survival, and adverse events [AEs]) vary across different studies [9–15].

Therefore, this study (a phase III randomized controlled trial [RCT]-based meta-analysis) aimed to assess and compare the efficacy of CDK4/6 inhibitors+ET versus placebo+ET for HR+/HER2- breast cancer patients.

Materials and methods

Search strategy

We searched PubMed, Scopus, EMBASE, ScienceDirect, Ovid MEDLINE, the Cochrane Library, and Web of Science from their inception until April 1, 2024, as detailed in Table S1. The search utilized keywords such as 'CDK4/6 Inhibitors' (including Palbociclib, Ribociclib, Abemaciclib, and Dalpiciclib), 'Randomized' (Randomized OR Randomly OR Randomised), and 'Breast Cancer'. Furthermore, we reviewed the references of the selected RCTs to identify additional pertinent research.

Selection criteria

The studies selected for inclusion were published in English and adhered to the PICOS criteria:

(1) Participants: patients diagnosed with HR+/HER2- advanced breast cancer.

(2) Intervention: CDK4/6 inhibitors+ET, defined as the CET group.

(3) Control: placebo+ET, defined as the PET group.

(4) Outcomes: survival, responses, and AEs.

(5) Study design: phase III RCTs.

Studies lacking original data, such as meta-analyses, conference presentations, and case studies, were omitted. Various articles stemming from a single RCT that reported different results were evaluated. For outcomes that were the same, only the latest findings were incorporated.

Data extraction

The extracted data include: study characteristics (including registration number and study duration), patient particulars (menopausal status, ECOG PS, etc.), treatment details (CDK4/6 inhibitor utilized, ET utilized, etc.), cancer attributes (hormone receptor status, etc.), antitumor efficacy (overall survival [OS], objective response rate [ORR], etc.), and adverse event frequencies (total AEs, etc.). Two researchers independently gathered the data, and any inconsistencies were settled by deliberation.

Outcome assessments

The main endpoints examined in this investigation were OS and PFS. Additionally, we assessed the overall survival rate (OSR) and progression-free survival rate (PFSR) at intervals of 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months. We also examined OS and PFS within specific subgroups. These subgroups included variables such as age, race category, menopausal status, hormone receptor status, ECOG PS, disease-free interval, number of metastatic sites, presence of liver or lung metastases, presence of bone-only disease, choice of CDK4/6 inhibitor therapy partner, choice of endocrine therapy partner, history of previous adjuvant or neoadjuvant ET, type of previous ET, and history of previous neoadjuvant or adjuvant chemotherapy.

Quality assessment

The quality of RCTs was evaluated using the Jadad scale, assessing randomization, blinding, and inclusion of patients based on a scale of five points. Trials achieving a score of three or higher were deemed of high quality [16]. Additionally, the Cochrane Risk of Bias Assessment Tool was employed to evaluate biases related to selection, performance, detection, attrition, and reporting. Risks were classified as low, unclear, or high, and depicted in a bias graph [17].

Moreover, the GRADE approach was applied to analyze result quality, examining bias, indirectness, imprecision, and publication bias. This method ranks certainty across four levels: very low, low, moderate, and high [18].

Statistical analysis

This meta-analysis was performed according to PRISMA guidelines (Table S2). Data was analyzed via Review Manager 5.3. Data on survival employed hazard ratios (HRs), which indicated an advantage for the CET group when HR was less than 1. Risk ratios (RRs) were used for dichotomous variables, RR>1 favored the PET group in the analysis of AEs. Conversely, in analyzing OSR and PFSR, RR>1 favored the CET group. To assess heterogeneity, the I^2 statistic and $\chi 2$ test were utilized. Low heterogeneity, indicated by I^2 being less than 50% or p-value greater than 0.1, led to the employment of a fixed-effects model. In contrast, a random-effects model was implemented. The determination of statistical significance was based on p-values less than 0.05. Publication bias was assessed visually using funnel plots. (Registered in PROSPERO: CRD42024539851)

Results

Search results

The analysis included twenty-six studies from seven RCTs (DAWNA-2, MONALEESA-2, MONALEESA-3, MONALEESA-7, MONARCH-3, PALOMA-2, and PALOMA-4) (Fig. 1) [9–15, 19–37]. Table 1 presents baseline information of the seven RCTs. The CET group comprised 2,103 patients, while the PET group comprised 1,463 patients. Of the RCTs, five (MONALEESA-2, MONALEESA-3, MONALEESA-7, MONARCH-3, and PALOMA-2) were global multicenter, one (PALOMA-4) was Asia multicenter, and one (DAWNA-2) was China multicenter. All seven phase III RCTs were deemed of high quality (Figure S1 and Table S3). According to the GRADE approach, the outcomes were assessed as medium to high quality (Table S4).

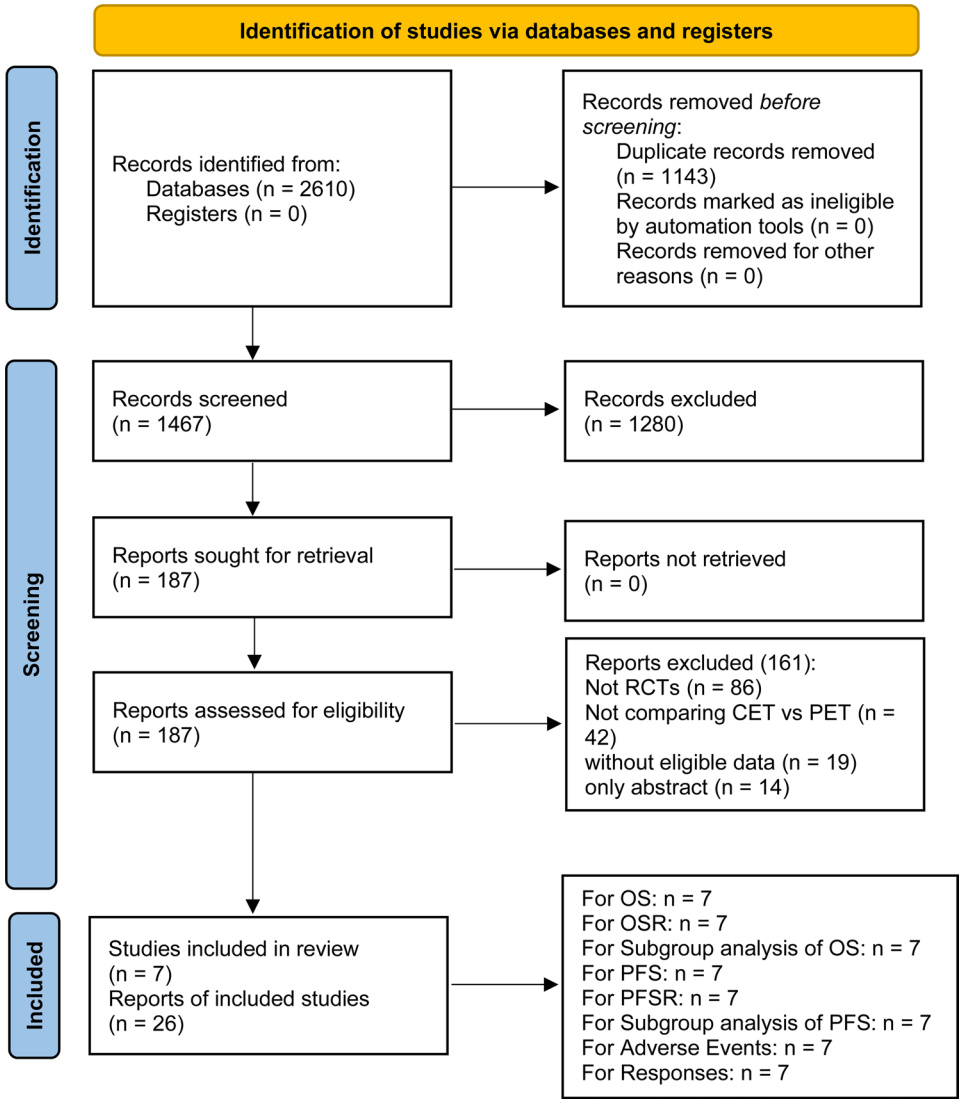

Fig. 1 Study selection flow

Table 1 Characteristics of the included studies

Study	Register number	Phase	Period	Groups	Patients	Age (Mean, year)	CDK4/6 inhibitor	Endocrine therapy	Menopausal status		ECOG PS			Hormone receptor status		Follow up (months)
									Post-M	Pre-M	0	1	2	ER+	PR+	
DAWNA-2 [9]	NCT03966898	III	2019.07-2020.12	CET group	303	55	Dalpiciclib	Letrozole or Anastrozole	183	120	141	161	0	302	258	21.6
				PET group	153	55			99	54	69	84	0	153	134	
MONALEESA-2 [10,19–23]	NCT01958021	III	2014.01-2015.03	CET group	334	62	Ribociclib	Letrozole	334	0	205	129	0	332	271	80.0
				PET group	334	63			334	0	202	132	0	333	278	
MONALEESA-3 [11,24–26]	NCT02422615	III	2015.06-2016.06	CET group	237	63	Ribociclib	Fulvestrant	237	0	152	92	0	236	173	70.8
				PET group	128	63			128	0	77	44	0	127	88	
MONALEESA-7 [12,27,28]	NCT02278120	III	2014.12-2016.08	CET group	288	43	Ribociclib	Tamoxifen or Letrozole or Anastrozole	0	288	211	75	0	285	249	53.5
				PET group	290	45			0	290	219	67	1	288	248	
MONARCH-3 [13,29–32]	NCT02246621	III	2014.11-2015.11	CET group	328	63	Abemaciclib	Letrozole or Anastrozole	328	0	192	136	0	328	255	70.2
				PET group	165	63			165	0	104	61	0	165	127	
PALOMA-2 [14,33–37]	NCT02246621	III	2013.02-2014.07	CET group	444	62	Palbociclib	Letrozole	444	0	257	178	9	444	-	90.1
				PET group	222	61			222	0	102	117	3	222	-	
PALOMA-4 [15]	NCT02297438	III	2015.03-2020.08	CET group	169	54	Palbociclib	Letrozole	169	0	88	85	0	169	-	52.8
				PET group	171	54			171	0	81	90	0	171	-	

Abbreviations CET: CDK4/6 inhibitors plus endocrine therapy; CDK4/6: Cyclin-dependent kinase 4/6; ECOG PS: Eastern Cooperative Oncology Group Performance Status; M: Menopausal; PET: Placebo plus endocrine therapy

Survival (OS and PFS)

The CET group achieved better OS (HR: 0.81 [0.74, 0.88], $p<0.00001$) and PFS (HR: 0.57 [0.52, 0.63], $p<0.00001$) (Fig. 2). OSR 24–60 m significantly favored the CET group (Figure S2). Meanwhile, PFSR 6–60 m significantly favored the CET group (Figure S3). As survival prolonged, CET also exhibited a growing OS and PFS advantage over PET (Fig. 3).

Subgroup analysis of survival (OS and PFS)

We subgroup analyzed survival (OS and PFS) according to Age, Race category, Menopausal status, Hormone receptor status, ECOG PS, Disease-free interval, Metastatic status, CDK4/6 inhibitor therapy partner, ET partner, Previous adjuvant or neoadjuvant ET, Previous ET type, and Previous neoadjuvant or adjuvant chemotherapy. OS and PFS generally favored the CET group in all subgroups (Table 2).

Responses

In all patients, the ORR (RR: 1.31 [1.20, 1.43]) and clinical benefit rate (CBR, RR: 1.11 [1.07, 1.15]), along with partial response (PR, RR: 1.30 [1.19, 1.43]), were better in the CET group. Although the complete response (CR, RR: 1.53 [0.90, 2.59]) tended to favor the CET group, it lacked statistical significance. Conversely, the rate of stable disease (SD, RR: 0.90 [0.82, 0.98]) was higher in the PET group (Fig. 4).

Among patients with measurable disease, the ORR (RR: 1.31 [1.21, 1.42]), CBR (RR: 1.13 [1.08, 1.18]), and PR (RR: 1.29 [1.19, 1.41]) were better in the CET group. The CR (RR: 1.64 [0.93, 2.87]) tended to favor the CET group without statistical significance. The rate of SD (RR: 0.85 [0.77, 0.94]) was lower in the CET group (Figure S4).

Toxicity

In summary, the CET group resulted in more total AEs (RR: 1.05 [1.03, 1.06]), grade 3–5 AEs (RR: 2.96 [2.30, 3.81]), serious AEs (RR: 1.67 [1.37, 2.03]), AEs leading to treatment discontinuation (RR: 2.61 [1.88, 3.62]), AEs leading to dose reduction (RR: 11.70 [3.76, 36.36]), and AEs leading to dose interruption (RR: 5.67 [2.59, 12.43]). However, AEs leading to death (RR: 1.31 [1.21, 1.42]) were similar between the two groups (Fig. 5).

In the assessment of any grade AEs, more cases of neutropenia, decreased white blood cell count, leukopenia, nausea, fatigue, diarrhea, anemia, hyponatremia, thrombocytopenia, alopecia, vomiting, hypokalemia, cough, constipation, decreased appetite, abdominal pain, increased blood creatinine, rash, pruritus, urinary tract infection, hypokalaemia, stomatitis, pyrexia, prolonged electrocardiogram QT, dry skin, hypophosphataemia, dysgeusia, and oropharyngeal pain were observed in the CET group (Table S5). The top 5 any grade AEs were neutropenia (74.66%), decreased white blood cell count (49.55%), leukopenia (42.80%), nausea (37.54%), and fatigue (33.56%) (Table 3). Incidence rate of any grade interstitial lung diseases (ILDs) tended to be higher in the CET group without statistical significance (Figure S5).

In the assessment of grade 3–5 AEs, more cases of neutropenia, leukopenia, decreased white blood cell count, increased alanine aminotransferase, anemia,

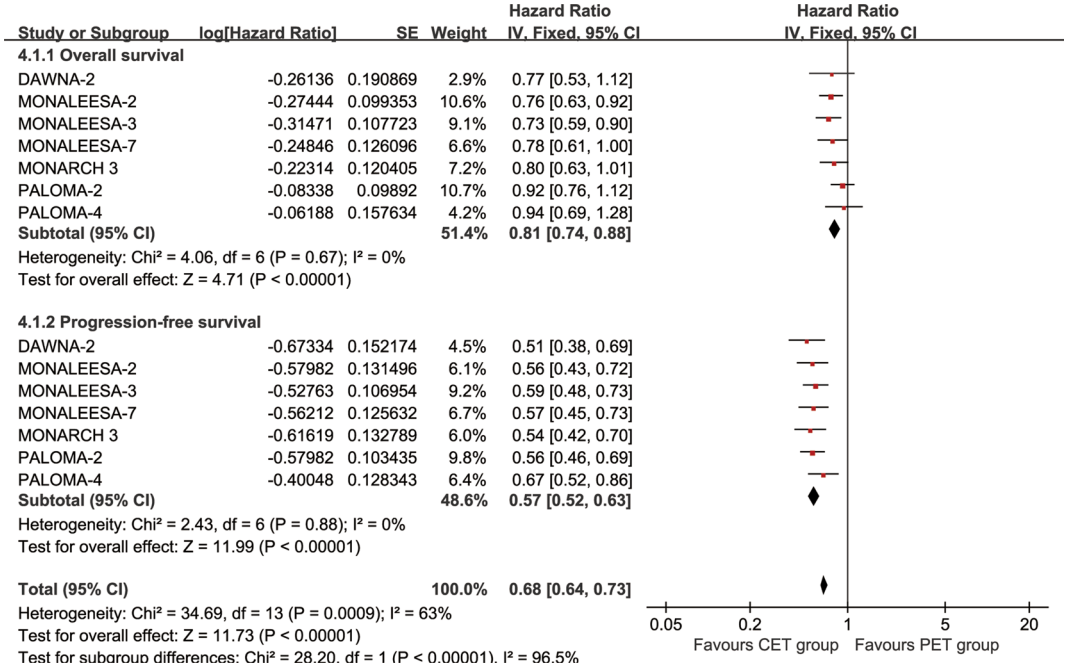

Fig. 2 Forest plots of overall survival and progression-free survival associated with CET group versus PET group

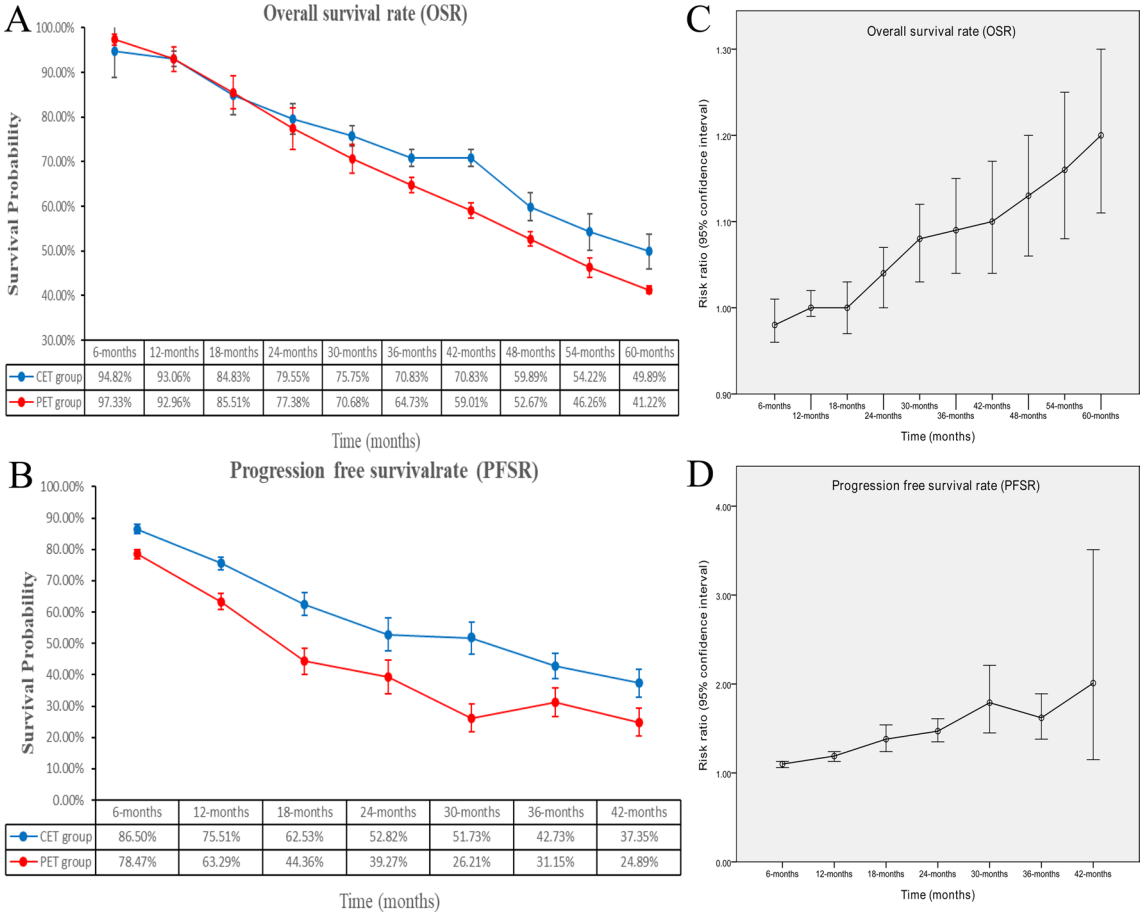

Fig. 3 Comparisons of overall survival rate (6–60 months, **A**: trend of overall survival rate; **C**: trend of risk ratios) and progression-free survival rate (6–42 months, **B**: trend of progression-free survival rate; **D**: trend of risk ratios) associated with CET group versus PET group

hyponatremia, increased aspartate aminotransferase, thrombocytopenia, diarrhea, fatigue, and decreased appetite were found in the CET group (Table S6). The top 5 grade 3–5 AEs were neutropenia (59.39%), leukopenia (24.11%), decreased white blood cell count (12.99%), hypertension (7.03%), and increased alanine aminotransferase (5.91%) (Table 4). Incidence rate of grade 3–5 ILDs also tended to be higher in the CET group without statistical significance (Figure S5).

Sensitivity analysis

Analysis of OSR-6 m, PFS (Asian race category), and Grade 3–5 AEs revealed notable heterogeneity. The stability and reliability of the results remained unaffected by the exclusion of any study, as demonstrated by sensitivity analysis (Figure S6).

Publication bias

Funnel plots were observed for survival (OS and PFS), OSR, responses, and AEs summary, suggesting acceptable publication bias (Fig. 6).

Discussion

Although ET has established itself as the standard treatment for HR+breast cancer patients, its widespread application has gradually unveiled issues of drug resistance, diminishing its benefits and prompting clinicians to explore more effective and rational treatment strategies. Recent studies have highlighted the link between HR+/HER2- breast cancer and abnormal activation of the cyclin D1-CDK4/6 pathway [38]. Notably, CDK4/6 inhibitors such as Palbociclib have garnered FDA approval for breast cancer treatment [39, 40]. The use of CDK4/6 inhibitors in combination with other agents has emerged as a significant focus of recent research. The Phase III trial PALOMA-2 demonstrated Palbociclib's ability to extend the median PFS of patients with advanced HR+breast cancer by over two years, underscoring its substantial efficacy in improving PFS outcomes [14]. Similarly, a study by Slamon et al. provided compelling evidence that Palbociclib in combination with letrozole significantly enhances PFS [37]. Furthermore, investigations have indicated that compared to the fulvestrant

Table 2 Subgroup analysis of overall survival and progression-free survival

Subgroups	No. of studies	Overall Survival		No. of studies	Progression-free survival	
		HR (95% CI)	*P*		HR (95% CI)	*P*
Total	7	0.81 [0.74, 0.88]	< 0.00001	7	0.57 [0.52, 0.63]	< 0.00001
Age						
< 65 years	4	0.79 [0.69, 0.91]	0.001	6	0.55 [0.49, 0.62]	< 0.00001
> 65 years	4	0.80 [0.69, 0.94]	0.007	6	0.55 [0.49, 0.62]	< 0.00001
Race category						
Asian	7	0.78 [0.66, 0.93]	0.005	6	0.51 [0.38, 0.70]	< 0.0001
Others	5	0.81 [0.73, 0.91]	0.0004	4	0.61 [0.53, 0.70]	< 0.00001
ECOG PS						
0	5	0.80 [0.67, 0.96]	0.02	7	0.56 [0.50, 0.64]	< 0.00001
1	5	0.78 [0.67, 0.90]	0.0009	7	0.57 [0.50, 0.66]	< 0.00001
Menopausal status						
Postmenopausal	4	0.78 [0.70, 0.88]	< 0.00001	6	0.58 [0.52, 0.64]	< 0.00001
Premenopausal or perimenopausal	1	0.78 [0.61, 1.00]	0.05	2	0.56 [0.45, 0.70]	< 0.00001
Hormone receptor status						
ER positive + PR positive	4	0.80 [0.70, 0.90]	0.0004	4	0.58 [0.50, 0.67]	< 0.00001
Others	4	0.63 [0.51, 0.79]	< 0.0001	4	0.39 [0.29, 0.52]	< 0.00001
Disease-free interval						
De-novo metastatic disease	4	0.69 [0.48, 1.01]	0.06	6	0.50 [0.42, 0.60]	< 0.00001
Existing disease	3	0.89 [0.76, 1.03]	0.12	4	0.58 [0.49, 0.68]	< 0.00001
Number of metastatic sites						
< 3	3	0.77 [0.66, 0.90]	0.001	3	0.59 [0.49, 0.71]	< 0.00001
> 3	5	0.81 [0.70, 0.94]	0.004	5	0.55 [0.47, 0.64]	< 0.00001
Visceral metastases at study entry						
Yes	2	0.81 [0.66, 0.99]	0.04	4	0.61 [0.52, 0.72]	< 0.00001
No	1	0.98 [0.74, 1.30]	0.89	3	0.53 [0.43, 0.65]	< 0.00001
Presence of liver or lung metastases						
Yes	3	0.39 [0.10, 1.58]	0.19	3	0.57 [0.48, 0.67]	< 0.00001
No	3	0.72 [0.60, 0.86]	0.0003	3	0.58 [0.48, 0.71]	< 0.00001
Bone-only disease						
Yes	5	0.72 [0.58, 0.88]	0.002	5	0.50 [0.40, 0.64]	< 0.00001
No	4	0.81 [0.72, 0.91]	0.0004	4	0.59 [0.52, 0.67]	< 0.00001
CDK4/6 inhibitor therapy partner						
Dalpiciclib	1	0.77 [0.53, 1.12]	0.17	1	0.51 [0.38, 0.69]	< 0.00001
Ribociclib	3	0.75 [0.67, 0.85]	< 0.00001	3	0.58 [0.50, 0.66]	< 0.00001
Abemaciclib	1	0.80 [0.63, 1.01]	0.06	1	0.54 [0.42, 0.70]	< 0.00001
Palbociclib	2	0.93 [0.79, 1.09]	0.36	2	0.60 [0.51, 0.70]	< 0.00001
Endocrine therapy partner						
Letrozole	3	0.85 [0.75, 0.97]	0.01	5	0.58 [0.51, 0.65]	< 0.00001
Anastrozole	-	-	-	2	0.51 [0.37, 0.71]	< 0.0001
Fulvestrant	1	0.73 [0.59, 0.90]	0.003	1	0.59 [0.48, 0.73]	< 0.00001
Tamoxifen	1	0.70 [0.47, 1.04]	0.08	1	0.59 [0.39, 0.89]	0.01
Previous adjuvant or neoadjuvant endocrine therapy						
Yes	4	0.81 [0.70, 0.94]	0.005	5	0.57 [0.49, 0.66]	< 0.00001
No	5	0.79 [0.65, 0.96]	0.02	6	0.56 [0.49, 0.65]	< 0.00001
Previous endocrine therapy type						
Selective oestrogenreceptor modulator	2	0.88 [0.68, 1.14]	0.32	5	0.61 [0.51, 0.74]	< 0.00001
Aromatase inhibitors	2	0.58 [0.40, 0.83]	0.003	5	0.56 [0.47, 0.68]	< 0.00001
Previous neoadjuvant or adjuvant chemotherapy						
Yes	3	0.83 [0.70, 0.98]	0.03	3	0.58 [0.48, 0.70]	< 0.00001
No	3	0.79 [0.59, 1.06]	0.11	3	0.53 [0.43, 0.64]	< 0.00001

Abbreviations CET: CDK4/6 inhibitors plus endocrine therapy; CDK4/6: Cyclin-dependent kinase 4/6; CI: Confidence interval; ECOG PS: Participants, Intervention, Control, Outcome and Study design Performance Status; HR: Hazard ratio; PET: Placebo plus endocrine therapy

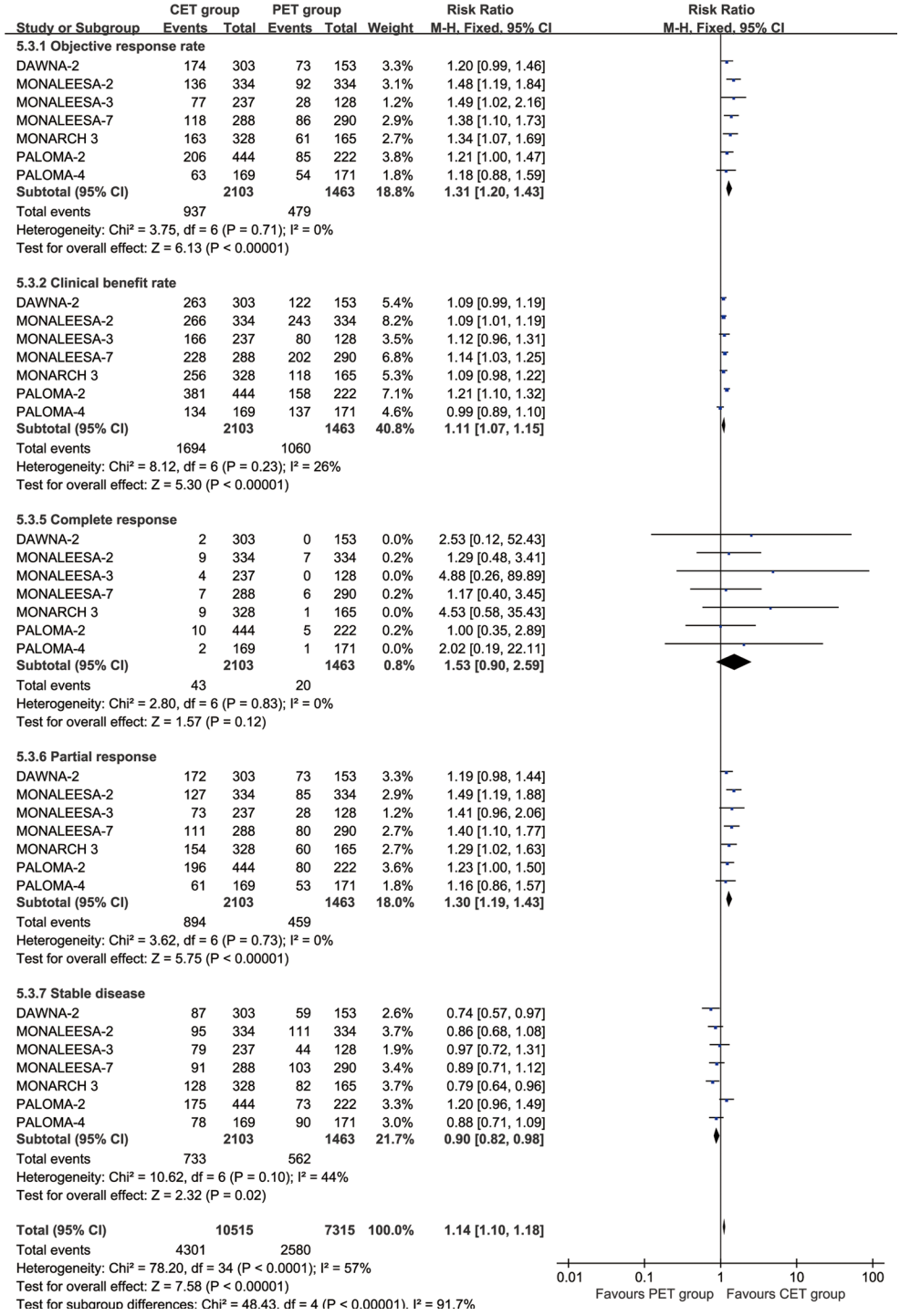

Fig. 4 Forest plots of responses associated with CET group versus PET group in all patients

monotherapy group, the Ribociclib+fulvestrant combination therapy group exhibits significantly prolonged PFS [12].

This study further confirms the potential benefits of CET for HR+/HER2- breast cancer patients in terms of OS and PFS. However, previous clinical trials have yielded inconsistent OS data, leading to controversy regarding whether OS benefits are achieved. Notably, OS outcomes in combined drug treatment groups in the PALOMA-1 and PALOMA-3 studies did not demonstrate statistically significant differences. Nevertheless, recent updates from the MONALEESA-7 and MONALEESA-3 studies suggest significantly better OS for HR+/HER2- breast cancer in the CET group [11, 12, 41, 42].

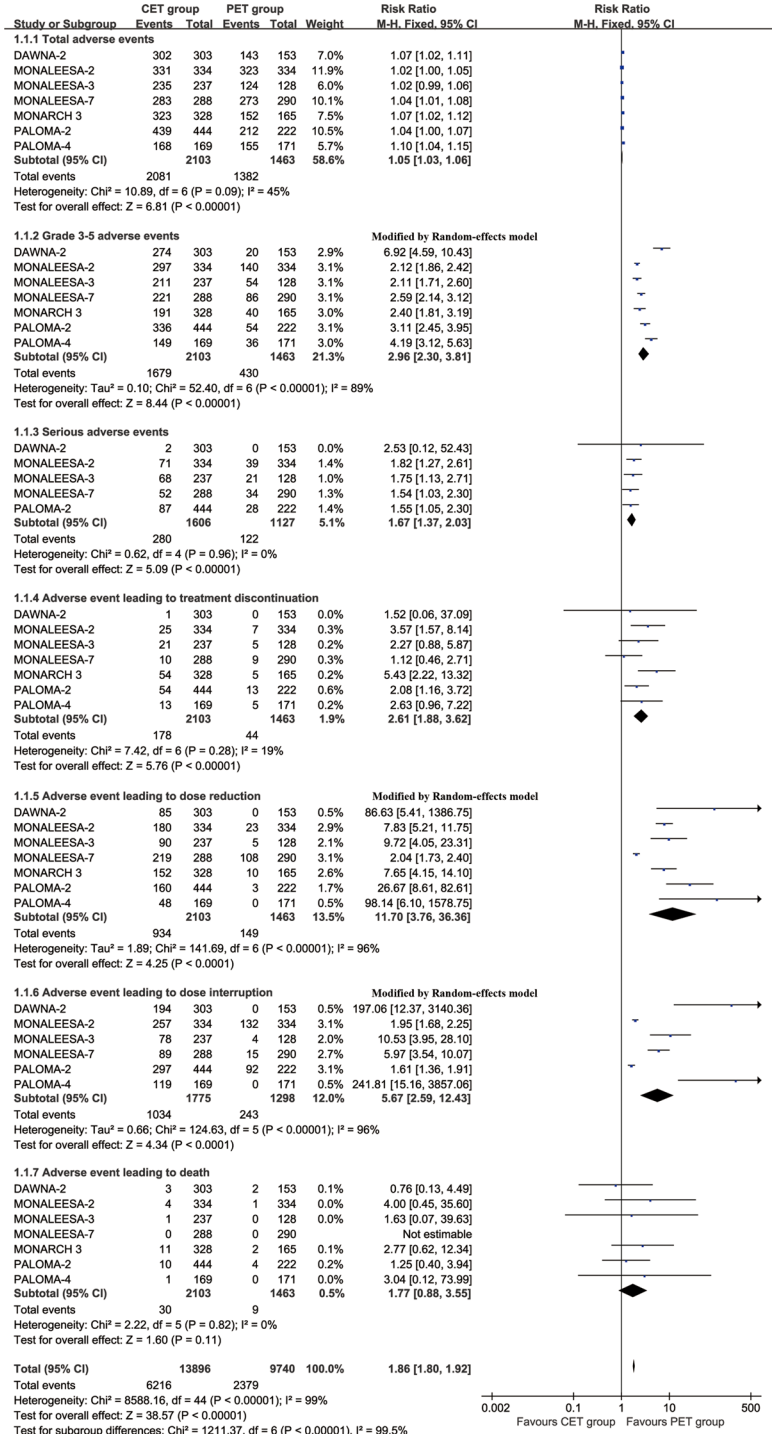

Fig. 5 Forest plots of adverse events summary associated with CET group versus PET group

In exploratory analyses of other secondary factors, this study found that CET significantly improved the ORR in the Intent-to-Treat (ITT) population. Incorporating data from MONALEESA-7 and MONALEESA-3 did not alter the overall conclusions of the study, and the consistency between these study results increased the reliability of the research. Furthermore, the analysis also confirmed that combined medication can increase the clinical benefit rate, with statistically significant differences observed [26, 32]. This contrasts with another meta-analysis, which indicated no significant differences, suggesting that the variation between the two study outcomes may be related to more comprehensive data updates. As of now, the MONALEESA-3 study, which has enrolled the

Table 3 Any grade adverse events (> 20% in the CET group)

Adverse events	Studies involved	CET group		PET group		Risk ratio [95% CI]	*P*
		Event/total	%	Event/total	%		
Neutropenia	7	1570/2103	74.66%	106/1463	7.25%	10.92 [7.62, 15.65]	< 0.00001
White blood cell count decreased	2	328/662	49.55%	50/499	10.02%	4.93 [1.74, 13.99]	0.003
Leukopenia	7	900/2103	42.80%	79/1463	5.40%	7.41 [5.69, 9.66]	< 0.00001
Nausea	6	726/1934	37.54%	301/1292	23.30%	1.67 [1.47, 1.90]	< 0.00001
Fatigue	6	604/1800	33.56%	359/1310	27.40%	1.18 [1.05, 1.32]	0.003
Diarrhea	7	697/2103	33.14%	288/1463	19.69%	1.51 [1.16, 1.96]	0.002
Anemia	7	670/2103	31.86%	122/1463	8.34%	3.64 [2.57, 5.14]	< 0.00001
Hypercalcemia	1	96/328	29.27%	50/165	30.30%	0.97 [0.73, 1.29]	0.81
Hyponatremia	1	90/328	27.44%	37/165	22.42%	1.22 [0.88, 1.71]	0.24
Thrombocytopenia	4	328/1204	27.24%	27/836	3.23%	7.59 [4.86, 11.86]	< 0.00001
Alopecia	6	472/1800	26.22%	159/1310	12.14%	2.10 [1.78, 2.48]	< 0.00001
Arthralgia	7	550/2103	26.15%	409/1463	27.96%	0.98 [0.88, 1.09]	0.61
Hot flush	4	305/1303	23.41%	275/974	28.23%	0.86 [0.71, 1.05]	0.05
Headache	5	375/1631	22.99%	257/1139	22.56%	1.05 [0.87, 1.26]	0.50
Vomiting	6	436/1934	22.54%	192/1292	14.86%	1.63 [1.18, 2.25]	0.003
Hypokalemia	2	110/497	22.13%	29/336	8.63%	2.25 [1.51, 3.35]	< 0.0001
Hypocalcemia	1	72/328	21.95%	28/165	16.97%	1.29 [0.87, 1.92]	0.20
Cough	5	320/1472	21.74%	201/1145	17.55%	1.21 [1.03, 1.42]	0.02
Aspartate aminotransferase increased	5	308/1422	21.66%	167/1113	15.00%	1.50 [0.94, 2.41]	0.0002
Constipation	5	349/1631	21.40%	182/1139	15.98%	1.37 [1.16, 1.62]	0.0001
Alanine aminotransferase increased	5	301/1422	21.17%	165/1113	14.82%	1.55 [0.90, 2.66]	0.11
Back pain	5	331/1631	20.29%	229/1139	20.11%	1.04 [0.89, 1.21]	0.64

Abbreviations CET: CDK4/6 inhibitors plus endocrine therapy; CI: Confidence interval; PET: Placebo plus endocrine therapy; RR: Risk ratio

Table 4 Grade 3–5 adverse events (> 1% in the CET group)

Adverse events	Studies involved	CET group		PET group		Risk ratio [95% CI]	*P*
		Event/total	%	Event/total	%		
Neutropenia	7	1249/2103	59.39%	20/1463	1.37%	42.16 [20.45, 86.90]	< 0.00001
Leukopenia	7	507/2103	24.11%	7/1463	0.48%	27.95 [12.00, 65.11]	< 0.00001
White blood cell count decreased	2	86/662	12.99%	3/499	0.60%	21.99 [6.99, 69.19]	< 0.00001
Hypertension	3	65/925	7.03%	57/777	7.34%	1.11 [0.79, 1.54]	0.55
Alanine aminotransferase increased	5	84/1422	5.91%	15/1113	1.35%	3.51 [1.31, 9.44]	0.01
Hypokalemia	2	25/497	5.03%	4/336	1.19%	3.06 [0.04, 240.13]	0.62
Anemia	7	105/2103	4.99%	25/1463	1.71%	2.45 [1.54, 3.89]	< 0.00001
Hyponatremia	1	16/328	4.88%	0/165	0.00%	16.65 [1.01, 275.82]	0.05
Aspartate aminotransferase increased	5	54/1422	3.80%	13/1113	1.17%	3.38 [1.84, 6.21]	< 0.0001
Thrombocytopenia	4	33/1204	2.74%	4/836	0.48%	4.45 [1.41, 14.02]	0.001
Diarrhea	7	51/2103	2.43%	10/1463	0.68%	2.53 [1.16, 5.53]	0.0008
Electrocardiogram QT prolonged	3	18/760	2.37%	3/614	0.49%	2.85 [0.81, 9.95]	0.03
Pneumonia	1	6/303	1.98%	1/153	0.65%	3.03 [0.37, 24.94]	0.30
Fatigue	6	33/1800	1.83%	5/1310	0.38%	3.76 [1.62, 8.76]	0.002
Dyspnea	2	13/778	1.67%	5/556	0.90%	1.77 [0.38, 8.34]	0.20
Back pain	5	27/1631	1.66%	9/1139	0.79%	2.10 [0.97, 4.52]	0.03
γ-Glutamyltransferase increased	3	12/760	1.58%	13/614	2.12%	0.72 [0.33, 1.61]	0.52
Vomiting	6	27/1934	1.40%	12/1292	0.93%	1.39 [0.49, 3.91]	0.14
Hypokalaemia	1	4/303	1.32%	0/153	0.00%	4.56 [0.25, 84.14]	0.31
Asthenia	3	13/1035	1.26%	0/665	0.00%	4.66 [0.82, 26.49]	0.04
Abdominal pain	3	13/1060	1.23%	3/677	0.44%	2.19 [0.67, 7.18]	0.16
Blood creatinine increased	2	7/631	1.11%	0/318	0.00%	7.57 [0.43, 131.71]	0.16
Dyspnoea	1	3/288	1.04%	1/290	0.34%	3.02 [0.32, 28.87]	0.34

Abbreviations: CET: CDK4/6 inhibitors plus endocrine therapy; CI: Confidence interval; PET: Placebo plus endocrine therapy; RR: Risk ratio

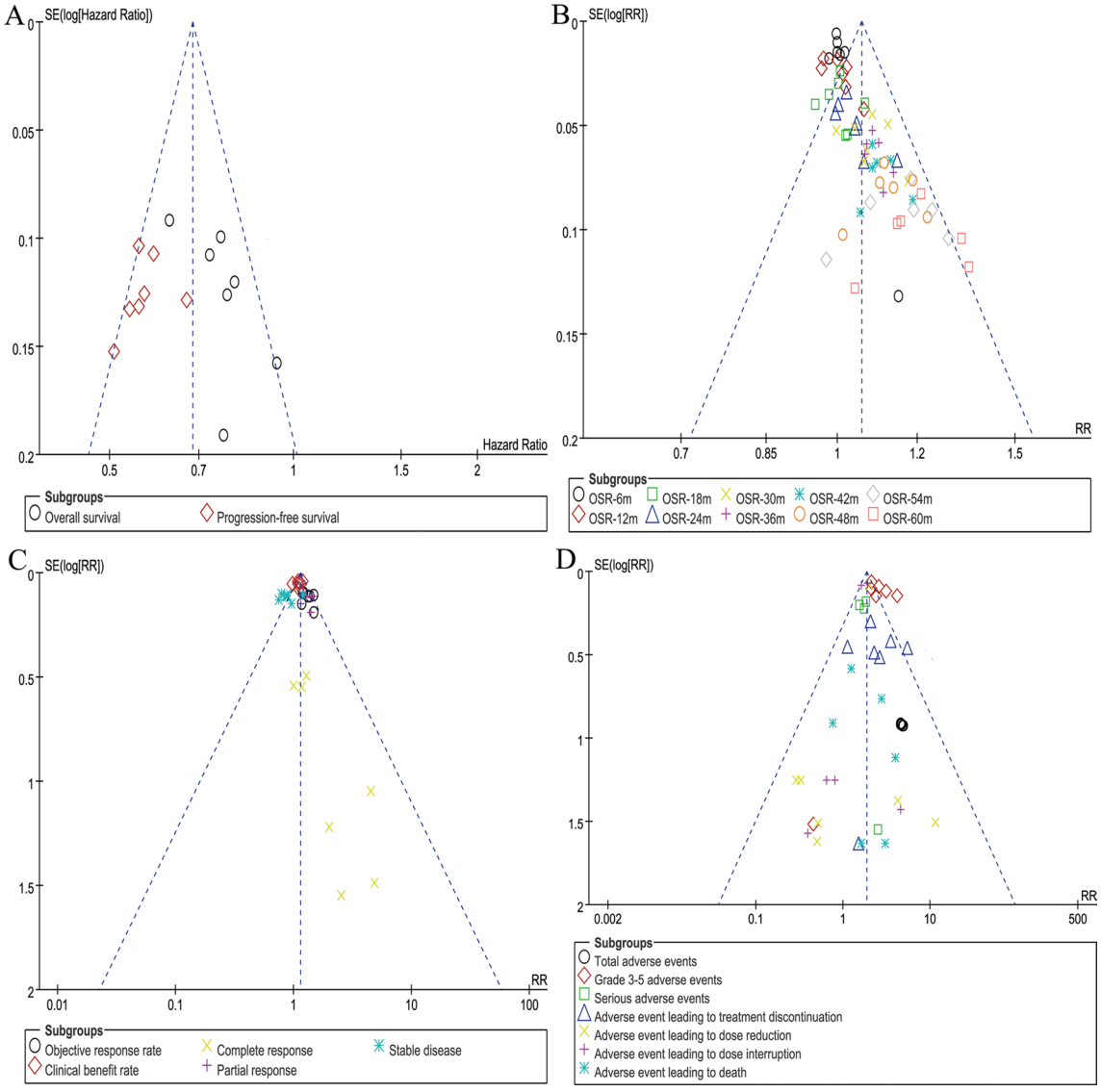

Fig. 6 Funnel plots of survival summary (**A**), OSR (**B**), responses (**C**), and AEs summary (**D**) associated with CET group versus PET group

most patients, indicates that Ribociclib combined with fulvestrant, compared to fulvestrant alone, offers a higher ORR and a clear PFS benefit advantage, consistent with the results of this study [26]. These findings underscore the significant impact of CET on the efficacy for patients with HR+/HER2- breast cancer.

The subgroup analysis indicate consistent improvement in OS and PFS prognosis across the included subgroups, even though some subgroups did not show statistically significant differences in OS. A systematic review conducted by Piezzo et al. demonstrated that CDK4/6 inhibitors improved PFS prognosis regardless of the presence of metastases, including bone metastases [43]. This result aligns with our findings, suggesting that CET is particularly effective for patients with visceral metastases. However, when considering OS outcomes, the study by Lin et al. suggested OS benefits for patients with visceral metastases [44]. In contrast, our study's results indicated that patients with bone metastases also experienced improved OS prognosis. Nonetheless, it's essential to acknowledge that the number of studies and total patient numbers varied across subgroups, suggesting potential bias. Therefore, further expansion of the study population is warranted to validate these findings. Importantly, our study found that patients who had previously received ET exhibited similar OS and PFS benefits compared to those who had not undergone adjuvant or neoadjuvant ET. Preclinical research suggested cyclin D-CDK4/6-retinoblastoma pathway changes link to breast cancer's endocrine resistance. Thus, the CET could potentially offer clinical efficacy to the patients with HR+/HER2- breast cancer experiencing progression after ET [38].

In terms of safety, our results suggested that CET increased the incidence rates of neutropenia, decreased white blood cell count, leukopenia, and anemia in both any grade and grade 3–5 AEs. This suggests that CDK4/6 inhibitors may contribute to a higher frequency of hematotoxic AEs, with neutropenia being the most common, occurring at rates of 74.66% in any grade and 59.39% in grade 3–5, significantly higher than other adverse event rates. However, unlike chemotherapy drugs that induce DNA damage and cell apoptosis, CDK4/6 inhibitors primarily inhibit progenitor cells of neutrophils, thereby arresting the cell cycle and causing neutropenia, which often resolves quickly upon discontinuation of the CDK4/6 inhibitors [45]. This highlights the controllability of Neutropenia risk associated with CDK4/6 inhibitors, with no severe death events reported due to Neutropenia. Nonetheless, close monitoring of patients' blood counts is still essential during CDK4/6 inhibitor use to promptly prevent or manage serious AEs [46]. The incidence of Grade 3–5 hypertension is higher in the CET group, highlighting the importance of monitoring blood pressure, managing thromboembolic risks, and addressing cardiovascular health in patients undergoing CDK4/6 inhibitor therapy. Meanwhile, in CDK4/6 inhibitor therapy, interstitial lung disease (ILD) is a rare but serious adverse event that requires close monitoring. In our analysis, the incidence of ILD is higher in the CET group (without statistical significance). To effectively manage ILD, it is recommended to conduct baseline lung function assessments and high-resolution chest CT scans before treatment, and regularly monitor respiratory symptoms and lung function changes during treatment [47]. If suspected ILD symptoms occur, treatment should be immediately paused, and further lung evaluations and appropriate medical interventions should be carried out [48].

Limitations of this study: (1) Including only English articles may introduce language bias; (2) The research includes fewer than 10 studies, and although a funnel plot test did not show significant publication bias, accurately determining publication bias results remains challenging. (3) No individual patient data hindered patient-level meta-analysis, possibly reducing clinical value. (4) Differences in follow-up times among RCTs may increase data heterogeneity.

Conclusion

CET appears to outperform PET in HR+/HER2- advanced breast cancer, demonstrating improved survival (OS and PFS) and responses. Survival benefits were consistent across most subgroups. However, the increased incidence of AEs, particularly hematologic AEs, requires careful consideration. Due to the limited number and quality of included studies, these conclusions require further validation through high-quality research.

Abbreviations

AEs	Adverse effects
CBR	Clinical benefit rate
CET	CDK4/6 inhibitors plus endocrine therapy
CDK4/6	Cyclin-dependent kinase 4/6
CI	Confidence interval
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ER+	Estrogen receptor-positive
ET	Endocrine therapy
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HER2-	Human epidermal growth factor receptor 2-negative
HR	Hazard ratio
HR+	Hormone receptor-positive
ITT	Intent-to-Treat
ORR	Objective response rate
OS	Overall survival
OSR	Overall survival rate
PFS	Progression-free survival
PFSR	Progression-free survival rate
PET	Placebo plus endocrine therapy
PICOS	Participants, Intervention, Control, Outcome and Study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PR	Partial response
PR+	Progesterone receptors-positive
SD	Stable disease
RCT	randomized controlled trial
RR	Risk ratio

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

Supplementary Material 11

Supplementary Material 12

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Author contributions

Zhongkui Jin had full access to all of the data in the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Cailu Luo, Kunlin Yu, Xiaodan Luo, Tao Lian, Xuejuan Liu, Wang Xu, and Zhongkui Jin. Acquisition, analysis, or interpretation of data: Cailu Luo, Kunlin Yu, Xiaodan Luo, Tao Lian, Xuejuan Liu, Wang Xu, and Zhongkui Jin. Drafting of the manuscript: Cailu Luo, Kunlin Yu and Zhongkui

Jin. Critical revision of the manuscript for important intellectual content: Cailu Luo, Kunlin Yu, and Zhongkui Jin. Statistical analysis: Cailu Luo, Kunlin Yu, and Xiaodan Luo. Supervision: Cailu Luo, Kunlin Yu, and Zhongkui Jin.

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Data availability
The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Declarations

Consent for publication
Not Applicable.

Ethical approval
Due to the nature of this study no ethical approval was required.

Informed consent
For this type of study formal consent is not required.

Competing interests
The authors declare no competing interests.

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