BMC Cancer

SYSTEMATIC REVIEW

Open Access

Efficacy and safety of first-line CDK4/6 inhibitors plus AI therapy for patients with HR +/HER2- advanced breast cancer: a network meta-analysis

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Abstract

Background CDK4/6 inhibitors plus aromatase inhibitors (AI) significantly improve the therapeutic effect of initial treatment for HR + /HER2- advanced breast cancer. However, there is a lack of head-to-head randomized controlled trials involving the four CDK4/6 inhibitors in current clinical treatments. This article aims to compare the efficacy and safety of the four CDK4/6 inhibitors in previously untreated HR + /HER2- advanced breast cancer for a better clinical medication selection.

Methods We performed a systematic search on databases published up to May 19, 2024 in the PubMed, Embase, and Cochrane library, and we focused on the data of phase II/III trials that met inclusion criteria. Pooled data on progression-free survival (PFS), objective response rate (ORR), clinical benefit rate (CBR), all adverse events (AE), and 3/4 adverse events were analyzed using the fixed-effect consistency models.

Results Dalpiciclib plus AI showed the best survival benefit in PFS (SUCRA value 77.9%) for all patients. In terms of ORR and CBR, Abemaciclib plus AI were ranked the best benefit (89.3% and 68.9%, respectively). Furthermore, Abemaciclib plus AI was ranked at the top for prolonging PFS in majority of the subgroups. In terms of AEs and grade 3/4 AEs, dalpiciclib plus AI had the greatest probability (91.3% and 99.8%). Ribociclib plus AI had lowest adverse events (29.3%), and grade 3/4 adverse events of abemaciclib plus AI were the least (26.2%).

Conclusion There was no statistically significant difference in PFS among the four CDK4/6 inhibitors. Dalpiciclib has the best therapeutic effect in PFS. Meanwhile, dalpiciclib has the highest risk of adverse events and the 3/4 adverse events incidence compared with the others.

Keywords CDK4/6 inhibitors, Dalpiciclib, Breast cancer, Endocrine therapy

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Introduction

Global Cancer Observatory (GLOBOCAN) 2020 data estimated that female breast cancer (BC) is the leading cause of malignancy incidence worldwide in 2020 [1]. Great progress has been made in early diagnosis of breast cancer with only about 3% of cases diagnosed at an advanced stage, but the 5-year relative survival was 25% for patients diagnosed as advanced breast cancer, which was significantly lower than that of the early stage of cancer (almost 100% survival) [2–4]. The majority of breast cancer subtypes are hormone receptor(HR)-positive, for which endocrine therapy (ET) is the preferred initial treatment [5]. However, single-agent endocrine therapy eventually leads to drug resistance. Identification of new therapeutic targets is considered the major challenge and urgently needed.

The cyclin-dependent kinases(CDKs)-cyclin complexs are the critical mediator of cellular proliferation [6]. CDK4/6-cyclin D complex phosphorylates the retinoblastoma (Rb) protein, which releases E2F transcription factors, activates cell cycle progression genes, and makes cell cycle from G1 phase to S phase [7, 8]. CDK4/6 inhibitor competitively occupies the ATP binding pocket of CDK4 and CDK6 to prevent Rb phosphorylation, leading to cell cycle arrest [9], genotoxic stress, and DNA damage [10]. Several preclinical and clinical evidences indicated that CDK4/6 inhibition may be effective in overcoming endocrine resistance [11–13]. Currently, The NCCN Guidelines recommend three CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) incorporating AI as preferred first-line options in the HR +/HER2- metastatic breast cancer [14]. The DAWNA- 2 trial demonstrated that PFS was significantly improved in the dalpiciclib plus letrozole/anastrozole group versus placebo plus letrozole/anastrozole group(30.6 month vs 18.2 month) [15], and dalpicicilb was therefore included in the Guidelines for breast cancer diagnosis and treatment by China Anti-cancer Association (2024 edition) [16]. Although all CDK4/6 inhibitors shared the same primary mechanism and certain efficacy, there are considerable differences in pharmacology, dosing schedules, and toxicity among these agents [17–19]. Nowadays, four CDK 4/6 inhibitors have not been directly comparison head-to-head randomized controlled trials (RCTs) in patients with HR +/HER2- metastatic breast cancer.

In the current study, we compared the efficacy and safety of four CDK4/6 inhibitors as initial treatment for HR +/HER2- advanced breast cancer. Our studies provided critical insights for improving clinical medication decision for breast cancer treatment.

Methods

Search strategy

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, and our study protocol was registered on PROSPERO (CRD42022303986). We searched relevant literature from PubMed, Embase, and Cochrane Library published until May 19, 2024. To ensure data integrity, the relevant supplement or conference abstracts were also searched. Search terms included MeSH terms and free-text terms such as "breast neoplasms", "palbociclib", "ribociclib", "abemaciclib" and "dalpiciclib". Two authors assessed independently the eligibility of all trials, and disagreements were resolved through discussion to reach a consensus.

Selection criteria

The selection criteria were as follows: 1) the locally advanced or metastatic breast cancer patients pathologically proven HR-positive/HER2-negative; 2) previously untreated for metastatic breast cancer; 3) the treatment used CDK4/6 inhibitors plus AI vs AI; 4) data regarding progression-free survival (PFS) were available; and 5) prospective phase II or III non-single arm RCTs.

Date extraction and quality assessment

From the included studies, the following contents were extracted: title, sample sizes, patient characteristics, interventions, adverse events, and outcomes. Meanwhile, the risk of bias was assessed using the Cochrane collaboration's tool, including random sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessment, incomplete outcome data, selective reporting, and other biases. The studies were assigned high risk, low risk, or unclear risk, and exhibited by the Review Manager (version 5.4). Two independent authors assessed the data extracted from the eligible trials and their quality and disagreements were adjudicated through discussion to consensus.

Data synthesis and statistical analysis

We conducted pairwise meta-analyses for all direct comparisons in STATA. The I^2 statistical analysis and Q test were used to assess heterogeneity. If I^2 value is greater than 50% (significant heterogeneity), random effects model was chosen. If not, fixed effects model was chosen. PFS were reported by hazard ratio(HR), and the effect value of categorical variables was reported by odds ratios(OR), such as ORR, CBR, all AEs, and grade 3 to 4 AEs.

For indirect and mixed comparisons of HR, the network meta-analyses (NMA) were conducted using

Bayesian framework in WinBUGS (version 1.4). Three Markov chains ran 150,000 iterations in total utilizing WinBUGS model, and each chain ran 50,000, of which the first 5,000 iterations were used as the burn-in period. Model fit was showed by the deviance information criterion (DIC), and lower DIC implied better model. Due to lacking of closed-loop between various treatments, a consistency model was directly utilized for analysis. Strategies were ranked using rank grams and the surface under the cumulative ranking (SUCRA) probabilities. The closer SUCRA value was to 1, the better efficacy and the higher security risk of intervention. Moreover, we analysed different subgroups based on age, ECOG performance status score, visceral metastasis, previous endocrine therapy, de-novo metastatic disease, post-menopausal status, bone metastasis only, Asian, and aimed to assess the optimal therapy in different situations. *P*-values < 0.05 was deemed as statistical significance.

Result

Search studies

A total of 3231 records were identified through the search strategy, including 1509 in PubMed, 622 in Embase, 1100 in Cochrane Library. Among them, 952 records were repeated and removed. After screening titles and abstracts, 171 records were eligible for full text review. Finally, 18 records were selected as they met all inclusion criteria. Among these, 8 studies were included because data from the same trial were extracted from multiple records (Fig. 1).

Characteristics and quality of included studies

The included studies characteristics were reported in Table 1. Eight studies were performed for the comparisons with patients treated with CDK4/6 inhibitors (dalpiciclib, palbociclib, ribociclib, abemaciclib) plus AI versus AI only. In MONALEESA- 7, the results of

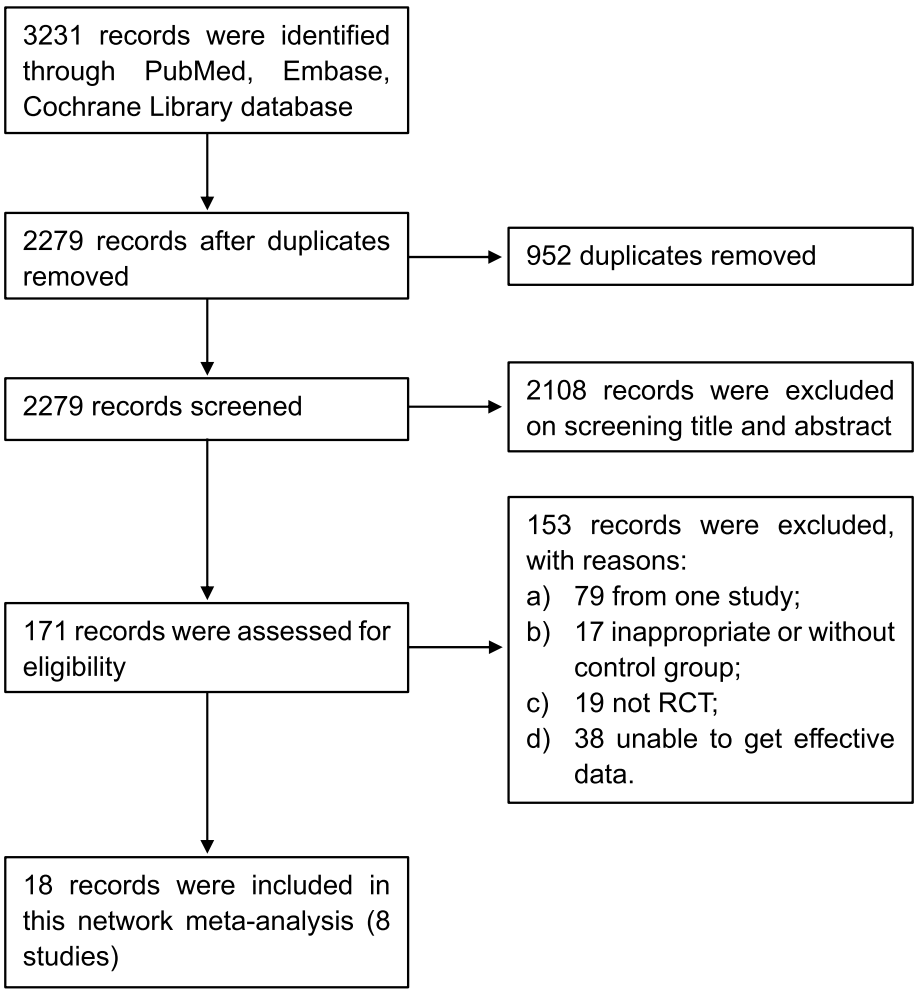


Fig. 1 The flow chart summarizing the process for the identification of the eligible studies

Table 1 Study characteristics of studies included in the network meta-analysis

Study	DAWNA- 2		PALOMA- 1		PALOMA- 2		PALOMA- 4		MONALEESA- 2		MONALEESA- 7		MONARCH- 3		MONARCH PLUS A	
Treatment	dalpi + AI	AI	palbo + letro	pla + letro	palbo + letro	pla + letro	palbo + letro	pla + letro	ribo + letro	pla + letro	ribo + AI	pla + AI	abema + NSAI	pla + NSAI	abema + NSAI	pla + NSAI
N	303	153	84	81	444	222	169	171	334	334	248	247	328	165	207	99
PFS (HR and 95%CI)	0.51(0.38–0.69)		0.49(0.32–0.75)		0.56(0.46–0.69)		0.68(0.53–0.87)		0.57(0.46–0.70)		0.57(0.44–0.74)		0.54(0.42–0.70)		0.50(0.35–0.72)	
OS (HR and 95%CI)	NA		0.90(0.62–1.29)		0.96(0.78–1.18)		NA		0.76(0.63–0.93)		0.80(0.62–1.04)		0.80(0.64–1.02)		NA	
ORR	174/303	73/153	36/84	27/81	187/444	77/222	63/169	54/171	142/334	96/334	NA		163/328	61/165	116/207	30/99
CBR	263/303	122/153	68/84	47/81	377/444	156/222	134/169	137/171	267/334	244/334	NA		256/328	118/165	171/207	62/99
De-novo metastatic disease (HR and 95%CI)	0.50(0.32–0.80)		NA		0.61(0.44–0.85)		0.54(0.31–0.96)		0.57(0.38–0.84)		NA		0.47(0.31–0.71)		1.35(0.59–3.10)	
previous endocrine therapy (HR and 95%CI)	0.50(0.29–0.85)		0.46(0.22–0.96)		0.54(0.42–0.71)		0.68(0.50–0.93)		NA		NA		NA		NA	
Postmeno-pausal (HR and 95%CI)	0.52(0.36–0.75)		0.49(0.32–0.75)		0.56(0.46–0.69)		0.68(0.53–0.87)		0.57(0.46–0.70)		NA		0.54(0.42–0.70)		0.50(0.35–0.72)	
Premeno-pausal (HR and 95%CI)	0.53(0.33–0.85)		NA		NA		NA		NA		0.57(0.44–0.74)		NA		NA	
ECOG 0 (HR and 95%CI)	0.43(0.28–0.66)		0.43(0.25–0.77)		0.65(0.48–0.87)		0.62(0.43–0.90)		0.58(0.44–0.77)		NA		0.54(0.39–0.75)		0.45(0.25–0.81)	
ECOG 1 (HR and 95%CI)	0.61(0.41–0.90)		0.40(0.22–0.72)		NA		0.71(0.51–1.00)		0.54(0.39–0.77)		NA		0.53(0.35–0.79)		0.53(0.33–0.85)	

PFS Progression free survival, *OS* Overall survival, *ORR* Objective response rate, *CBR* Clinical benefit rate, *ECOG* Eastern Cooperative Oncology Group, *dalpi* dalpiciclib, *palbo* palbociclib, *abeam* abemaciclib, *ribo* ribociclib, *AI* Aromatase inhibitor, *pal* placebo

subgroup ribociclib plus AI versus placebo plus AI were included [20]. The risk of bias assessment for all trials is illustrated in Supplementary Fig. 1.

Network meta-analysis

This NMA identified 8 studies for the progression free survival (PFS) analysis. Figure 2 displays the network relationships between different approaches. Compared to AI alone, dalpiciclib plus AI (0.51; 0.38–0.69), palbociclib plus AI (0.59; 0.51–0.68), ribociclib plus AI (0.57; 0.48–0.67), and abemaciclib plus AI (0.53; 0.43–0.65) all demonstrated significantly better PFS benefits (Table 2). Additionally, no statistically significant differences were observed in the pairwise comparisons between the CDK4/6 inhibitors. In terms of ORR and CBR, we included 7 trials for the analysis. Palbociclib plus AI (0.73; 0.57–0.94), ribociclib plus AI (0.55; 0.39–0.76), abemaciclib plus AI (0.49; 0.35–0.68) showed a better efficacy than that of AI in ORR (Table 3). There was no significant ORR benefit between AI in combination with dalpiciclib plus AI (0.68; 0.46–1.01) versus AI alone. Meanwhile, no statistical differences were observed in pooled network OR value of CBR.

As shown in Table 4, after comparing the odds ratio of adverse events, it was found that the risk caused by AI was lower than that of dalpiciclib plus AI (0.02; 0.00–0.46), palbociclib plus AI (0.14; 0.04–0.45), abemaciclib plus AI (0.12; 0.03–0.48) groups. Compared with AI, dalpiciclib plus AI (65.56; 25.61–167.82), palbociclib plus AI (14.24; 8.41–24.11), ribociclib plus AI (10.89; 4.81–24.67), abemaciclib plus AI (4.48; 2.44–8.20) increased the risk of 3/4 adverse events.

Ranking of treatment regimens

Bayesian ranking profiles of all competing treatments on efficacy and safety are shown in Fig. 3A-E. Dalpiciclib

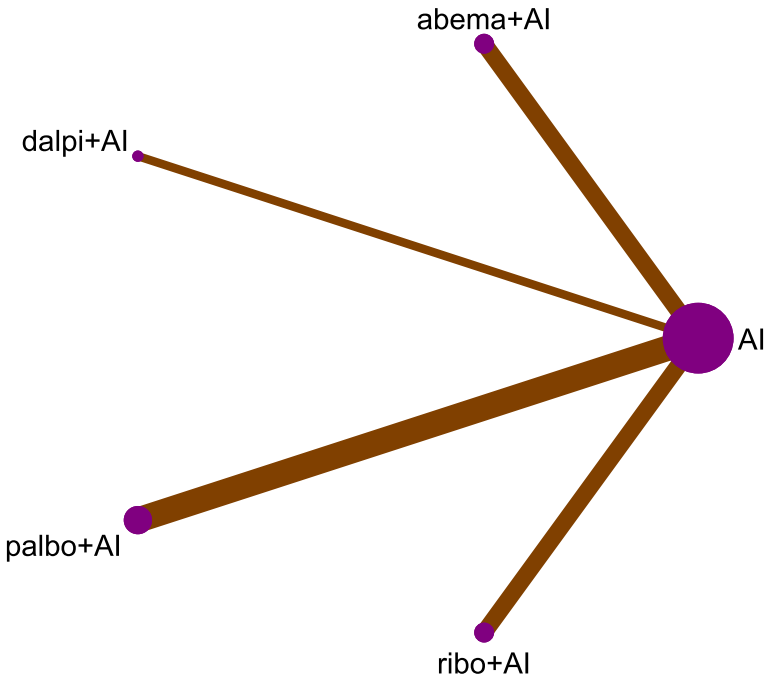


Fig. 2 Network meta-analysis plot of direct comparison for PFS. dalpi, dalpiciclib; palbo, palbociclib; abema, abemaciclib; ribo, ribociclib; AI, aromatase inhibitor; PFS, progression-free survival

Table 2 Network meta-analysis comparison of 5 first-line therapies for PFS

AI	**0.51(0.38–0.69)**	**0.59(0.51–0.68)**	**0.57(0.48–0.67)**	**0.53(0.43–0.65)**
1.96(1.45–2.64)	dalpi + AI	1.16(0.83–1.61)	1.12(0.79–1.57)	1.03(0.72–1.48)
1.70(1.46–1.96)	0.87(0.62–1.21)	palbo + AI	0.97(0.78–1.20)	0.89(0.69–1.15)
1.76(1.49–2.07)	0.90(0.64–1.26)	1.04(0.83–1.29)	ribo + AI	0.92(0.71–1.20)
1.90(1.54–2.34)	0.97(0.67–1.39)	1.12(0.87–1.45)	1.08(0.83–1.41)	abema + AI

dalpi dalpiciclib, *palbo* palbociclib, *abema* abemaciclib, *ribo* ribociclib, *AI* aromatase inhibitor, *PFS* Progression-free survival

Table 3 Pooled estimates of the Network meta-analysis for ORR (lower triangle) and CBR (upper triangle)

AI	**1.67 (0.55,5.06)**	**1.88 (0.99,3.59)**	**1.47 (0.52,4.18)**	**1.97 (0.91,4.27)**
0.68 (0.46,1.01)	dalpi + AI	1.13 (0.31,4.06)	0.88 (0.19,4.03)	1.18 (0.31,4.56)
0.73 (0.57,0.94)	1.08 (0.68,1.73)	palbo + AI	0.78 (0.23,2.67)	1.05 (0.38,2.87)
0.55 (0.39,0.76)	0.81 (0.48,1.35)	0.74 (0.49,1.12)	ribo + AI	1.34 (0.37,4.92)
0.49 (0.35,0.68)	0.72 (0.43,1.20)	0.66 (0.44,1.00)	0.89 (0.56,1.42)	abema + AI

dalpi dalpiciclib, *palbo* palbociclib, *abema* abemaciclib, *ribo* ribociclib, *AI* Aromatase inhibitor, *ORR* Objective response rate, *CBR* Clinical benefit rate

Table 4 Pooled estimates of the Network meta-analysis for AE (lower triangle) and 3/4 AE (upper triangle)

AI	**65.56(25.61,167.82)**	**14.24(8.41,24.11)**	**10.89(4.81,24.67)**	**4.48 (2.44,8.20)**
0.02 (0.00,0.46)	dalpi + AI	0.22 (0.07,0.64)	0.17 (0.05,0.58)	0.07 (0.02,0.21)
0.14 (0.04,0.45)	6.03(0.24,153.92)	palbo + AI	0.76 (0.29,2.02)	0.31 (0.14,0.70)
0.42 (0.08,2.26)	18.51(0.59,585.73)	3.07(0.39,24.20)	ribo + AI	0.41 (0.15,1.14)
0.12 (0.03,0.48)	5.46(0.20,149.35)	0.91 (0.17,4.89)	0.29 (0.03,2.59)	abema + AI

dalpi, dalpiciclib, *palbo* palbociclib, *abema* abemaciclib, *ribo* ribociclib, *AI* aromatase inhibitor, *AE* Adverse event, *3/4 AE* grade 3/4 of adverse event

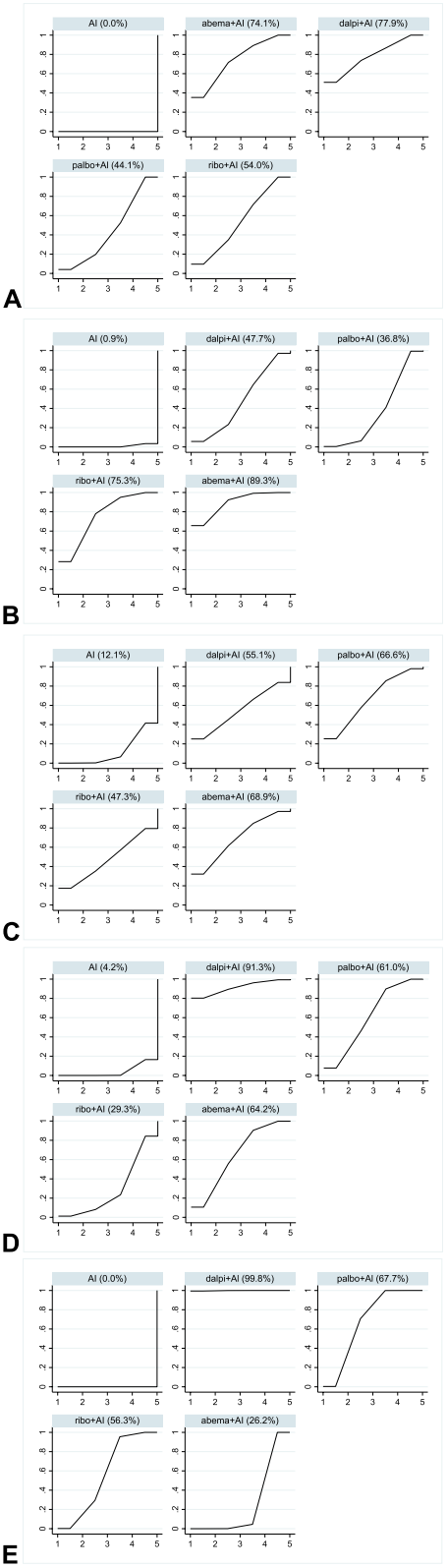
plus AI and abemaciclib plus AI had the highest (SUCRA value 77.9%) and second-highest (74.1%) possibilities respectively for improving PFS, and then followed by ribociclib plus AI (54.0%) and palbociclib plus AI (44.1%) groups. In terms of ORR and CBR, abemaciclib plus AI was most likely to rank the first, with cumulative probabilities of 89.3% and 68.9%. Furthermore, high survival benefits may be associated with high adverse effects. In terms of adverse events (AEs), dalpiciclib plus AI and abemaciclib plus AI mean a higher likelihood of AEs (91.3% and 64.2%, respectively), compared with the groups of palbociclib plus AI (61.0%) and ribociclib plus AI (29.3%). In addition, dalpiciclib plus AI (99.8%) ranked highest for grade 3/4 adverse events (AEs).

Inconsistency and heterogeneity assessments

In our studies, heterogeneities could not be found ($p=$ 0.825, H= 1.0). The fix-model (− 6.412) was used due to the superiority of lower DIC than that from the radom-model (− 4.712). As shown in Supplementary Fig. 3, all studies evenly distributed on both sides, thus no evident signs of bias.

Subgroup analysis and sensitivity analysis

We next analyzed the effect of age, ECOG, visceral metastases, previous chemotherapy for recurrent/metastatic disease, menopausal status, and Asia on PFS. When stratified by age, abemaciclib plus AI had the highest probability of ranking first in populations with < 65 years (Supplementary Fig. 5A). In the ≥ 65 years group, dalpiciclib plus AI showed the best performance (Supplementary Fig. 5B), but abemaciclib plus AI (0.68; 0.46–1.01) had not better PFS benefits in Supplementary Table 1. Regardless of ECOG score (0 or 1), CDK4/6 inhibitors plus AI demonstrated superior efficacy compared to AI alone (Supplementary Table 2). In the ECOG 0 group, dalpiciclib ranked highest (Supplementary Fig. 6A), while in the ECOG 1 group, abemaciclib showed the best performance (Supplementary Fig. 6B). In the group with visceral metastasis, CDK4/6 inhibitors plus AI demonstrated superior efficacy compared to AI alone, with ribociclib plus AI showing the best PFS (Supplementary Fig. 7A). In the bone metastasis subgroup, only palbociclib showed statistically benefits (Supplementary Table 3, Supplementary Fig. 7B). For patients with de-novo metastasis or those without previous endocrine therapy, CDK4/6 inhibitors plus AI demonstrated clear efficacy (Supplementary Table 4). Among these, abemaciclib had the highest SUCRA value in the subgroup of patients without previous endocrine therapy, while dalpiciclib ranked highest in the de-novo metastasis subgroup (Supplementary Fig. 8A, 8B). In Asian patients, ribociclib plus AI and abemaciclib plus AI were not only superior to AI (3.70; 1.92–7.14; 3.03; 1.86–4.95), but also better than palbociclib plus AI (2.39;1.20–4.80; 1.96;1.14–3.37) (Supplementary Table 5). Additionally, ribociclib had the highest SUCRA value (Supplementary Fig. 9A). Similarly, in postmenopausal women, CDK4/6 inhibitors plus AI had superior efficacy compared to AI alone, with abemaciclib having the highest SUCRA value (Supplementary Fig. 9B).



◀ **Fig. 3** Surface under cumulative ranking curves of different treatments. The higher the SUCRA value, the higher the ranking. **A** Curve of 5 treatment options for progression free survival; **B** Curve of 5 treatment options for objective response rate; **C** Curve of 5 treatment options for clinical benefit rate; **D** Curve of 5 treatment options for adverse event; **E** Curve of 5 treatment options for grade 3/4 of adverse event

Discussion

Hormone receptor-positive subtype is the most common subtype of breast malignancy, which has a better prognosis compared to the other types and provides more possibilities for treatment [21]. Endocrine therapy was previously the standard initial treatment for HR +/HER2- advanced breast cancer, but the curative effect was limited [22, 23]. The PALOMA trials, MONARCH trials, MONALEESA trials, and DAWNA trials all show that CDK4/6 inhibitors plus AI established total supremacy in the first-line therapy of advanced breast cancer [15, 20, 24–28]. So far, there are four kinds of CDK4/6 inhibitors available in clinic [16]. However, there is a lack of randomized clinical trials to directly compare the efficacy and tolerability of four CDK4/6 inhibitors.

In our NMAs, we investigated the survival outcomes of HR-positive metastatic breast cancer patients with different CDK4/6 inhibitors plus AI to identify the optimal therapeutic strategy:

- Dalpiciclib plus AI performed somewhat better in PFS (SUCRA value 77.9%) for total patients. In terms of ORR and CBR, Abemaciclib plus AI were most likely to rank the first, with cumulative probabilities of 89.3% and 68.9%.
- Abemaciclib plus AI ranked at the top for prolonging PFS in majority of the subgroups (patients with baseline ECOG of 1 75.0%, those aged < 65 89.2%, post-menopausal women 74.7%, and patients without previous endocrine therapy 77.0%). If the analysis was restricted to patients aged ≥ 65 95.1%, ECOG of 0 88.7%, de-novo metastatic disease 77.0%, dalpiciclib plus AI may have the best survival benefit. Additionally, ribociclib plus AI showed the greatest probability of profits in visceral metastasis (75.4%) and Asian patients (90.9%). Palbociclib plus AI presented better progression free survival benefits on bone metastasis only.
- In terms of adverse events (AEs) and AEs of grade 3/4, dalpiciclib plus AI had the greatest probability (91.3% and 99.8%). Ribociclib plus AI had lowest adverse events (29.3%), and grade 3/4 adverse reactions of abemaciclib and AI were the least (26.2%).

Consistent with other CDK4/6 inhibitors, dalpiciclib shows anti-tumor potency by inhibiting CDK4 or CDK6 [29, 30]. Dalpiciclib and palbociclib have similar inhibitory potencies for CDK4 and CDK6, but ribociclib and abemaciclib had greater activity against CDK4 than CDK6 in enzymatic analyse [31–33]. Besides, abemaciclib can inhibit CDK9 and has additional kinase activities (27 human protein kinases) at the same time through biochemical interaction analyses. This may be the reason for the single agent activity of abemaciclib, but whether this can explain abemaciclib plus AI being optimal in ORR and CBR requires further validation [29, 34–36]. Several real-world studies suggest that patients treated with abemaciclib may achieve longer PFS than with ribociclib and palbociclib as initial treatment for advanced breast cancer, but those results are not statistical significance [37–39]. In the previous network meta-analysis, abemaciclib ranking in term of PFS is optimal in the first line treatment groups when combined with AI therapy [40, 41]. These results coincide with those obtained from our NMA. Due to dalpiciclib recently approved by the China FDA for HR +/HER2- advanced breast malignancy, there is lack of relevant retrospective studies currently. We are the first network meta-analysis reporting efficacy and adverse events of four CDK4/6 inhibitors as initial therapy of hormone receptor positive advanced breast cancer when combined with AI.

As the initial treatment of patients with HR +/HER2- metastatic breast cancer, CDK4/6 inhibitors plus fulvestrant or tamoxifen significantly improved clinical outcomes compared with placebo plus fulvestrant/tamoxifen [42–44]. Regarding the optimal endocrine partner of CDK4/6 inhibitors, PARSIFAL study directly compared the therapeutic efficacy of fulvestrant or letrozole in combination with palbociclib as initial treatment for HR +/HER2- advanced breast cancer [45]. At a median follow-up of 59.7 months, extended follow-up of PARSIFAL study showed that there was no remarkable difference between two groups in mPFS (31.4 vs 34.5 months, $p = 0.985$) and mOS (68.5 vs 62.9 months, $p = 0.635$) [46]. Therefore, regardless of whether advanced breast cancer patients have received endocrine therapy in the past, clinical doctors may prefer to choose the AI combination therapy.

The overall survival data of dalpiciclib was currently immature. The final OS data of MONARCH 3 study presented at SABCS 2023 [47]. The median OS of abemaciclib plus AI was 66.8 months, which is currently the longest OS data of CDK4/6 inhibitors plus AI as the initial treatment for HR+/HER2- advanced breast cancer. It was extended by 13.1 months compared to AI alone. The result is clinically significant, but statistically significant is not found (0.804, 0.637–1.015, $p = 0.0664$) [48]. From the MONALEESA- 2 and MONALEESA- 7 trials, ribociclib combined with letrozole showed absolute overall survival benefits compared to letrozole only (0.76, 0.63–0.93; 0.76, 0.61–0.96) [49, 50]. So far, ribociclib is the only CDK4/6 inhibitor to achieve positive overall survival results in first-line treatment. Unlike abemaciclib and ribociclib, the final OS data of palbociclib combined with AI did not significant improvement (53.9 vs 51.2 months, 0.96, 0.78–1.18) [51]. We can observe that improvement of abemaciclib in PFS has not been translated into an extension of overall survival. Similarly, whether dalpiciclib, which ranking first in PFS, will benefit from overall survival, we need to see direct data to set suspicions aside.

In terms of adverse events, dalpiciclib has a quite high incidence rate. Consistent with proviously result of palbociclib, the most common adverse event of dalpiciclib is hematological toxicity, which is considered to be associated with high inhibition of CDK6 [52]. Previous population pharmacokinetic-pharmacodynamic modeling shows palbociclib has a notably weaker antiproliferative effect on precursor cells than chemotherapies, and related neutropenia is reversible and noncumulative [53]. This is consistent with the conclusion observed in the trial that the vast majority of neutropenia can be effectively managed. The most frequent AE with abemaciclib is diarrhea, which is associated with the inhibition of GSK3β leading to Wnt pathway/β-catenin activation [54]. As for whether this process is modified by CDK9, more research is needed [18, 55]. Similarly to the matching adjusted indirect comparison results, ribociclib had the lowest incidence of adverse event [56]. Meanwhile, our network-meta date agree with a retrospective study that the incidence of significant adverse events was higher with palbociclib (36%) than with abemaciclib (27.3%) [57].

This network meta-analysis has some limitations worth nothing. First, the risk of bias is not high in our study, but the median follow-up time varies among different trials, ranging from 21.6 months to 90 months. These difference may have an impact on the results of survival analysis. And the geographical regions and populations also vary. Second, the overall survival is an important outcome, but the median OS of DAWNA- 2 trial is not yet mature. For this reason, we did not include the overall survival results in the meta-analysis. Third, because the relapse occurring ≥ 12 months after completing adjuvant endocrine therapy was not clearly defined as more than 12 months, the first-line treatment in this study cannot be equated with endocrine sensitivity. Finally, our analysis revealed no statistically significant difference in the pooled OR of CBR, and the optimal effect of dalpiciclib on PFS was not reflected in ORR and CBR values. We consider CDK4/6

inhibitors may prolong PFS by controlling micrometastatic lesions or delaying clinical progression, rather than inducing direct tumor shrinkage. Additionally, potential heterogeneity across subgroups (e.g., hormone receptor expression levels) could influence these observations. However, confirmation of these hypotheses is limited by the unavailability of individual patient-level data for comprehensive subgroup analysis.

Conclusion

Based on this network meta-analysis, CDK4/6 inhibitors are essential as initial treatment for HR +/ HER2- advanced breast cancer. There is no statistically significant difference in PFS among the four CDK4/6 inhibitors, but dalpiciclib had the best therapeutic effect in PFS. Meanwhile, dalpiciclib has the highest risk of adverse events, and the 3/4 adverse events incidence is statistically significant compared with the others. Our study can provide a reference for clinicians in selecting different CDK4/6 inhibitors to achieve safe and favorable results.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14194-w.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements
Not applicable.

Authors' contributions
Nan Zhang and Shuai Liu performed conceptualization, writing-review; Bing Han performed formal analysis, writing-review and editing; Yanrong Kang performed writing-original draft preparation, methodology, data curation; Yongmei Kong performed data curation. All authors reviewed the manuscript.

Funding
This work was supported by Big data, science and technology program from Jinan Health Commission (grant no. 2022-YBD-03); Clinical Research Fund -- Qilu Special Project supported by Shandong Medical Association (grant no. YXH2022ZX02168); Shandong Provincial Medical and Health Technology Project (grant no. 202409031051); Scientific public welfare research projects on tumor translational medicine supported by China Health & Medical Development Foundation (grant no. chmdf2024-xrzx06-01).

Data availability
The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 10 October 2024 Accepted: 21 April 2025
Published online: 08 May 2025

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