



Comparative Efficacy of CDK4/6 Inhibitors Plus Aromatase Inhibitors Versus Fulvestrant for the First-Line Treatment of Hormone Receptor-Positive Advanced Breast Cancer: A Network Meta-Analysis

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Abstract

Background Several endocrine therapies are available for postmenopausal women with hormone receptor-positive (HR+) advanced breast cancer (ABC). Given the absence of direct comparisons between fulvestrant and cyclin-dependent kinase 4/6 inhibitors (CDK4/6is) in combination with aromatase inhibitors (AIs), which are both used as standard first-line treatments for ABC, an indirect comparison using a network meta-analysis may be advantageous for decision making.

Objective We performed a network meta-analysis to compare the efficacies of fulvestrant and CDK4/6is plus AIs as the first-line treatment of postmenopausal breast cancer patients.

Patients and Methods In order to compare these treatments, we searched the PubMed, Cochrane Library, and EMBASE databases for randomized controlled trials of first-line endocrine treatment for advanced or metastatic breast cancer until October 2018. We included a total of 11 eligible trials with 5448 patients. The hazard ratios (HRs) for the efficacies of the different treatments were used as inputs in the network meta-analysis.

Results In the overall analysis, CDK4/6is plus AIs, including palbociclib plus letrozole, ribociclib plus letrozole, and abemaciclib plus nonsteroidal AI (letrozole or anastrozole), are all superior to 500 mg fulvestrant (HR = 0.50, 95% confidence interval [CI] 0.37–0.68; HR = 0.50, 95% CI 0.35–0.71; and HR = 0.49, 95% CI 0.34–0.71; respectively).

Conclusions Within the limitations of this network meta-analysis, the comparison indicates that CDK4/6is plus AIs might represent a better option for HR+ ABC as a first-line endocrine treatment compared with fulvestrant.

Key Points

Several endocrine therapies are available for postmenopausal women with hormone receptor-positive advanced breast cancer, including fulvestrant and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in combination with aromatase inhibitors (AIs).

In the current network meta-analysis with progression-free survival/time to progression as the outcome measure, CDK4/6 inhibitors plus AIs are all superior to 500 mg fulvestrant.

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1 Introduction

Breast cancer is the most frequently diagnosed cancer worldwide, and it is the leading cause of cancer-related death among women [1]. For post-menopausal, hormone

receptor-positive (HR+) advanced breast cancer patients, endocrine therapy with an aromatase inhibitor (AI) is recommended because of longer disease control compared with tamoxifen [2]. Recently, several combination regimens of AIs and the cyclin-dependent kinase 4/6 (CDK4/6) inhibitors palbociclib [3–6], ribociclib [7], and abemaciclib [8] have been approved by the US Food and Drug Administration (FDA) and other regulatory authorities around the world for the first-line treatment of these patients. Other endocrine options in this setting include fulvestrant and anastrozole plus fulvestrant.

Preclinical studies have demonstrated that CDK4/6 inhibitors are active in estrogen receptor-positive (ER+) breast cancer [9], and subsequent clinical trials have established the clinical use of CDK4/6 inhibitors: PALOMA-1 [3] was a randomized phase II study that evaluated the efficacy of palbociclib plus letrozole versus letrozole as the first-line treatment for ER+, HER2-negative (HER2-) breast cancer patients. Median progression-free survival (PFS) was increased to 20.2 months with the combination regimen compared with 10.2 months for letrozole alone (hazard ratio [HR] = 0.488; 95% confidence interval [CI] 0.319–0.748). The phase III PALOMA-2 trial [4–6] compared these two regimens in 666 postmenopausal women who had not received prior treatment for advanced disease. The median PFS was 24.8 months in the palbociclib-letrozole group compared with 14.5 months in the placebo-letrozole group (HR = 0.58; 95% CI 0.46–0.72; $p < 0.001$). The MONALEESA-2 trial [7] assessed the efficacy and safety of ribociclib combined with letrozole compared to placebo plus letrozole as first-line treatment in 668 postmenopausal women with HR+, HER2- advanced breast cancer, and the results showed that PFS was significantly longer in the ribociclib group than in the placebo group (HR = 0.56; 95% CI 0.43–0.72; $p < 0.001$). Abemaciclib, another CDK4/6 inhibitor, demonstrated a significantly prolonged PFS in combination with a nonsteroidal AI (letrozole or anastrozole) compared to a placebo with nonsteroidal AI (HR = 0.54; 95% CI 0.41–0.72; $p = 0.000021$) as first-line treatment of HR+, HER2- advanced breast cancer in the MONARCH-3 trial [8].

Fulvestrant is a selective ER degrader that is approved for the treatment of postmenopausal women with ER+ advanced breast cancer. The phase III CONFIRM study demonstrated an improvement in PFS and overall survival (OS) for 500 mg fulvestrant compared with 250 mg fulvestrant [10, 11]. The FIRST [12–14] trial is a phase II study that demonstrated the clinical benefit rate was similar for fulvestrant (500 mg) and anastrozole (1 mg) at 72.5% versus 67.0%, respectively (odds ratio = 1.30; 95% CI 0.72–2.38; $p = 0.386$). Median time to progression (TTP) was 23.4 months for fulvestrant versus 13.1 months for anastrozole, yielding a 34% reduction in risk of progression (HR = 0.66; 95% CI 0.47–0.92;

$p = 0.01$). The phase III FALCON [15] study enrolled 462 patients and demonstrated that fulvestrant exhibits superior efficacy compared with anastrozole for patients with HR + metastatic breast cancer in this indication. PFS was significantly increased in the fulvestrant group (HR = 0.797, 95% CI 0.637–0.999, $p = 0.0486$).

These data support both the use of a CDK4/6 inhibitor plus AI and use of fulvestrant in postmenopausal women with advanced breast cancer, but a direct head-to-head comparison of these agents would be challenging. Network meta-analysis is a method that can be used to perform indirect treatment comparisons that may predict the relative efficacy of different treatment regimens [16, 17] when there are no prospective controlled study data available.

2 Methods

2.1 Literature and Search Strategy

A systematic review of published data was conducted in October 2018 to identify randomized controlled trials as input to compare CDK4/6 inhibitors plus AI with fulvestrant as the first-line treatment of hormonal therapies for advanced breast cancer in postmenopausal women. Studies that included either a CDK4/6 inhibitor or fulvestrant for advanced or metastatic breast cancer were identified from a database search of PubMed, Cochrane Library, and EMBASE. A prespecified search strategy was employed using terms applicable to the population of interest. Search terms included breast or mammary and disease descriptors (cancer, oncology, tumor, or carcinoma) as well as metastasis, advanced, and recurrent. Search terms for treatments included aromatase inhibitors, letrozole, anastrozole, tamoxifen, CDK4/6 inhibitor, palbociclib, ribociclib, abemaciclib, and fulvestrant.

2.2 Selection Criteria and Data Extraction

Eleven studies were selected based on population, intervention, comparison, outcome, and study design. The study selection flowchart is shown in Fig. 1. Each potential study identified was independently evaluated by two reviewers to ensure its relevance based on the predetermined criteria. We used the Cochrane Collaboration's tool [18] for assessing the risk of bias. The quality of the trials was assessed through Review Manager, and the results are shown as Fig. 2. Trial participants included HR+ (ER+ and/or progesterone receptor-positive [PR+]) postmenopausal women with advanced or metastatic breast cancer who had not received previous endocrine treatment for advanced disease. The analysis assessed relative efficacy (OS/PFS/TTP) between a CDK4/6 inhibitor

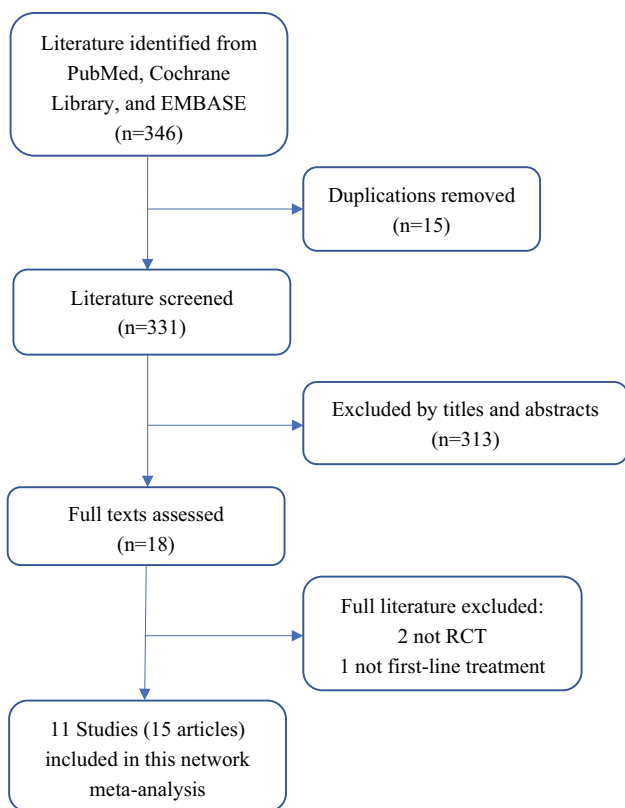
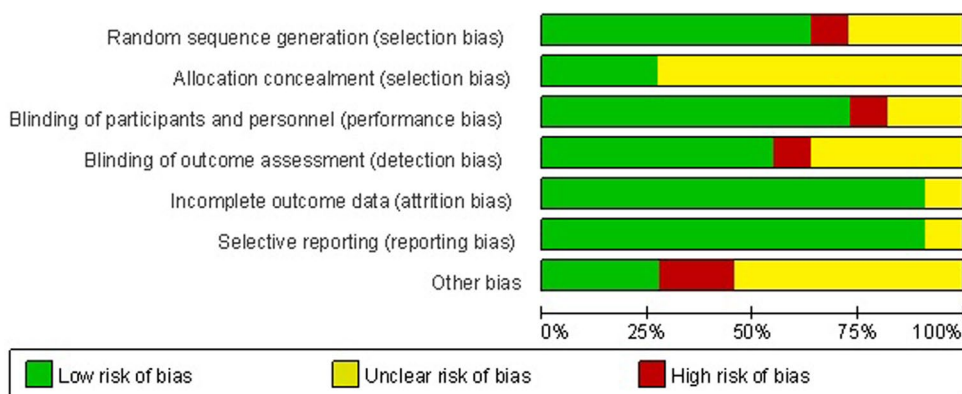


Fig. 1 Flow chart for the selection of studies and articles included in the network meta-analysis. *RCT* randomized controlled trial

plus AI and fulvestrant in the full patient population of the studies that were included in the network. Data extracted from each trial included first author’s name, study design, patient population, information on the intervention (dose and treatment duration), characteristics of participants (such as median age, ER or PR status, HER2 status, prior treatment, disease sites, etc.) and outcome measures.

Fig. 2 Representation of potential bias within the included studies



2.3 Statistical Analysis

The HRs for PFS/TTP/OS were collected from published reports. The mean log HR and its standard error were calculated and inputted into the model [19]. The Bayesian approach was used to perform indirect treatment comparisons between CDK4/6 inhibitor plus AI and fulvestrant. The model parameters were estimated using the Markov chain Monte Carlo (MCMC) software WinBUGS (version 1.4.3). Two chains were performed in this analysis and were run simultaneously with different initial values. The WinBUGS model ran 50,000 iterations of each chain, and the first 5000 iterations were a burn-in, which indicated that convergence was already achieved. Data were analyzed using a fixed-effect model because the deviance information criterion (DIC) of the model was lower compared with that of a random-effect model. Median HRs and the 95% CIs, which are based on the 2.5 and 97.5 percentiles from the distribution of the calculated data, are presented for the HR. The data suggest a difference between the treatments if the 95% CI does not include 1.

3 Results

Fifteen articles (11 randomized controlled trials) including a total of 5448 participants with HR + advanced breast cancer were included in the analysis. All studies were phase II or III randomized multicenter trials with postmenopausal breast cancer women. The network with the connections between the comparators is shown in Fig. 3 [3, 4, 7, 8, 10–15, 20–24]. Details of the individual study designs are shown in Table 1 and the patient characteristics in Table 2. Most patients were ER + or/and PR +, and some of the articles did not provide data on HER2 status. The trials also differed in regard to the percentage of prior adjuvant chemotherapy, prior adjuvant hormonal therapy, and the visceral involvement. All the studies reported PFS/TTP outcomes, and only a portion

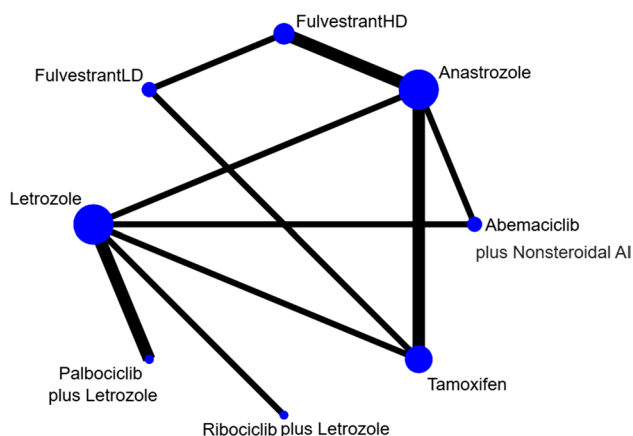


Fig. 3 Network including nodes representing treatments and reflecting the size of the patient population, and connections representing direct comparisons. *AI* aromatase inhibitor, *HD* high dose (500 mg), *LD* low dose (250 mg)

of studies reported OS. Additionally, the objective response rate is shown in Table 3.

The forest plot of the HRs for the comparators of interest relative to 500 mg fulvestrant is presented in Fig. 4. Palbociclib plus letrozole, ribociclib plus letrozole, and abemaciclib plus nonsteroidal AI are all more effective for PFS/TTP compared with 500 mg fulvestrant (HR = 0.50 95% CI 0.37–0.68; HR = 0.50, 95% CI 0.35–0.71; and HR = 0.49, 95% CI 0.34–0.71; respectively). Only letrozole exhibited a value of 1 in the HR forest plot (HR = 0.90, 95% CI 0.71–1.15). The remaining endocrine treatments, including 250 mg fulvestrant, tamoxifen and anastrozole, are significantly less effective than 500 mg fulvestrant (HR = 1.36, 95% CI 1.18–1.57; HR = 1.29, 95% CI 1.07–1.54; and HR = 1.19, 95% CI 1.02–1.40; respectively). Adverse events are summarized in Table 4 to compare fulvestrant 500 mg with CDK4/6 inhibitors plus AIs.

4 Discussion

Fulvestrant is considered a reasonable first-line option for advanced breast cancer, and so are CDK4/6 inhibitors. Therefore, the optimal choice of first-line treatment is not clear. In this article, we used a network meta-analysis to compare the efficacies of CDK4/6 inhibitors plus AIs and fulvestrant 500 mg. Our analysis includes abemaciclib, which was not included in a previous analysis [25]. However, both articles have shown that the CDK4/6 inhibitors combined with AIs show improved PFS/TTP compared to fulvestrant 500 mg as first-line endocrine therapy for advanced breast cancer. As far as OS is concerned, fulvestrant 500 mg is better than fulvestrant 250 mg and anastrozole according to the FIRST and FALCON trials. This makes fulvestrant

500 mg the standard treatment in clinical practice. In contrast, the PALOMA-1 trial showed no statistical difference for OS, and the MONARCH-3 trial of abemaciclib only provided numerical results without *p* values, both due to the limited follow-up of the studies to date.

Regarding the side effect profiles of these treatments, grade 3 or higher treatment-related side effects for CDK4/6 inhibitors mainly include neutropenia, leukopenia, and anemia [26]. Fulvestrant is generally well tolerated, with gastrointestinal symptoms, hot flashes, and skeletal muscle symptoms, similar to anastrozole. In addition to the efficacy and side effects, we also consider the cost of a medicine when making a treatment decision, and CDK4/6 inhibitors are currently much more expensive than fulvestrant.

In terms of the mechanisms of action, cyclin-dependent kinase inhibitors prevent unchecked cell division by blocking CDK4/6 binding to cyclin D1 and their kinase activity [27]. Fulvestrant competitively binds to the ER and down-regulates ER via functional blockade and increased turnover. The PALOMA-1 study demonstrated that palbociclib has activity when combined with endocrine therapy. The PALOMA-2 study is designed to further confirm the efficacy of palbociclib as a first-line treatment. The PALOMA-3 [28] trial assigned advanced HR+, HER2– breast cancer patients who had relapsed or progressed during prior endocrine therapy to receive palbociclib and fulvestrant or placebo and fulvestrant. This study supports the idea that the cyclin D1–CDK4–CDK6 complex is a key downstream effector in HR+ breast cancer [29]. More interestingly, one study [30] showed that CDK6 is highly expressed in fulvestrant-resistant breast cancer cells and that palbociclib is effective in inhibiting the growth of ER+ breast cancer cells with high expression of CDK6 that respond poorly to fulvestrant alone. These findings provide preclinical and clinical evidence for the use of CDK6 as a predictive biomarker of response to fulvestrant treatment in ER+ metastatic breast cancer, and might help select patients who may benefit from combination targeted therapy with CDK4/6 inhibitors and fulvestrant.

The heterogeneity of the patient populations included in our analysis, especially with regard to previous adjuvant treatment, is an area of concern. The FALCON trial enrolled locally advanced or metastatic breast cancer patients who had not received previous endocrine therapy. By contrast, the CDK4/6 inhibitor trials could include patients who had received adjuvant or neoadjuvant endocrine therapy. Therefore, these conditions may weaken the efficacy of CDK4/6 inhibitors to some extent. Also, the populations included in the CDK4/6 trials had substantially higher levels of previous chemotherapy (39–48%) or hormonal therapy (33–58%) than the fulvestrant trials (13–26% and 0–25%, respectively), which also might have an impact on the results. Another problem involves endocrine resistance. Only the

Table 1 Details of trials included in the network meta-analysis

	Di Leo et al. [10, 11] (CONFIRM)	Howell et al. [20]	Robertson et al. [12–14] (first)	Robertson et al. [15] (FALCON)	Nabholtz et al. [21]	Bonneterre et al. [22]	Mouridsen et al. [23, 24]	Finn et al. [3] (PAL-OMA-1)	Finn et al. [4] (PAL-OMA-2)	Hortobagyi et al. [7] (MONALEESA-2)	Goetz et al. [8] (MON-ARCH-3)
Design	Phase III, randomized, double-blind, parallel group, multicenter	Phase III, randomized, double-blind, multicenter	Phase II, randomized, open-label, multicenter	Phase III, randomized, double-blind, international multicenter	Phase (NR), randomized, double-blind, multicenter	Phase (NR), randomized, double-blind, multicenter	Phase III, randomized, double-blind, multicenter	Phase II, randomized, open-label, multicenter	Phase III, randomized, open-label, double-blind, multicenter	Phase III, randomized, double-blind, placebo-controlled, multicenter	Phase III, randomized, double-blind, placebo-controlled, multicenter
Patient population	Postmenopausal ER+ with or PR+ or with both receptors unknown	Postmenopausal with ER+ and/or PR+ or both receptors unknown	Postmenopausal with ER+ or PR+ or both receptors unknown	Postmenopausal with HR+ (ER+ or PR+, or both) with both receptors unknown	Postmenopausal with ER+ and/or PR+ or with both receptors unknown	Postmenopausal with ER+ and/or PR+ or with both receptors unknown	Postmenopausal with ER+ and/or PR+ or with both receptors unknown	Postmenopausal with ER+ and/or PR+ or with both receptors unknown	Postmenopausal with ER+ and/or PR+ or with both receptors unknown	Postmenopausal with HR+, HER2–	Postmenopausal with HR+, HER2–
Treatment 1	Fulvestrant (500 mg IM) (n=362)	Fulvestrant (250 mg IM) (n=313)	Fulvestrant (500 mg IM) (n=102)	Fulvestrant (500 mg IM) (n=230)	Tamoxifen (20 mg PO) (n=182)	Tamoxifen (20 mg PO) (n=328)	Letrozole (2.5 mg PO) (n=453)	Palbociclib (125 mg PO) plus letrozole (2.5 mg PO) (n=84)	Palbociclib (125 mg PO) plus letrozole (2.5 mg PO) (n=444)	Ribociclib (600 mg PO) plus letrozole (2.5 mg PO) (n=334)	Abemaciclib (150 mg PO) plus anastrozole (1 mg PO) or letrozole (2.5 mg PO) (n=328)
Treatment 2	Fulvestrant (250 mg IM) (n=374)	Tamoxifen (20 mg PO) (n=274)	Anastrozole (1 mg PO) (n=103)	Anastrozole (1 mg PO) (n=232)	Anastrozole (1 mg PO) (n=171)	Anastrozole (1 mg PO) (n=340)	Tamoxifen (20 mg PO) (n=454)	Letrozole (2.5 mg PO) (n=81)	Placebo plus letrozole (2.5 mg PO) (n=222)	Placebo plus letrozole (2.5 mg PO) (n=334)	Placebo plus anastrozole (1 mg PO) or letrozole (2.5 mg PO) (n=165)
HER2– (%)	NR	NR	47.3	100	100	NR	NR	NR*	NR**	NR*	NR*
HR+ (%)	NR	100	78.2	100	88.7	44.5	66.0	NR*	NR**	ER+ 99.6%, PR+ 82.2%	NR*

ER+ estrogen receptor-positive, HER2– HER2-negative, HR+ hormone receptor-positive, IM intramuscular, NR not reported, PO oral, PR+ progesterone receptor-positive

*The trial recruited ER+, HER2– advanced breast cancer patients

**Women with ER+, HER2– advanced breast cancer were eligible for enrollment

Table 2 Baseline patient characteristics

Trial	Di Leo et al. [10, 11] (CONFIRM)	Howell et al. [20]	Robertson et al. [12] (FIRST)	Robertson et al. [15] (FALCON)	Nabholtz et al. [21]	Bonneterre et al. [22]	Mouridsen et al. [23, 24]	Finn et al. [3] (PAL-OMA-1)	Finn et al. [4] (PAL-OMA-2)	Hortobagyi et al. [7] (MONALEESA-2)	Goetz et al. [8] (MON-ARCH-3)
Patients randomized	736	587	205	462	353	668	907	165	666	668	493
Median age (years)	Fulvestrant 500 mg (61)	Fulvestrant (67)	Fulvestrant (66)	Fulvestrant (64)	Anastrozole (68)	Anastrozole (67)	Letrozole (65)	Palbociclib plus letrozole (63)	Palbociclib plus letrozole (62)	Ribociclib plus letrozole (62)	Abemaciclib plus non-steroidal AI (63)
Prior adjuvant chemotherapy (%)	Fulvestrant 250 mg (61)	Tamoxifen (66)	Anastrozole (68)	Anastrozole (62)	Tamoxifen (67)	Tamoxifen (66)	Tamoxifen (64)	Letrozole (64)	Placebo plus letrozole (61)	Placebo plus letrozole (63)	Placebo plus nonsteroidal AI (63)
Prior adjuvant hormonal therapy (%)	NR	23.3	26.3	13.4	19.5	18.9	21.8	43.0	48.3*	43.6**	38.7**
Visceral involvement (%)	NR	23.3***	25.4	0	11.6****	7.6****	18.4	33.3	56.3	51.8**	46.7
Lung metastases (%)	NR	NR	51.7	55.0	48.2	34.0	12.5 (visceral only)	48.5	48.6	58.8	52.9
Liver metastases (%)	NR	24.9	35.1	NR	40.8	26.0	NR	NR	NR	NR	NR
Bone metastases (%)	NR	9.7	14.1	NR	12.2	9.4	NR	NR	18.2	NR	NR
Bone metastases (%)	NR	29.8	8.8 (bone only)	10.4 (bone or musculo-skeletal only)	59.3	47.0	15.5 (bone only)	17.7 (bone only)	22.7 (bone only)	22.0 (bone only)	22.1 (bone only)

AI aromatase inhibitor, NR not reported

*Including 12.9% of patients who received neoadjuvant chemotherapy

**Including neoadjuvant chemotherapy or neoadjuvant hormonal therapy

***Only adjuvant tamoxifen treatment

****Hormonal therapy only

Table 3 Hazard ratios for PFS/TTP input into the network meta-analysis

Trial	Treatment 1	Treatment 2	HR	HR (LCI)	HR (UCI)	<i>P</i> value	Objective response rate
Di Leo et al. [10] (CONFIRM)	Fulvestrant 500 mg	Fulvestrant 250 mg	0.80 (PFS)	0.68	0.94	0.006	Fulvestrant 500 mg vs 250 mg (9.1% vs 10.2%)
Di Leo et al. [11] (CONFIRM)	Fulvestrant 500 mg	Fulvestrant 250 mg	0.81 (median OS)	0.69	0.96	0.02	NR
Howell et al. [20]	Fulvestrant 250 mg	Tamoxifen	1.18 (TTP)	0.98	1.44	0.088	Fulvestrant 250 mg vs tamoxifen 20 mg for ER + and/or PR + tumors (33.2% vs 31.1%)
Howell et al. [20]	Fulvestrant 250 mg	Tamoxifen	1.16 (OS)	0.88	1.54	0.3	
Robertson et al. [12] (FIRST)	Fulvestrant 500 mg	Anastrozole	0.66 (TTP)	0.47	0.92	0.01	Fulvestrant 500 mg vs anastrozole 1 mg (36.0% vs 35.5%)
Robertson et al. [13] (FIRST)	Fulvestrant 500 mg	Anastrozole	0.70 (OS)	0.50	0.98	0.04	NR
Robertson et al. [15] (FALCON)	Fulvestrant 500 mg	Anastrozole	0.797 (PFS)	0.637	0.999	0.0486	Fulvestrant 500 mg vs anastrozole 1 mg (46% vs 45%)
Robertson et al. [15] (FALCON)	Fulvestrant 500 mg	Anastrozole	0.88 (OS)	0.63	1.22	0.4277	
Nabholtz et al. [21]	Tamoxifen	Anastrozole	1.44 (TTP)	1.13*	1.96*	0.005	Tamoxifen 20 mg vs anastrozole 1 mg (45.6% vs 59.1%)
Bonnerterre et al. [22]	Tamoxifen	Anastrozole	0.99 (TTP)	0.75**	1.30**	0.941	Tamoxifen 20 mg vs anastrozole 1 mg (32.6% vs 32.9%)
Mouridsen et al. [23, 24]	Letrozole	Tamoxifen	0.7 (TTP)***	0.60	0.82	0.0001	Letrozole 2.5 mg vs tamoxifen 20 mg (30% vs 20%)
Finn et al. [3] (PALOMA-1)	Palbociclib plus letrozole	Letrozole	0.488 (median PFS)	0.319	0.748	0.0004	Palbociclib plus letrozole vs placebo plus letrozole (43% vs 33%)
Finn et al. [3] (PALOMA-1)	Palbociclib plus letrozole	Letrozole	0.813 (median OS)	0.492	1.345	0.42	
Finn et al. [4] (PALOMA-2)	Palbociclib plus letrozole	Placebo plus letrozole	0.58 (median PFS)	0.46	0.72	< 0.001	Palbociclib plus letrozole vs placebo plus letrozole (55.3% vs 44.4%)
Hortobagyi et al. [7] (MONALEESA-2)	Ribociclib plus letrozole	Placebo plus letrozole	0.56 (median PFS)	0.43	0.72	3.29×10^{-6}	Ribociclib plus letrozole vs placebo plus letrozole (52.7% vs 37.1%)
Goetz et al. [8] (MONARCH-3)	Abemaciclib plus nonsteroidal AI	Placebo plus nonsteroidal AI	0.54 (median PFS)	0.41	0.72	0.000021	Abemaciclib plus nonsteroidal AI vs placebo plus nonsteroidal AI (59% vs 44%)
Goetz et al. [8] (MONARCH-3)	Abemaciclib plus nonsteroidal AI	Placebo plus nonsteroidal AI	0.97 (OS)****	NR	NR	NR	

AI aromatase inhibitor, ER + estrogen receptor-positive, HR hazard ratio, LCI lower confidence interval, NR not reported, OS overall survival, PFS progression-free survival, PR + progesterone receptor-positive, TTP time to progression, UCI upper confidence interval

*The article provided the lower 95% confidence limit, 1.16, so STATA software was used to calculate the statistics

**The article provided the lower one-sided 95% confidence limit, 0.86, so STATA software was used to calculate the statistics

***Median OS was 34 months for the randomized letrozole arm and 30 months for the randomized tamoxifen arm, and the overall log-rank test was not significant

****Data on OS were immature at the time of this analysis

Fig. 4 Forest plot comparing treatments with fulvestrant 500 mg for the outcome measure PFS/TTP. *AI* aromatase inhibitor, *CrI* Confidence Interval, *PFS* progression-free survival, *TTP* time to progression

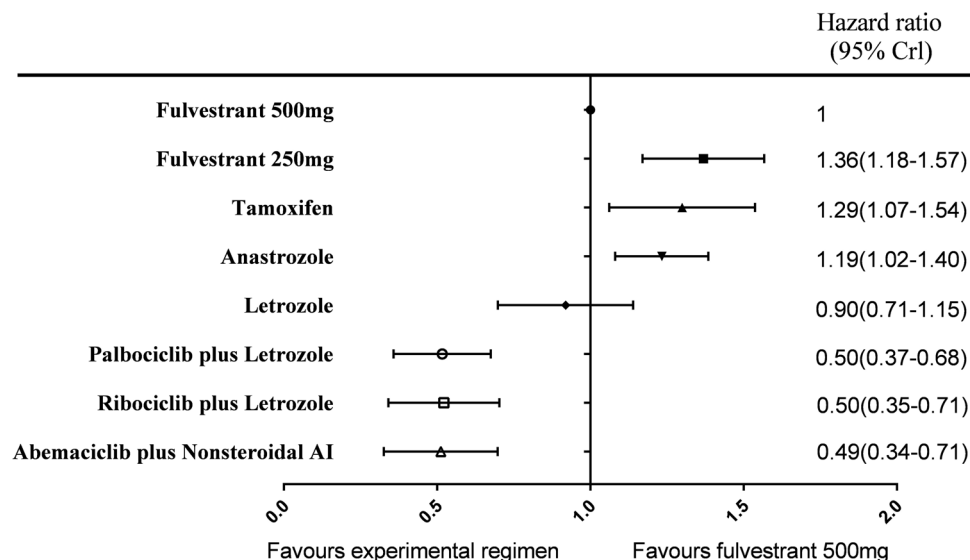


Table 4 Adverse events

Adverse events	Trial and treatment					
	Di Leo et al. [10] (CON-FIRM) Fulvestrant 500 mg	Robertson et al. [12] (FIRST) Fulvestrant 500 mg	Robertson et al. [15] (FALCON) Fulvestrant 500 mg	Finn et al. [3] (PALOMA-1) Palbociclib plus letrozole*	Hortobagyi et al. [7] (MONALEESA-2) Ribociclib plus letrozole*	Goetz et al. [8] (MONARCH-3) Abemaciclib plus nonsteroidal AI*
Gastrointestinal disturbances	20.2%	27.7%	NR	NR	NR	NR
Injection site reactions	13.6%	NR	NR	NR	NR	NR
Joint disorders	18.8%	13.9%	NR	NR	NR	NR
Hot flashes	8.3%	12.9%	11%	0	0.3%	NR
Arthralgia	NR	NR	17%	1%	0.9%	NR
Back pain	NR	NR	9%	1%	2.1%	NR
Fatigue	NR	NR	11%	4%	2.4%	1.8%
Nausea	NR	NR	11%	2%	2.4%	0.9%
Diarrhea	NR	NR	6%	4%	1.2%	9.5%
Neutropenia	NR	NR	NR	54%	59.3%	21.1%
Leukopenia	NR	NR	NR	19%	21%	7.6%
Thromboembolic events	0.8%	0	NR	NR	NR	NR
Ischemic cardiovascular disorders	1.4%	0	NR	NR	NR	NR
Osteoporosis	0.3%	0	NR	NR	NR	NR
Urinary tract infection	2.2%	4.0%	NR	NR	NR	NR
Vaginitis	0.8%	0	NR	NR	NR	NR
Weight gain	0.3%	1.0%	NR	NR	NR	NR

AI aromatase inhibitor, *NR* not reported

*Only adverse events over grade 3

PALOMA-1 trial reported data from subgroup analysis of patients who relapsed within 12 months from the end of adjuvant treatment, and the HR for this group was 0.765 (95% CI 0.232–2.523). Considering that most postmenopausal breast cancer patients, including primary or secondary

endocrine resistant patients, will receive AIs during adjuvant therapy, it remains unclear whether the CDK4/6 inhibitors are still beneficial for these patients.

Our study has several limitations. First, given the lack of OS results, the analysis did not calculate the HR of OS.

Some trial publications stated that OS data were immature at the time of analysis because of the insufficient follow-up time. For example, the PALOMA-2 trial and the MONALEESA-2 trial did not present OS results, and the MONARCH-3 trial only provided the HR of OS without *p* values. The TTP/PFS can provide some evidence for clinical practice. However, without OS results, the evidence may not be sufficiently powerful to support decision making between the use of a CDK4/6 inhibitor with an AI versus treatment with fulvestrant. Second, we did not perform a subgroup analysis, because of the lack of additional data, such as lung metastasis, etc. As a result, this lack of information will influence clinical decision making. Third, PFS and TTP are two different outcome measures that we included in this study. TTP is defined as the time from randomization until objective tumor progression. TTP does not include deaths, whereas PFS does, leading to different results.

Finally, there are many ongoing clinical trials that will provide additional data in this field. For example, PALOMA-4 (NCT02297438) is a phase III study that compares palbociclib plus letrozole with placebo plus letrozole in Asian people, with an estimated primary completion date of March 2019. Another study is MONARCH plus (NCT02763566), which is a randomized, double-blind, phase III study to compare nonsteroidal AI (anastrozole or letrozole) plus abemaciclib (or plus placebo) with fulvestrant plus abemaciclib (or plus placebo) in postmenopausal women with HR+, HER2– locoregionally recurrent or metastatic breast cancer. The estimated study completion date is November 27, 2019. We are looking forward to these results because the study compares a CDK4/6 inhibitor to fulvestrant head-to-head as the first-line treatment. Moreover, we want to assess whether fulvestrant plus a CDK4/6 inhibitor is superior to AI plus fulvestrant, but no current clinical trial is addressing this question.

In conclusion, the network meta-analysis demonstrates that CDK4/6 inhibitors may represent an effective first-line treatment compared with fulvestrant (500 mg) for HR + advanced breast cancer. However, additional clinical studies are needed to provide more evidence.

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Compliance with Ethical Standards

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Conflicts of Interest Qianqian Guo, Xiaojie Lin, Lingling Ye, Rui Xu, Yan Dai1, Yuzhu Zhang, and Qianjun Chen declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

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