

RESEARCH ARTICLE

The efficacy and safety of targeted therapy plus fulvestrant in postmenopausal women with hormone-receptor positive advanced breast cancer: A meta-analysis of randomized-control trials

Gao Chanchan, Su Xiangyu, Shi Fangfang, Chen Yan, Gu Xiaoyi *

Department of Oncology, Zhongda Hospital of Southeast University, Nanjing, China

* xy_gu@sohu.com



Abstract

Objective

To evaluate the efficacy and safety of targeted therapy plus fulvestrant for postmenopausal patients with hormone receptor-positive advanced breast cancer.

Methods

Pubmed, Embase and Web of Science databases were systematically searched on February 26, 2018. Eligible studies were screened according to selection criteria, and two reviewers independently extracted outcome data which included progression-free survival, overall survival, objective response rate, clinical benefit rate and toxicities. RevMan 5.3 and STATA 11.0 software were used to conduct meta-analysis.

Results

Thirteen articles including twelve randomized-control trials fulfilled selection criteria. There was no evidence regarding the existence of publication bias and high-risk bias of quality in the selected studies. In previously endocrine therapy-treated postmenopausal patients with hormone-receptor positive advanced breast cancer, the PFS (HR = 0.77, 95%CI: 0.66–0.91) and ORR (RR = 1.78, 95%CI: 1.35–2.34) of combination therapy group were significantly higher than that from fulvestrant monotherapy group. Besides, a statistically significant difference in PFS was found across the two arms in postmenopausal women with PIK3CA-mutant ctDNA tumor (HR = 0.52, 95% CI: 0.39–0.69). Moreover, the risk of adverse events (RR = 1.09, 95%CI: 1.05–1.13), CTCAE \geq 3 (RR = 1.97, 95%CI: 1.49–2.60) and discontinuation due to adverse events (RR = 4.91, 95%CI: 3.37–7.15) were also significantly different between two treatment groups. Sensitivity analysis showed PLOMA-3 trial was an important factor of heterogeneity.

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Discussion

Even though the combination of targeted therapy plus fulvestrant improved PFS and increased ORR in advanced breast cancer patients, the toxicities of combination therapy were also higher than fulvestrant monotherapy. Further studies related to inhibitors targeting the specific signaling pathway or receptors are urgently needed, and more efforts concerning precision medicine of targeted therapy plus endocrine therapy should be taken to improve the clinical benefits.

Introduction

Breast cancer is the most common cancer in women worldwide[1], it estimates that one in eight to ten women might suffer from this malignancy during her lifetime[2]. Early breast cancer is believed to a potential curable disease, and the appropriate treatments include breast-conserving surgery, radiotherapy and neoadjuvant endocrine/chemotherapy therapy. A meta-analysis conducted by Early Breast Cancer Trialists' Collaborative Group suggests that after breast conservation, radiotherapy could effectively reduce the 10-year risk of recurrence (RR = 0.52, 95% CI: 0.48–0.56) and the 15-year risk of death (RR = 0.82, 95% CI: 0.75–0.90) [3]. However, advanced breast cancer (ABC, locally advanced or metastatic breast cancer) are incurable where the goals of treatments are prolongation of survival and maintaining the quality of life. It has been documented that, postmenopausal women with hormone-receptor positive (HR+), human epidermal growth factor receptor type2-negative (HER2-) tumors represent the majority of advanced breast cancer patients[4, 5]. International guidelines recommend endocrine therapy (tamoxife, anastrozole, letrozole, exemestane and fulvestrant, etc) are the first-line treatment while these incurable patients don't have immediately life-threatening disease[6, 7].

Fulvestrant, an analog of 17-beta estradiol, is the first-generation selective estrogen receptor downregulator (SERD), which is approved for the treatment of HR+ postmenopausal patients. Fulvestrant binds to the estrogen receptor and makes it more hydrophobic, resulting in its accelerated degradation[8]. For postmenopausal ABC patients, several studies indicates that fulvestrant is at least as effective as other endocrine therapies[9, 10], and adverse events of patients treated with fulvestrant is usually mild or moderate, including nausea, injection site reactions, weakness, and elevated transaminases, etc[11, 12].

However, for treatment of advanced breast cancer, intrinsic or acquired endocrine resistance are major obstacle in achieving better clinical outcomes[13]. And the possible mechanisms of endocrine resistance involves alterations to the ER and its co-regulators, key cell cycle checkpoints, cell survival pathway and apoptosis, overexpression and/or amplification of growth factor, etc[14, 15]. The intensive efforts to overcome this resistance led to the development of combination therapies which also include targeted agents plus endocrine therapy, such as everolimus plus exemestane [16] and palbociclib plus fulvestrant[17]. Herein, we conduct a meta-analysis of randomized-controlled trials (RCTs) to quantitatively assess the efficacy and toxicities of targeted therapy plus fulvestrant in postmenopausal women with hormone-receptor positive advanced breast cancer.

Materials and methods

Search strategy

Electronic databases including Embase, Pubmed and Web of Science were systematically searched on February 26, 2018. The key search terms were selective estrogen receptor

downregulator OR fulvestrant OR faslodex, breast cancer OR breast neoplasm OR breast carcinoma OR breast malignancy. No language restriction was used during the literature search. The bibliography of relevant studies, reviews, and conferences were manually searched.

Selection criteria

The following inclusion criteria were applied for subsequent analysis: (1) randomized-controlled trial; (2) postmenopausal women with hormone receptor-positive (estrogen-receptor positive and/or progesterone-receptor positive) advanced breast cancer; (3) studies about targeted therapy plus fulvestrant (the intervention group) and fulvestrant alone (the comparator); (4) at least one of efficacy or tolerability index was sufficiently reported. Efficacy was chosen as the primary outcome, including progression-free survival (PFS), overall survival (OS), overall response rate (ORR) and clinical benefit rate (CBR, best overall response of complete response, partial response, or stable disease ≥ 24 weeks). Toxicity was chosen as the secondary outcome, which contained adverse events, severe adverse events, discontinuation and National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) ≥ 3 . Moreover, only the most recent or detailed study was selected for duplicate publication.

Data extraction and quality assessment

Two investigators (Gao CC and Su XY) independently reviewed articles and extracted data, the following information were acquired from each eligible study: first author, publication time, study design, setting, follow-up, characters of participants, interventions, efficacy and toxicity. For time-to-event outcomes (PFS and OS), we extracted hazard ratio (HR) and 95% confidence interval (CI) as treatment effect. For HR and 95%CI data that could not be directly extracted from the main text and supplementary materials, they were obtained indirectly from published Kaplan-Meier curves using the Tierney's method [18]. For dichotomous outcomes (ORR, CBR and toxicity), we extracted the number of patients who had relevant events and total number of patients, the risk ratio (RR) with 95%CI was expressed as treatment effect.

To measure the bias risk, two reviewers (Gao CC and Su XY) independently assessed the quality of each study according to the Cochrane Collaboration criteria, which includes the following seven points: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Any disagreements during extraction and quality assessment were resolved by consensus.

Statistical analysis

We estimated heterogeneity using the Cochran's Q and the I^2 statistic. When $P < 0.10$ or $I^2 > 50\%$, a random-effect model was selected to pool effect size, otherwise, a fixed-effect model was used. Egger's test and Begg's test were used to assess the potential publication bias, and $P < 0.10$ indicated statistical significance. Sensitivity analysis was performed by step-wise removal of single study. STATA software 11.0 and RevMan 5.3 software were used to perform statistical analyses.

Results

Characteristics of included studies

The primary databases search yielded 4458 relevant studies. After screening titles, abstracts and full texts, 4445 records were excluded, and 13 studies that contained 12 RCTs met our inclusion criteria (Fig 1) [19–31]. Two articles reporting PLOMA-3 trial [25, 28] were selected

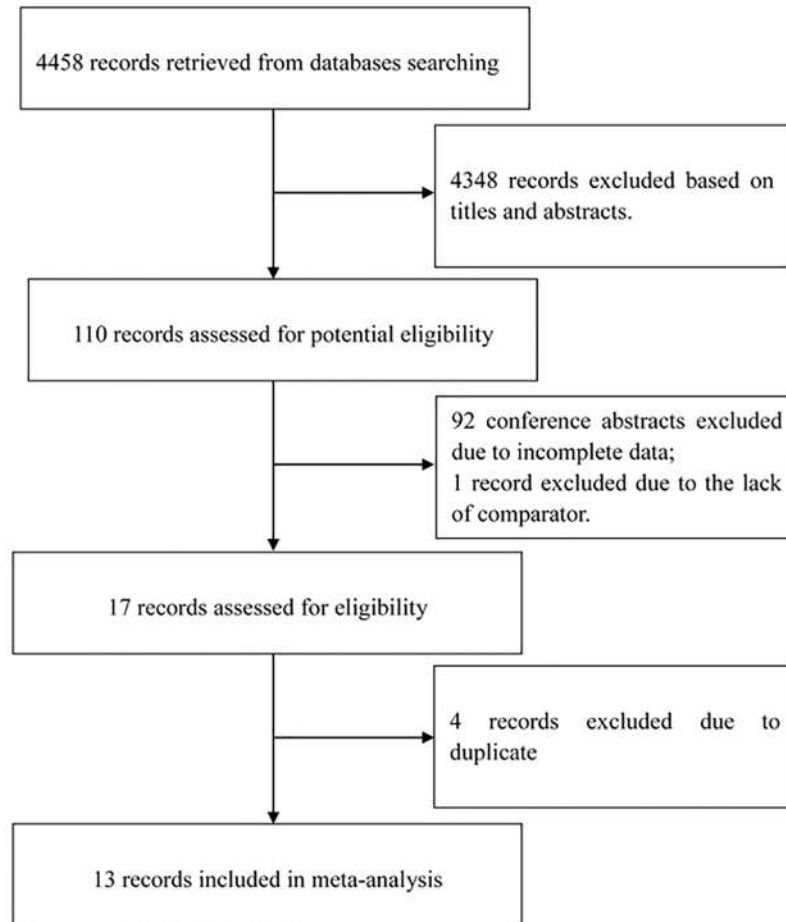


Fig 1. Flow chart of the included study.

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to calculate relevant efficacy and safety endpoints in postmenopausal patients. Each single article evaluated proteasome inhibitor in combination with fulvestrant[24], IGF inhibitor in combination with fulvestrant[20], EGFR inhibitor in combination with fulvestrant[21], MAPK inhibitor in combination with fulvestrant[23] and FGFR inhibitor in combination with fulvestrant[29]. Two articles assessed VEGF inhibitors in combination with fulvestrant[19, 22], three articles reported CDK4/6 inhibitors in combination with fulvestrant[25, 28, 30], and three articles assessed PI3K inhibitors in combination with fulvestrant[26, 27, 31]. Subjects of eleven RCTs with twelve articles were confirmed to ET-resistant. More details concerning characteristics of included studies were shown in Table 1.

Publication bias and quality assessment

Egger’s test and Begg’s test were used for research endpoints with more than two articles. There was no obvious evidence of publication bias in the selected studies ($P > 0.10$).

The quality assessments of included studies were summarized in Figs 2 and 3. The overall risk of bias was low, particularly in the selection bias and attribution bias. For blinding, one trial was an open-label[24], the other one[19] did not describe relevant information, these two articles were classified as unclear risk. Furthermore, most outcome assessments were blind and judged to be at low risk. For reporting bias, Hymas et al[19] only reported ORR of patients

Table 1. Characteristics of included studies.

Study	Design	Setting	Schedule	Follow-up	Patients
Hyams[19]	Phase II, 1:1 RCT	19 centres in Australia, Brazil and the USA	Cediranib [oral, 45 mg/day]+FUL [LD] (n = 31) VS Placebo+FUL(n = 31)	Recrument: March 2007-April 2008; cut-off: 12 December 2008.	HR+/HER unknown postmenopausal patients with evaluable disease whose disease had progressed on prior hormonal therapy. Age: mostly 18–65 yr. combined therapy VS comparator: Prior ET 1. Tamoxifen 24/31 VS 24 /31; 2. Letrozole 11/31 VS 15 /31;; 3. Anastrozole 12 /31 VS 10 /31 4. Exemestane 7/31 VS 6/31; Measurable disease: 18/31 VS 12/31.
Robertson[20]	Double-blind, phase II, 2:1 RCT	58 centres in the USA, Europe, Canada, and Australia.	Ganitumab [IM, 12mg/kg day 1, 15/ 28 days] +FUL [LD]/ exemestane[25mg/day] (n = 106) VS FUL/exemestane (n = 50)	Recrument: March 2008 -July 2009; cut-off: September 2011.	HR+ postmenopausal patients with endocrine-resistant or recurrent breast cancer. combined therapy VS comparator: Median age: 61yr VS 62yr. HER+: 7/106 VS 1/50. FUL treatment during study: 72/106 VS 34/50.
Clemons[22]	Double-blind, multicentre, phase II, 1:1 RCT	13 Canadian cancer centres	Vandetanib[100 mg/day]+ FUL [HD] (n = 61) VS Placebo +FUL(n = 68)	Recrument: October 2009-October 2011; cut-off: July 2013.	HR+, endocrine-resistant postmenopausal patients with bone metastases. combined therapy VS comparator: Mean age: 61.6yr VS 57.7yr. HER+: 3/61 VS 1/68. Prior ET: 1. Tamoxifen/AI treatment 42 /61 VS 53/68; 2. Tamoxifen/AI adjuvant treatment 9/61 VS 10 /68. Measurable disease: 21/61 VS 40/68. Metastatic disease: 1. Liver 14/61 VS 23 /68; 2. Lung 12/61 VS22/68; 3. Lymph node 14/61 VS 16/68; 4. Skin 3 /61 VS 0 /68.
Burstein[21]	Double-Blind, Phase III, 1:1 RCT	NA	Lapatinib[oral, 1500mg/day]+ FUL[LD] (n = 146) VS Placebo+ FUL (n = 145)	Recrument: September 2006; cut-off: June 2010.	HR+ postmenopausal patients. combined therapy VS comparator: Age: mostly 40-69yr. HER+: 24/146 VS 30/145. Prior ET treatment: 1. tamoxifen 83/146 VS 82/145; 2. AI 141/146 VS 140/145.

(Continued)

Table 1. (Continued)

Study	Design	Setting	Schedule	Follow-up	Patients
Zaman[23]	Double-blind, multicentre, phase II, 46:43 RCT	20 centres in Switzerland and Belgium	Selumetinib[oral, 75mg×2/day] + FUL [HD] (n = 23) VS Placebo+ FUL (n = 22)	Recrument: November 2010-March 2012; Median follow-up: 22 months.	HR+/HER2-, postmenopausal patients whose disease had progressed after AIs-treatment. combined therapy VS comparator: median age: 66yr VS 69yr. Prior TAM treatment: 14/22 VS 11/20. Visceral metastases: 13/22 VS 11/20. Measurable disease: 15/22 VS 15/20.
Cristofanilli [25] and Loibl [28]	Double-blind, multicentre, phase III, 2:1 RCT	144 centres in 17 countries	Palbociclib [oral, 125 mg/day for 3 weeks, followed by a week off in a 28-day cycle] + FUL[HD] (n = 345) VS Placebo+ FUL (n = 172)	Recrument: October 2013-August 2014; Cut-off: March 2015.	HR+/HER2- female patients whose disease had progressed after previous endocrine therapy. combined therapy VS comparator: median age: 57yr VS 56yr. postmenopausal: 275/345 VS 138/172. measurable disease: 268/345 VS 138/172. Prior ET: 1. first-line 160/345 VS 91/172; 2. second-line 140/345 VS 61/172.
Krop[26]	double-blind, phase II, 1:1/1:2 RCT	123 medical centres in 21 countries	Part1: Pictilisib[oral, 340mg/day]+ FUL [HD](n = 89) VS Placebo+FUL (n = 79) Part 2: Pictilisib [oral, 260mg mg/day] +FUL [HD] (n = 41) VS Placebo+FUL (n = 20)	Part 1: Recrument: September 2011-January 2013; Median follow-up: 17.5 months. Part 2: Recrument: March 2013-January 2014; Median follow-up: 12.9 months.	Part 1: HR+/HER2- postmenopausal patients with AIs resistance. combined therapy VS comparator: median age: 60yr VS 63yr. measurable disease: 51/89 VS 43/79. visceral metastases: 51/89 VS 42/79. PIK3CA mutation positive: 38/89 VS 32/79. Part 2: HR+ /HER2-, AIs-resistant postmenopausal patients with PIK3CA mutation. combined therapy VS comparator: median age: 58yr VS 63yr. measurable disease: 29/41 VS 13/20. visceral metastases: 21/41 VS 10/20.
Adelson[24]	Open-label, multicenter, phase II, randomized trial	NA	Bortezomib[intravenous infusion, 1.6 mg/m ² at day 1, 8, 15/28 days]+ FUL[500mg IM days 14, 1, 15 and then day 1/each 28 days] (n = 57) VS FUL (n = 59)	Recrument: June 2010-October 2013; Cut-off: NA.	ER+/HER2-, AIs-resistant postmenopausal patients. combined therapy VS comparator: Age: 57yr VS 59yr. Metastatic sites: 1. Bone 46/57 VS 45 /59; 2. Lung 9/57 VS 23/59; 3. Liver 22/57 VS 21/59.

(Continued)

Table 1. (Continued)

Study	Design	Setting	Schedule	Follow-up	Patients
Baselga[27]	Double-blind, multicenter, phase III, 1:1 RCT	267 centres in 29 countries	Buparlisib [oral, 100 mg/day]+FUL[HD] (n = 576) VS Placebo + FUL (n = 571)	Recrument: September 2012-September 2014; cut-off: April 2015.	HR+/HER2-, AIs-resistant postmenopausal patients. combined therapy VS comparator: Age: 62yr VS 61yr. PI3K pathway status in tumor tissue: Activated 188/576 VS 184/571; Non-activated 239/576 VS 240/571; Unknown or missing 149/576 VS 147/571.
Musolino[29]	Double-blind, multicenter, phase II, 1:1 RCT	36 centers in 12 countries	Dovitinib [oral, 500 mg/5 day one week]+FUL[IM, 500mg/each 2 weeks](n = 47) VS Placebo+FUL (n = 50)	Recrument: May 2012 -November 2014; cut-off: April 2015.	HR+/HER2-, ET-resistant postmenopausal patients. combined therapy VS comparator: Age: 62yr VS 61yr. FGF pathway amplified: 15/47 VS 17/50. Metastatic site: 1. Bone 39/47 VS 36 /50; 2. Lymph nodes 21/47 VS 26/50; 3. Liver 22/47 VS 16/50. Prior ET: 1. Tamoxifen 27 /47 VS 21 /50; 2. Letrozole 18 /47 VS 23/50; 3. Anastrozole 16/47VS 18/50; 4. Exemestane 8/47 VS 9/50.
Sledge[30]	Double-blind, phase III, 2:1 RCT	142 centers in 19 countries.	Abemaciclib[oral, 150 mg×2/day]+FUL [HD](n = 446) VS Placebo+FUL(n = 223)	Recrument: August 2014-December 2015 cut-off: February 2017.	HR+/HER2-, ET-resistant patients. combined therapy VS comparator: Age: 59yr VS 62yr. Postmenopausal patients: 371/446 VS 180/223. Measurable disease: 318/446 VS 164/223. Prior AI: 316/446 VS 149/223. Metastatic site: 1. Visceral 245/446 VS 128 /223; 2. Bone only 123 /446 VS 57 /223.
Leo[31]	Double-blind, multicentre, phase III, 2:1 RCT	200 centres in 22 countries	Buparlisib[oral, 100 mg/day]+FUL[HD] (n = 289) VS Placebo+FUL(n = 143)	Recrument: January 2013-March 2016; cut-off: May 2016.	HR+/HER2-, postmenopausal patients who had relapsed on or after endocrine therapy and mTOR inhibitors. combined therapy VS comparator: Age: 60yr VS 62yr. mTOR inhibitor: 1. everolimus 286/289 VS 142 /143; 2. ridaforolimus 3/ 289 VS 1/143. Metastatic sites: 1. Bone219 /289 VS 111/143; 2. Visceral 212 /289 VS 103/143; 3. Liver 137 /289 VS 76/143.

LD: loading does, 500 mg IM on day 1, and 250 mg on days 15, 29 and every 28 days thereafter;

HD: high does, 500 mg IM days 1, 15, 29 and every 28 days afterwards; IM: intramuscular injection; FUL: fulvestrant.

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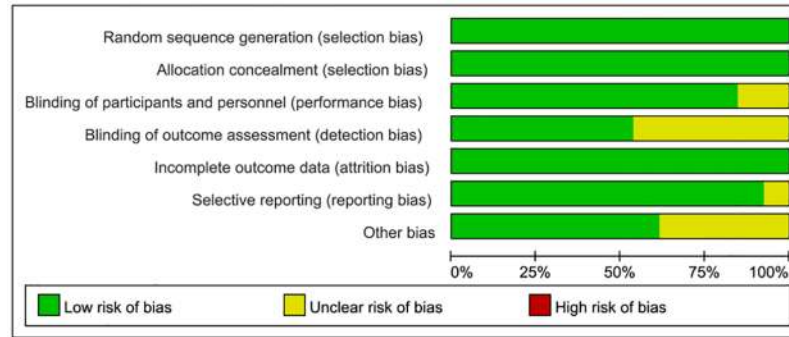


Fig 2. Risk of bias graph: Review authors’ judgements about each risk of bias item presented as percentages across all included studies.

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with measurable disease and did not report the ORR of total population, therefore, this trial was judged to be at unclear risk, other trials were judged at low risk.

Efficacy

Progression free survival. Data on hazard ratios of PFS were available in all 12 RCTs. The random-effect model ($P < 0.0001$, $I^2 = 72\%$) showed that pooled HR was 0.77(95%CI: 0.66–0.91) (Fig 4). Besides, there were nine trials provide PFS data for postmenopausal women with HR+, HER2- advanced breast cancer, the pooled HR of PFS determined by the random-effect model ($P = 0.004$, $I^2 = 72\%$) was 0.71(95%CI: 0.60–0.85). Moreover, nine articles clearly indicated the participants were endocrine-therapy resistant, the pooled effect size was 0.76 (95% CI: 0.63–0.92).

PFS data from patients with measurable disease at baseline were obtained from 2 trials and did not show a significant difference between two treatment arms (HR = 0.88, 95%CI: 0.55–1.40).

The relationship between PIK3CA mutation and clinical benefit of combination regimen remained unclear. There were three studies reported PFS concerning PIK3CA mutant status in archival or newly collected tumor tissue, random-effect model ($P = 0.07$, $I^2 = 57\%$) showed that there was not statistically significant difference in PFS between combination therapy and the comparator (HR = 0.70, 95%CI: 0.48–1.02). Besides, two trials of above three studies also reported data about PIK3CA mutation detected in circulating tumor DNA(ctDNA), and fixed effect model ($P = 0.50$, $I^2 = 0\%$) indicated that the combination therapy had longer PFS than fulvestrant monotherapy among patients with PIK3CA-mutated ctDNA (HR = 0.52, 95%CI: 0.39–0.69).

Overall survival. Most included studies did not have mature overall survival data at the cut-off date, the HR was only found in two trials, and no statistically significant difference was observed between treatment agents(HR = 0.88, 95%CI:0.67–1.17).

Overall response rate. Six articles including 2299 participants with HR+/HER2- tumor reported ORR data, the pooled RR was 1.78(95%CI:1.35–2.34) by using the fixed effect model ($P = 0.29$, $I^2 = 20\%$) (Fig 5). Besides, there were also three studies represented data related to patients with measurable disease. The fixed effect model ($P = 0.98$, $I^2 = 0\%$) indicated the combination therapy significantly improve overall response rate (RR = 2.35, 95%CI: 1.35–4.11).

Clinical benefit rate. CBR data were extracted from six trials, which included 2264 subjects. We did not observe a significant difference between the intervention arm and the comparator (HR = 1.22, 95%CI: 0.90–1.64) (Fig 6). Two studies presented relevant information in patients with measurable disease, the pooled RR was 1.15(95%CI: 0.68–1.94).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Adelson(2016)	+	+	?	?	+	+	?
Baselga(2017)	+	+	+	+	+	+	+
Burstein(2014)	+	+	+	?	+	+	?
Clemons(2014)	+	+	+	?	+	+	?
Cristofanilli(2016)	+	+	+	+	+	+	+
Hyams(2013)	+	+	?	?	+	?	?
Krop(2016)	+	+	+	+	+	+	+
Leo(2018)	+	+	+	+	+	+	+
Loibl(2017)	+	+	+	+	+	+	+
Musolino(2017)	+	+	+	+	+	+	+
Robertson(2013)	+	+	+	+	+	+	+
Sledge(2017)	+	+	+	?	+	+	+
Zaman(2015)	+	+	+	?	+	+	?

Fig 3. Risk of bias summary: Review authors' judgements about each risk of bias item for each included study.

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Tolerability

Adverse events. Data of adverse events were available for 4 RCTs. the results of fixed-effect model ($P = 0.13$, $I^2 = 46\%$) showed that the pooled RR was 1.09 (95%CI: 1.05–1.13).

Sever adverse events. There was no significant difference in the total incidence of sever adverse events (SAEs) between two treatment groups (RR = 1.44, 95%CI: 0.97–2.13) (Fig 7).

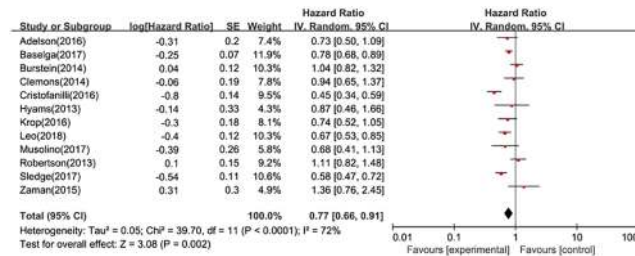


Fig 4. Forest plot for progression free survival in postmenopausal patients with HR+ advanced breast cancer.

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Additionally, three clinical trials reported SAEs related to treatment drugs, and the fixed-effect model ($P = 0.16$, $I^2 = 45\%$) showed that the pooled RR was 4.23(95%CI: 1.62–11.03).

CTCAE ≥ 3 . Data concerning CTCAE ≥ 3 was reported in eight studies. The results of random-effect model ($P = 0.001$, $I^2 = 71\%$) indicated that the combination therapy was associated with significantly greater risk of CTCAE ≥ 3 (RR = 1.97, 95%CI: 1.49–2.60) (Fig 8).

Discontinuation. The reasons for discontinuation include death, disease progression, adverse events, loss to follow-up, non-compliance to study treatment, physician decision, participant or guardian decision, protocol deviation, termination of the study by sponsor, technical problems. Data on discontinuation were available for five RCTs. The pooled RR was 1.00 (95%CI: 0.97–1.03) (Fig 9). Furthermore, seven studies reported data on treatment discontinuation due to AEs. The estimate was significantly different between two treatment arms (RR = 4.91, 95%CI: 3.37–7.15) (Fig 10).

Sensitivity analysis

For efficiency index, removal of the second period trial of krop et al, combination therapy had significant benefit for PFS in patients with PIK3CA mutation in tumor tissue (HR = 0.64, 95% CI: 0.4–0.98). Other effect size of PFS had not been significantly altered by any included trials, while there was one trial (PLOMA-3) obviously contributing heterogeneity. Sensitivity analysis concerning ORR and CBR demonstrated that pooled RR were not significantly changed by excluding individual study stepwise, but the value of I^2 for ORR decreased to 0% after removing the study conducted by Zaman et al.

For toxicity index, removal of Leo’s or Musolino’s study, the confidence interval of RR related to AEs would contain the number 1; in addition, removal of studies written by Clemons or Loibi, the pooled effect size demonstrated the incidence of SAEs was associated with targeted therapy plus fulvestrant (removal of Clemons’s study: pooled RR = 1.51, 95%CI: 1.01–2.26; removal of Loibi’s study: pooled RR = 1.57, 95%CI: 1.29–1.90). Moreover, PLOMA-3 was an important factor to heterogeneity of tolerability index, and Zaman et al’s article was also contributed to heterogeneity of CTCAE ≥ 3 .

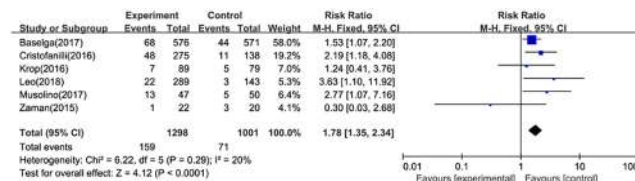


Fig 5. Forest plot for overall response rate in postmenopausal patients with HR+, HER2- advanced breast cancer.

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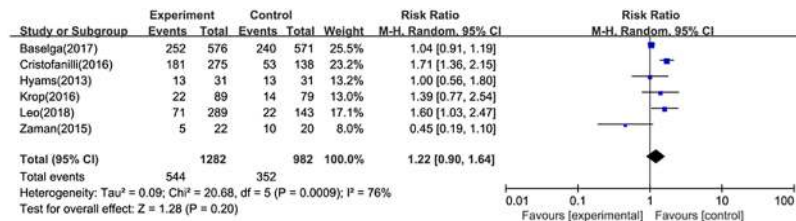


Fig 6. Forest plot for clinic benefit rate in postmenopausal patients with HR+, HER2- advanced breast cancer.

<https://doi.org/10.1371/journal.pone.0204202.g006>

Discussion

Endocrine therapy is a preferred approach for patients with HR-positive advanced breast cancer [32]. Some clinical studies have shown that estrogen antagonist and aromatase inhibitor can improve survival time and decrease mortality rate of HR-positive advanced breast cancer patients. However, side-effect and drug resistance hampered the long-term use of above two kinds of treatments [33–36]. Fulvestrant has become a new choice for advanced breast cancer with its unique mechanism of action, and it has been recommended as first-line treatment of postmenopausal women with advanced breast cancer [7]. Initially, patients should receive once-monthly intramuscular injections of fulvestrant 250 mg. CONFIRM trial demonstrated that, fulvestrant 500mg provided a significant improvement in both PFS and OS without an increasing in the toxicity compared with fulvestrant 250mg [12, 37]. Therefore, fulvestrant 500mg was adopted as the preferable dose.

To improve the therapeutic efficacy and overcome resistance, fulvestrant has been evaluated in combination with other endocrine agents or novel targeted drugs [8]. Regarding fulvestrant in combination with anastrozole, a meta-analysis including FACT trial [38] and SWOG S0226 trial [39] showed that, as first-line therapy in postmenopausal women with HR-positive advanced breast cancer, the addition of fulvestrant at loading does was not efficient than anastrozole alone [40]. Another trial was conducted to explore clinical benefits among NSAI-resistant patients, the results also showed fulvestrant plus anastrozole was not better than either fulvestrant alone or exemestane alone [41].

It has been documented that, fulvestrant could be combined with several kinds of targeted drugs, such as CDK4/6 inhibitor, PI3K inhibitor and mTOR inhibitor. Our meta-analysis indicated that, compared with fulvestrant alone, targeted therapy plus fulvestrant slightly prolonged PFS (HR = 0.77, 95%CI: 0.66–0.91) in postmenopausal patients with HR-positive advanced breast cancer. This finding is consistent with the previous published meta-analysis [42, 43]. Based on existing evidence, we could also draw forementioned conclusion in postmenopausal women with HR+ / HER- tumor (HR = 0.71, 95%CI: 0.60–0.85) or patients with ET-resistant advanced breast cancer (HR = 0.76, 95%CI: 0.63–0.92). Moreover, PIK3CA mutations represent one of the most common molecular aberrations in breast cancer [44, 45].

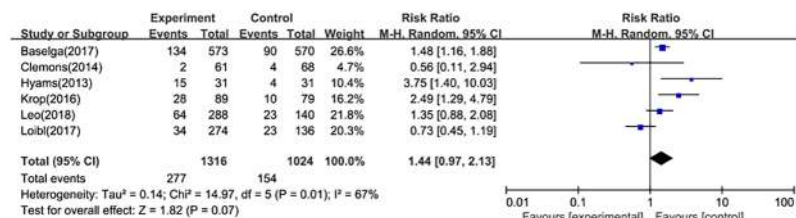


Fig 7. Forest plot for sever adverse events in postmenopausal patients with HR+ advanced breast cancer.

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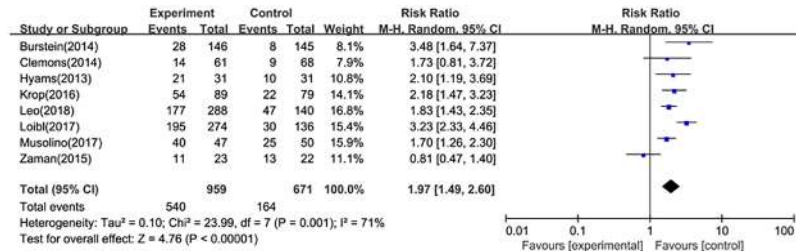


Fig 8. Forest plot for CTCAE ≥ 3 in postmenopausal patients with HR+ advanced breast cancer.

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Several trials were failed to find a significant association between PI3K inhibitors and PIK3CA-mutant breast cancer [26, 46], which brings into question whether PIK3CA mutation are targetable in the clinic setting [47]. The present analysis showed that combination therapy would prolong PFS for postmenopausal patients with PIK3CA-mutant ctDNA (HR = 0.52, 95%CI: 0.39–0.69), whereas patients with PIK3CA mutation detected in tumor issue failed to show the significant benefit (HR = 0.70, 95%CI: 0.48–1.02). And the other endpoints concerning patients with PIK3CA-mutant cancer were too sparsely reported for a meta-analysis to be feasible.

Besides PFS, targeted drugs plus fulvestrant also slightly improved ORR for postmenopausal women with HR-positive, HER2-negative advanced breast cancer (RR = 1.78, 95%CI: 1.35–2.34). And it is also an effective choice to improve ORR in patients with measurable disease (HR = 2.35 95%CI: 1.35–4.11).

For toxicity, the currently available clinical evidence indicated that there was a weak positive correlation between the combination therapy and the incidence of adverse events (RR = 1.09, 95%CI: 1.05–1.13), and we also draw the similar conclusion for the risk of CTCAE ≥ 3 (RR = 1.97, 95%CI: 1.49–2.60). Moreover, discontinuation due to adverse events reported in combination arms was higher than fulvestrant monotherapy (RR = 4.91, 95%CI: 3.37–7.15). Although SAEs related to drugs was significantly different between treatment groups (RR = 4.23, 95%CI: 1.62–11.03), this estimate required more robust evidence to support due to the broad range of 95%CI.

We found some limitations in this study: first, some pooled effect size, lower limit or upper limit of 95%CI were near the value 1, which might be an important factor to change significance of results in sensitivity analysis, and these relevant results in meta-analysis should be explain cautiously; second, some concerned endpoints, such as OS, adverse events related to treatment drugs were reported scarcely; third, studies of drugs targeting the same signal pathways or receptors were little, more RCTs concerning targeted therapy in combination with endocrine therapy should be conducted and published.

In conclusion, compared with fulvestrant monotherapy, targeted therapy plus fulvestrant slightly improved PFS and ORR of postmenopausal women with HR+ advanced breast cancer;

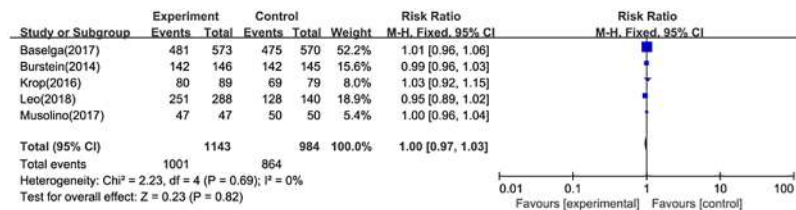


Fig 9. Forest plot for discontinuations in postmenopausal patients with HR+ advanced breast cancer.

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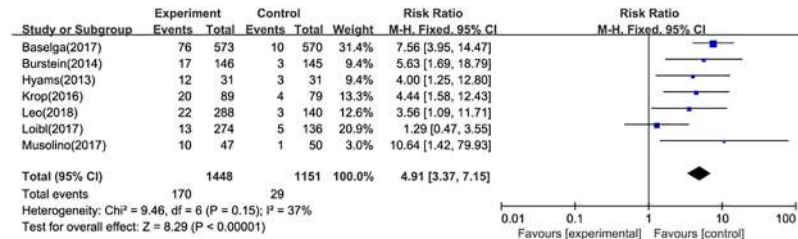


Fig 10. Forest plot for discontinuations due to adverse events in postmenopausal patients with HR+ advanced breast cancer.

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besides, combination therapy also increased toxicity. To date, the majority of RCTs have not identified cancer biomarkers, which might decrease the efficacy of target drugs. Therefore, more measures should be taken to promote the progress of precision medicine for advanced breast cancer.

Supporting information

S1 Table. PRISMA 2009 Checklist.
(DOC)

Author Contributions

Methodology: Su Xiangyu, Shi Fangfang, Chen Yan.

Project administration: Gu Xiaoyi.

Writing – original draft: Gao Chanchan.

Writing – review & editing: Shi Fangfang, Chen Yan.

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