Sun et al. BMC Cancer (2020) 20:180
https://doi.org/10.1186/s12885-020-6674-1

BMC Cancer

RESEARCH ARTICLE Open Access

# Efficacy of bevacizumab combined with chemotherapy in the treatment of HER2-negative metastatic breast cancer: a network meta-analysis

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## Abstract

**Background:** It is not known what combination of bevacizumab and chemotherapy agents is the best therapeutic regimen. Comparative study results among the efficacies of bevacizumab plus chemotherapy remain controversial in patients with HER2-negative metastatic breast cancer.

**Methods:** We searched Pubmed, Embase, and Cochrane Library Central Resister of Controlled Trials through were July 2019 for randomized controlled trials that evaluated the efficacy of bevacizumab plus chemotherapy in HER2-negative metastatic breast cancer. Data on included study characteristics, outcomes, and risk of bias were abstracted by two reviewers.

**Results:** A total of 16 RCT studies involving 5689 patients were included. The results showed that bevacizumab (Bev) - taxanes (Tax) - capecitabine (Cap) has highest-ranking and is probably more effective for prolonging progression-free survival (PFS) than Tax, Cap, Bev-Tax and Bev-Cap, which was no convincing differences among Bev-Cap-vinorelbine, Bev-Tax-everolimus, Bev-Tax-trebananib, Bev-exemestane, Bev-Cap-cyclophosphamide in Bev-containing regimens. For overall response rate (ORR), Bev-Tax-Cap is superior to Tax, Cap and Bev-Cap, while Bev-Tax-trebananib is superior to Cap. The cumulative probability ranking showed that Bev-Tax-Cap or Bev-Tax-trebananib may have best pathological response rate in HER2-negative metastatic breast cancer.

**Conclusion:** Our results provide moderate quality evidence that bevacizumab-taxanes-capecitabine maybe the most effective bevacizumab plus chemotherapy on PFS and ORR in HER2-negative metastatic breast cancer, however it should be also considered that bevacizumab may add toxicity to chemotherapy and whether improve overall survival (OS) or not.

**Keywords:** Bevacizumab, Chemotherapy, HER2-negative metastatic breast cancer, Network meta-analysis

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## Background

As vascular endothelial growth factor (VEGF) – neutralizing antibody, bevacizumab plays a vital role in the growth and progression of neoplasm angiogenesis [1–4]. Compared with chemotherapy alone, the addition of bevacizumab to chemotherapy improves overall response rates (ORR) and procession-free survival (PFS) in patients with HER2-negative metastatic breast cancer [5, 6].

In four randomized controlled trials (RCTs), adding bevacizumab to taxanes for HER2-negative metastatic breast cancer significantly increased PFS and ORR, while combination of bevacizumab with taxanes did certainly impact on the safety profile of taxanes [7–10]. The RCT has showed that patients receiving bevacizumab-taxanes have better PFS and objective response than receiving bevacizumab-capecitabine as first-line treatment for HER2-negative metastatic breast cancer [11]. For safety profiles, bevacizumab-capecitabine has good tolerability compared with bevacizumab- taxanes [12].

Previous studies have indicated that the addition of capecitabine to taxanes and bevacizumab significantly improved PFS, OS and ORR that compared with taxanes and bevacizumab as first-line treatment strategies [13, 14]. In contrast to previous studies, other study suggested that bevacizumab plus capecitabine and taxanes did not show an improvement of PFS and safety in patients with HER2-negative metastatic breast cancer [15]. Another concern has been the addition of second-line chemotherapy agents, such as vinorelbine, everolimus and trebananib, did not improve the efficacy of bevacizumab and taxanes, while adverse events were even enhanced [16–18].

However, the best bevacizumab plus chemotherapeutic strategy is not yet available in existing clinical trials. To explore the efficacy of bevacizumab plus chemotherapy in patients with HER2-negative metastatic breast cancer (MBC), we conducted a network meta-analysis addressing the relative impact of HER2-negative MBC on PFS and ORR.

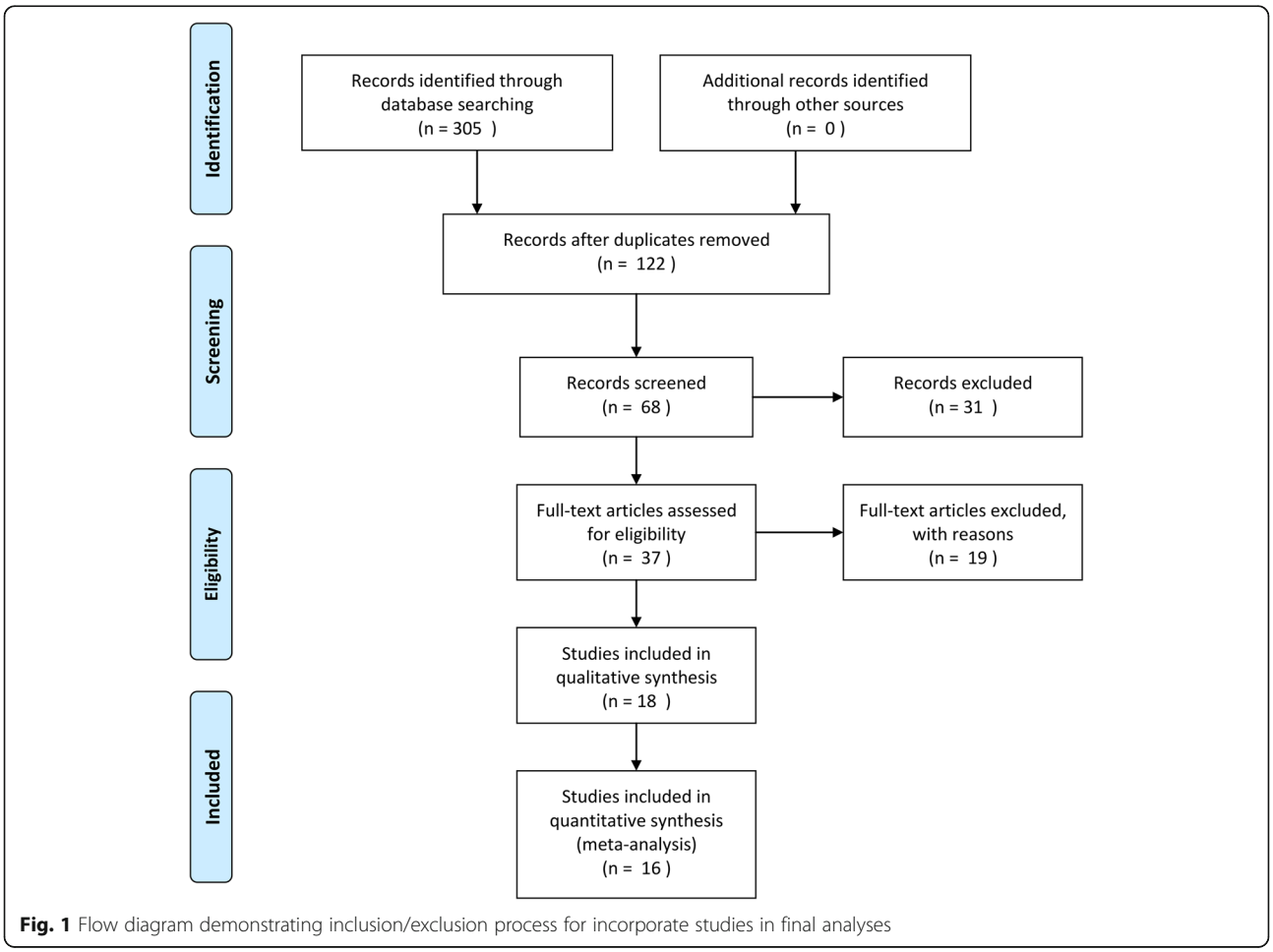


**Fig. 1** Flow diagram demonstrating inclusion/exclusion process for incorporate studies in final analyses

## Methods

### Search strategy

Relevant RCTs was searched in Pubmed, Embase and Cochrance library databases. Retrieval words including "bevacizumab" and "HER2 - negative Metastatic breast cancer". In this study, subject words, free words and Boolean logic operator connection was used for retrieval without language restriction. The retrieval time was from the establishment of each database to July 2019.

### Inclusion and exclusion criteria

We included studies that i) randomized controlled clinical trials of bevacizumab based chemotherapy for HER2-negative metastatic breast cancer; ii) the baseline characteristics of patients, including age, severity of disease and underlying disease, were consistent and comparable in patients with HER2-negative metastatic breast cancer. iii) the interventions were bevacizumab based chemotherapy and conventional chemotherapy as a control.

To preserve intergroup homogeneity, we excluded that i) patients were < 18 years; ii) types of publication were case reports, reviews, commentaries and editorials, or only reported in abstract form; and iii) outcome data was incomplete or incorrect; iv) the attrition rate is more than 10%.

The above procedures of study search and selection were independently performed by two investigators (Zhengwu Sun and Yalin Xi). Study eligibility was determined by all authors' consensus.

### Data extraction

Two investigators (Zhengwu sun and Yalin Xi) independently extracted relevant data on patient characteristics/demographics, treatment detail, outcomes, and study design, with discrepancies resolved by a third investigator. Relevant PFS and ORR were extracted for primary and secondary endpoint respectively.

### Statistical analysis

We performed direct meta-analysis for all treatment comparisons, and statistical heterogeneity tested was performed using $I^2$, a value of $I^2 > 50\%$ was considered to have substantial heterogeneity. A fixed-effects model was selected when the heterogeneity test showed $I^2$ value < 50%, otherwise a random-effects model was used. The hazard ratio (HR) with its 95% CI was calculated for PFS, while the odds ratio (OR) with 95% CI was calculated for ORR. We used a

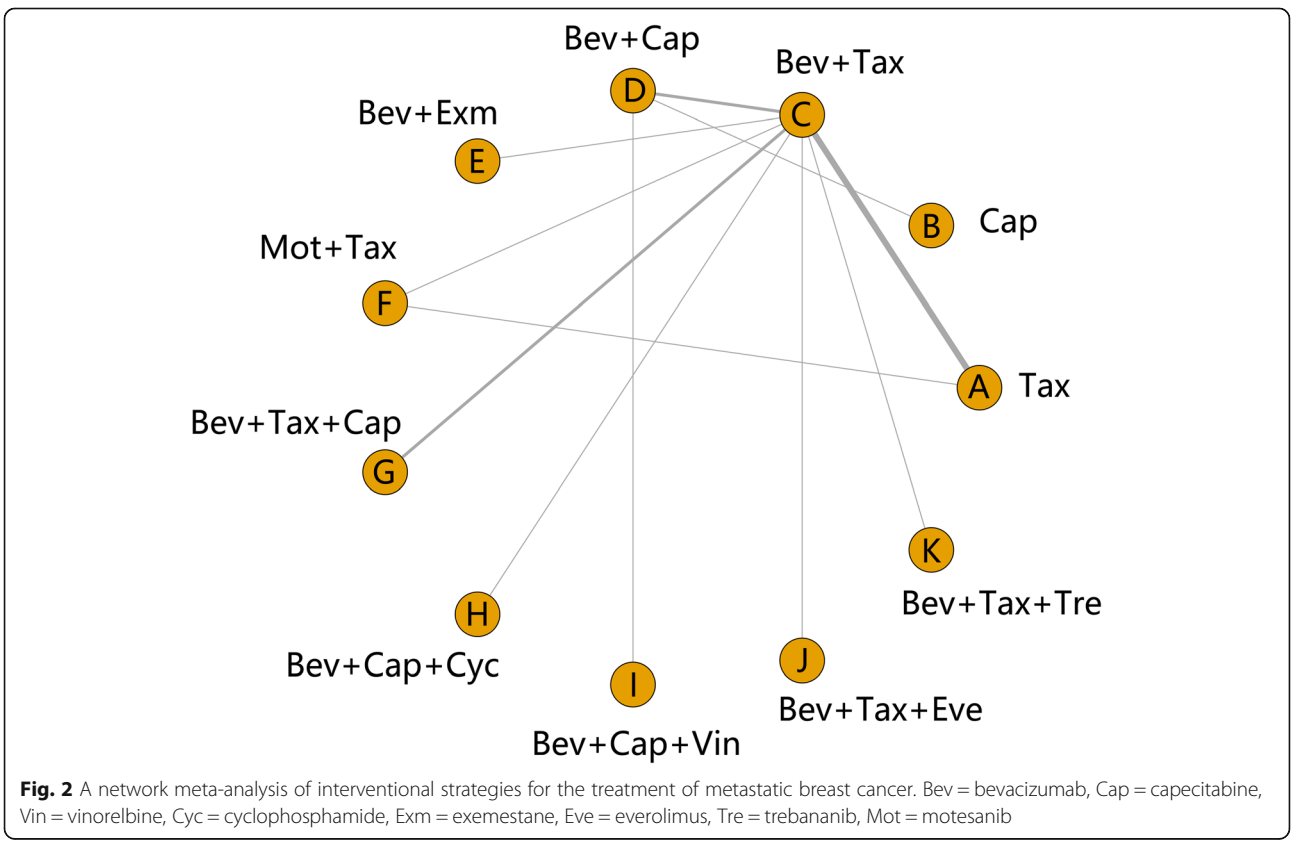


**Fig. 2** A network meta-analysis of interventional strategies for the treatment of metastatic breast cancer. Bev = bevacizumab, Cap = capecitabine, Vin = vinorelbine, Cyc = cyclophosphamide, Exm = exemestane, Eve = everolimus, Tre = trebananib, Mot = motesanib

**Table 1** Characteristics of the studies included in the network meta-analysis

| Study ID | Treatment 1 | | | | | | | | Treatment 2 | | | | | | | | Style |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Age (years) | | Intervention | Receptor status | | Prior therapy | | n | Age (years) | | Intervention | Receptor status | | Prior therapy | | |
| | | Median | Range | | ER+/PR+ | TN | Chemo | Hormono | | Median | Range | | ER+/PR+ | TN | Chemo | Hormono | |
| Norikazu Masuda 2017 [7] | 24 | 53 | 32–78 | Bev + Tax | 22 | 2 | 9 | 15 | 30 | 60 | 28–71 | Tax | 24 | 6 | 13 | 19 | RCT |
| David Miles 2017 [8] | 239 | 55 | 28–85 | Bev + Tax | 200 | 39 | 116 | 92 | 242 | 56 | 28–77 | Tax | 203 | 39 | 118 | 105 | RCT |
| Christoph Rochlitz 2016 [19] | 71 | 64 | 30–82 | Bev + Tax | 61 | 10 | 38 | NA | 68 | 62 | 29–81 | Bev + Cap+Cyc | 52 | 15 | 37 | NA | RCT |
| Christoph Zielinski 2016 [12] | 266 | NA | NA | Bev + Tax | 205 | 60 | 142 | 50 | 265 | NA | NA | Bev + Cap | 201 | 64 | 143 | 43 | RCT |
| A. Welt 2016 [16] | 295 | 63 | 34–88 | Bev + Cap+Vin | 233 | 61 | 195 | 169 | 297 | 61 | 29–85 | Bev + Cap | 236 | 61 | 193 | 171 | RCT |
| O. Trédan 2016 [20] | 58 | 56 | 35–77 | Bev + Exm | 57 | 1 | 35 | 33 | 59 | 55 | 35–86 | Bev + Tax | 59 | 0 | 38 | 39 | RCT |
| Denise A. Yardley 2015 [17] | 56 | 61 | 30–77 | Bev + Tax+Exr | 44 | 12 | 34 | 34 | 57 | 57 | 25–79 | Bev + Tax | 45 | 12 | 31 | 37 | RCT |
| Veronique Dieras 2015 [18] | 56 | 57 | 32–75 | Bev + Tax+Tre | 45 | 9 | 10 | NA | 58 | 52 | 31–74 | Bev + Tax | 45 | 12 | 11 | NA | RCT |
| Hans-Joachim Luck 2015 [15] | 111 | 57 | 31–78 | Bev + Tax+Cap | 111 | 0 | NA | NA | 116 | 57 | 31–80 | Bev + Tax | 116 | 0 | NA | NA | RCT |
| S.W. Lam 2014 [13] | 156 | 56 | 32–76 | Bev + Tax+Cap | 133 | 23 | 90 | 82 | 156 | 56 | 34–74 | Bev + Tax | 132 | 24 | 89 | 76 | RCT |
| Joseph Gligorov 2014 [14] | 91 | 49 | 24–80 | Bev + Tax+Cap | 66 | 25 | NA | NA | 94 | 54 | 24–77 | Bev + Tax | 73 | 21 | NA | NA | RCT |
| Istvan Lang 2013 [11] | 279 | 59 | 48–65 | Bev + Cap | 212 | 67 | 176 | 171 | 285 | 59 | 49–64 | Bev + Tax | 222 | 63 | 180 | 175 | RCT |
| Adam M. Brufsky 2011 [21] | 201 | 56 | 28–86 | Bev + Tax | 145 | 47 | NA | NA | 103 | 56 | 35–84 | Tax | 77 | 20 | NA | NA | RCT |
| | 97 | 57 | 31–78 | Bev + Cap | 74 | 18 | NA | NA | 47 | 50 | 23–90 | Cap | 36 | 10 | NA | NA | RCT |
| Miguel Martin 2011 [22] | 97 | 55 | 44–66 | Bev + Tax | 78 | 19 | 64 | 64 | 94 | 53 | 43–63 | Tax | 75 | 19 | 62 | 56 | RCT |
| | 91 | 55 | 44–66 | Mot + Tax | 73 | 18 | 60 | 58 | 94 | 53 | 43–63 | Tax | 75 | 19 | 62 | 56 | RCT |
| | 97 | 55 | 44–66 | Bev + Tax | 78 | 19 | 64 | 64 | 91 | 55 | 44–66 | Mot + Tax | 73 | 18 | 60 | 58 | RCT |
| David W. Miles 2010 [9] | 247 | 55 | 27–76 | Bev + Tax | 187 | 60 | 167 | 120 | 241 | 55 | 29–83 | Tax | 189 | 52 | 156 | 135 | RCT |
| Robert Gray 2009 [10] | 368 | 56 | 29–84 | Bev + Tax | 223 | 120 | 244 | NA | 354 | 55 | 27–85 | Tax | 223 | 99 | 231 | NA | RCT |

*Bev* bevacizumab, *Cap* capecitabine, *Vin* vinorelbine, *Cyc* cyclophosphamide, *Exm* exemestane, *Exr* everolimus, *Tre* trebananib, *Mot* motesanib, *RCTs* randomized controlled trials, *NA* not applicable, *n* number of patients, *Receptor Status* hormone receptor status, *ER+/PR+* estrogen receptor (ER) and/or progesterone receptor (PR) positive, *TN* triple negative, *Chemo* prior chemotherapy, *Hormono* prior hormonal therapy

**Table 2** Internal validity of included studies

| Study | Prospective design | Multicenter enrollment | Selection bias | Performance bias | Attrition bias | Detection bias | Multivariate adjustment for potential confounders |
|---|---|---|---|---|---|---|---|
| Norikazu Masuda 2017 [7] | ● | ○ | B | C | B | C | none reported |
| David Miles 2017 [8] | ● | ○ | A | A | B | A | probably adequate |
| Christoph Rochlitz 2016 [20] | ● | ● | B | B | B | C | none reported |
| Christoph Zielinski 2016 [13] | ● | ● | A | A | B | A | probably adequate |
| A. Welt 2016 [17] | ● | ● | A | A | A | A | probably adequate |
| O. Trédan 2016 [21] | ● | ● | B | C | B | C | none reported |
| Denise A. Yardley 2015 [18] | ● | ○ | B | C | A | C | none reported |
| Veronique Dieras 2015 [19] | ● | ● | B | C | A | C | none reported |
| Hans-Joachim Luck 2015 [16] | ● | ○ | A | A | A | B | probably adequate |
| S.W. Lam 2014 [14] | ● | ● | A | A | A | B | probably adequate |
| Joseph Gligorov 2014 [15] | ● | ● | A | A | B | B | probably adequate |
| Istvan Lang 2013 [12] | ● | ● | A | A | B | A | probably adequate |
| Adam M. Brufsky 2011 [22] | ● | ● | A | B | A | A | probably adequate |
| Miguel Martin 2011 [23] | ● | ● | A | B | A | B | probably adequate |
| David W. Miles 2010 [9] | ● | ● | A | A | A | A | probably adequate |
| Robert Gray 2009 [10] | ● | ● | A | A | A | A | probably adequate |

● = yes, ○ = no. Risk of bias is expressed as A = low, B = moderate, C = high, or D = incomplete reporting

bayesian random effects network meta-analysis approach to analyze the indirect data for multiple treatment comparisons. We compared the results of direct and indirect meta-analysis to determine the consistency of network meta-analysis. When it was not significant difference, we investigated consistency using consistency model, otherwise a node-splitting approach was used. All analyses were conducted in RevMan (version 3.5) and R (version 3.6.1), specifically the GeMTC package (version 0.8.2) was used for the network meta-analysis.

## Result

### Search results

The search identified 305 potentially relevant studies, of which 122 were included after duplicates removed. In total, 68 studies were retained for title and abstract review. By analyzing detail data, 37 studies were considered after full-text review. Moreover, 18 studies were included in qualitative synthesis, and two were duplicated data. Finally, sixteen studies were identified involving 589 patients that fulfilled the inclusion criteria in Fig. 1 [7–22]. Figure 2 demonstrates all available direct comparisons across outcomes in this network meta-analysis.

### Characteristics and methodological quality of the included studies

According to the PICOS principle (including "P" = patients, "I" = intervention, "C" = control, "O" = outcome, "S" = style), we presented the basic feature descriptions of the sixteen studies in Table 1. The age

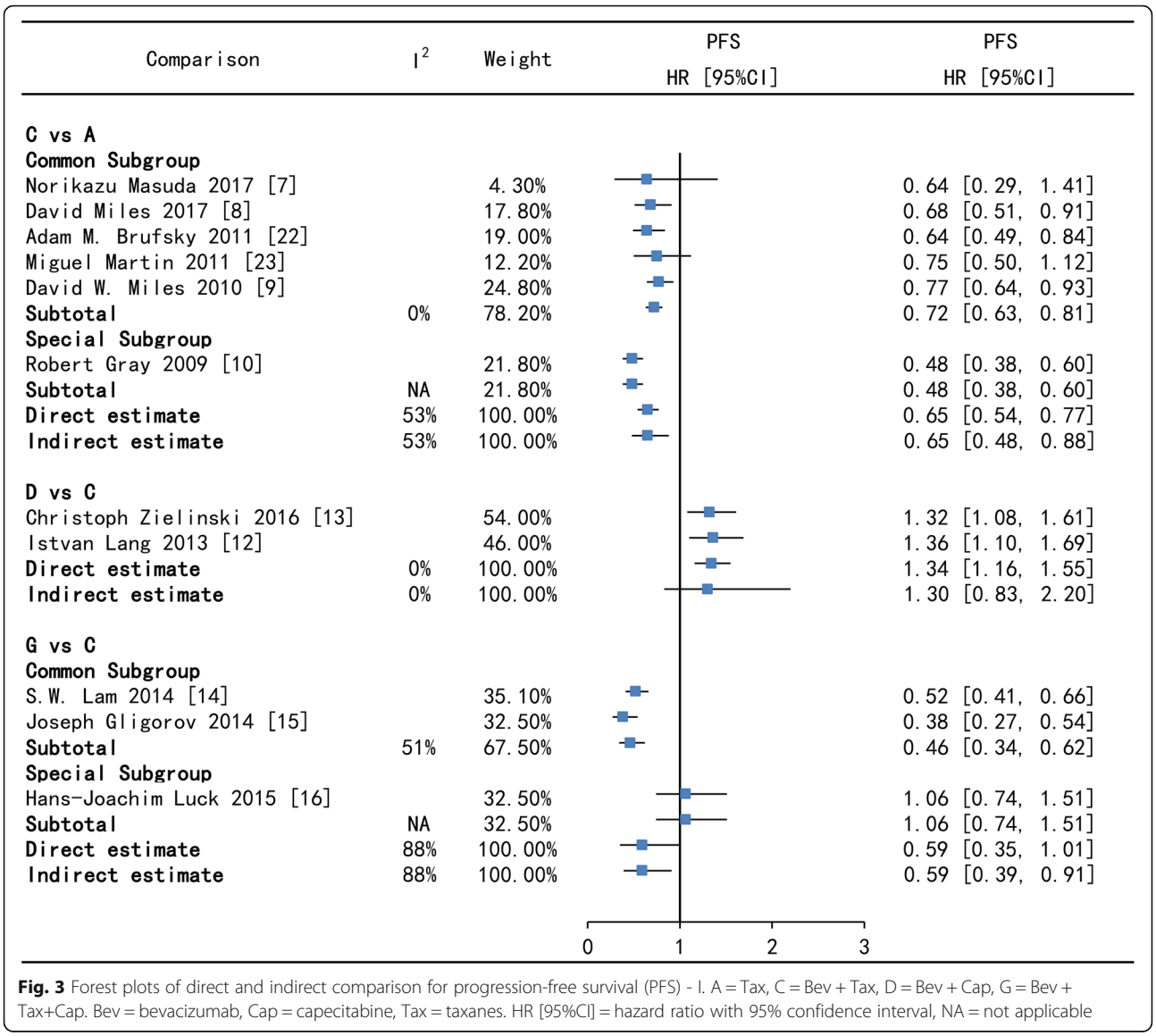


**Fig. 3** Forest plots of direct and indirect comparison for progression-free survival (PFS) - I. A = Tax, C = Bev + Tax, D = Bev + Cap, G = Bev + Tax+Cap. Bev = bevacizumab, Cap = capecitabine, Tax = taxanes. HR [95%CI] = hazard ratio with 95% confidence interval, NA = not applicable

of enrolled patients arranged from 23 to 90 years. In hormone receptor status, the majority of HER2-negtive MBC patients were estrogen receptor (ER) positive and / or progesterone receptor (PR) positive, but the minority is patients with triple negative breast cancer. Moreover, more than half of the enrolled patients had received prior chemotherapy, while more than half of the patients with ER positive and / or PR positive had received prior hormonal therapy. Outcomes of all studies included PFS and ORR. All including studies were RCTs with a total of 5689 patients, which include one 3-arm trial and sixteen 2-arm trials. Eleven treatments, including Tax, Cap, Bev + Tax, Bev + Cap, Bev + Exm, Mot + Tax, Bev + Tax+Cap, Bev + Cap+Cyc, Bev + Cap+Vin, Bev + Tax+Eve, Bev + Tax+Tre, were involved in patients with HER2-negative metastatic breast cancer (Table 1).

For the sixteen included studies, two investigators independently collected data and assessed methodological quality using the Cochrane collaboration's tool for assessing risk of bias. Remarkably, most assessment items have high/moderate levels of methodological quality in this network meta-analysis ("A" and "B" level on the risk of bias), which results are shown in Table 2.

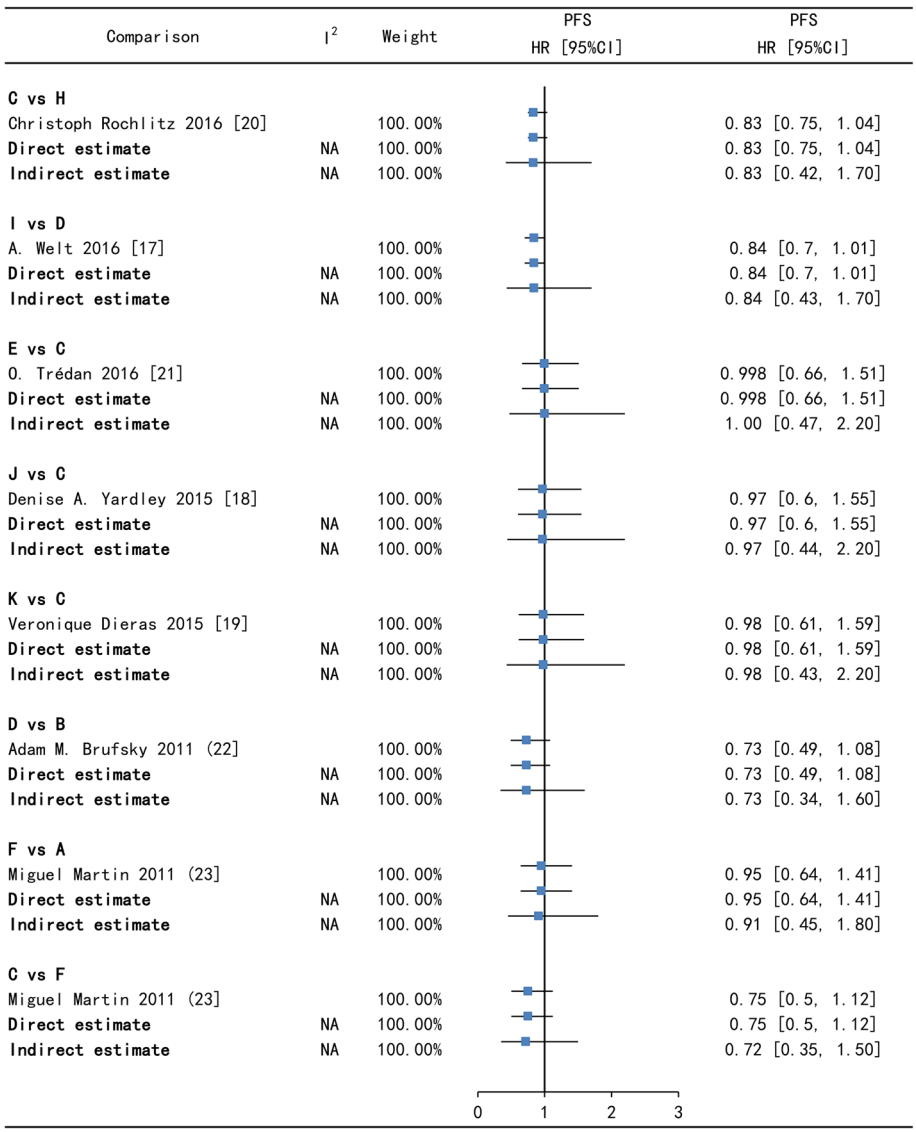


**Fig. 4** Forest plots of direct and indirect comparison for progression-free survival (PFS) - II. A = Tax, B = Cap, C = Bev + Tax, D = Bev + Cap, E = Bev + Exm, F = Mot + Tax, H = Bev + Cap+Cyc, I = Bev + Cap+Vin, J = Bev + Tax+ Eve, K = Bev + Tax+Tre. Bev = bevacizumab, Cap = capecitabine, Tax = taxanes, Vin = vinorelbine, Cyc = cyclophosphamide, Exm = exemestane, Eve = everolimus, Tre = trebananib, Mot = motesanib. HR [95%CI] = hazard ratio with 95% confidence interval, NA = not applicable

### Heterogeneity, consistency and publication bias analysis

Direct comparisons often suffered from limitations of risk of bias and imprecision, even heterogeneity after pooled. On PFS, Bev + Tax+Cap versus Bev + Tax has high heterogeneity (88%), however which reduce to moderate heterogeneity (51%) after subgroup analysis. Since one study show that Bev + Tax+Cap is not superior to Bev + Tax on PFS [15], which is contrary to the findings of two other studies [13, 14]. On ORR, Bev + Tax+Cap versus Bev + Tax has low heterogeneity (34%) in direct and indirect comparison, which may be because the ORR of Bev + Tax+Cap is higher than Bev + Tax, but close in one study [15]. The forest plot of direct and indirect comparison shows that Bev + Tax versus Tax has moderate heterogeneity (53%) on PFS and 47% on ORR. In subgroup analysis, there is no heterogeneity, except of one study which enrolled MBC not previously treated with chemotherapy [10]. The comparison of Bev + Cap versus Bev + Tax has no heterogeneity on PFS and ORR in Figs. 3 and 5.

For all comparisons across all outcomes, Node-splitting analysis suggested that there was no significantly consistency between direct and indirect estimates in Figs. 3, 4, 5 and 6. In Tax (A) - Bev + Tax (C) - Mot + Tax (F) closed loop, there is no significant difference on PFS and on ORR (the *p*-value of A versus C is 0.995775, A versus F is 0.997075 and C versus F is 0.993300) in Figs.3, 4, 5 and 6.

In addition, six direct comparisons, including Bev + Tax versus Tax, Bev + Cap versus Bev + Tax, Bev + Tax+Cap versus Bev + Tax on PFS and ORR were close to symmetric and no significant publication bias in Fig. 7.

### Progression-free survival

Sixteen RCTs with 5689 patients reported on PFS. For six comparisons, the network estimate provided moderate-quality evidence with Bev + Tax versus Tax (HR = 0.65, 95%CI = 0.48–0.88), Bev + Tax+Cap versus Tax (HR = 0.38, 95%CI = 0.23–0.65), Bev + Tax+Cap versus Cap (HR = 0.32, 95%CI = 0.12–0.87), Bev + Tax+Cap versus Bev + Tax (HR = 0.59, 95%CI = 0.39–0.91), Bev + Tax+Cap versus Bev + Cap (HR = 0.44, 95%CI = 0.23–0.83), Bev + Tax+Cap versus Mot + Tax (HR = 0.42, 95%CI = 0.18–0.99). Other pairwise comparisons were not statistically significant difference (Table 3). The cumulative probability statistic showed that Bev + Tax+Cap ranked first, followed by Bev + Cap+Vin, Bev + Tax+Eve, Bev + Tax+Tre, Bev + Tax, Bev + Exm, Bev + Cap, Bev + Cap+Cyc, Mot + Tax, Tax and Cap. To reasonable

| Comparison | Treatment 1 Events | Treatment 1 Total | Treatment 2 Events | Treatment 2 Total | $I^2$ | Weight | ORR OR [95%CI] | ORR OR [95%CI] |
|---|---|---|---|---|---|---|---|---|
| **C vs A** | | | | | | | | |
| **Common Subgroup** | | | | | | | | |
| N. Masuda 2017 [7] | 14 | 24 | 13 | 28 | | 5.10% | | 1.62 [0.54, 4.85] |
| David Miles 2017 [8] | 129 | 239 | 80 | 242 | | 21.80% | | 2.37 [1.64, 3.44] |
| A M. Brufsky 2011 [22] | 98 | 201 | 40 | 103 | | 16.80% | | 1.50 [0.92, 2.43] |
| M. Martin 2011 [23] | 50 | 97 | 39 | 94 | | 13.80% | | 1.50 [0.85, 2.66] |
| D W. Miles 2010 [9] | 158 | 247 | 112 | 231 | | 22.00% | | 1.89 [1.31, 2.72] |
| **Subtotal** | 449 | 808 | 284 | 698 | 0% | 79.60% | | 1.88 [1.52, 2.31] |
| **Special Subgroup** | | | | | | | | |
| Robert Gray 2009 [10] | 112 | 229 | 54 | 243 | | 20.40% | | 3.35 [2.25, 4.99] |
| **Subtotal** | 112 | 229 | 54 | 243 | NA | 20.40% | | 3.35 [2.25, 4.99] |
| **Direct estimate** | 561 | 1037 | 338 | 941 | 47% | 100.00% | | 2.06 [1.58, 2.70] |
| **Indirect estimate** | 561 | 1037 | 338 | 941 | 47% | 100.00% | | 2.06 [1.20, 2.81] |
| **D vs C** | | | | | | | | |
| C Zielinski 2016 [13] | 76 | 277 | 125 | 284 | | 49.90% | | 0.48 [0.34, 0.68] |
| Istvan Lang 2013 [12] | 76 | 279 | 125 | 285 | | 50.10% | | 0.48 [0.34, 0.68] |
| **Direct estimate** | 152 | 556 | 250 | 569 | 0% | 100.00% | | 0.48 [0.37, 0.62] |
| **Indirect estimate** | 152 | 556 | 250 | 569 | 0% | 100.00% | | 0.48 [0.26, 0.88] |
| **G vs C** | | | | | | | | |
| S.W. Lam 2014 [14] | 108 | 156 | 80 | 156 | | 43.00% | | 1.17 [0.70, 1.97] |
| J. Gligorov 2014 [15] | 78 | 91 | 72 | 94 | | 40.40% | | 2.14 [1.35, 3.40] |
| H-J Luck 2015 [16] | 57 | 111 | 55 | 116 | | 16.60% | | 1.83 [0.86, 3.91] |
| **Direct estimate** | 243 | 358 | 207 | 366 | 34% | 100.00% | | 1.67 [1.22, 2.29] |
| **Indirect estimate** | 243 | 358 | 207 | 366 | 34% | 100.00% | | 1.70 [0.95, 2.90] |

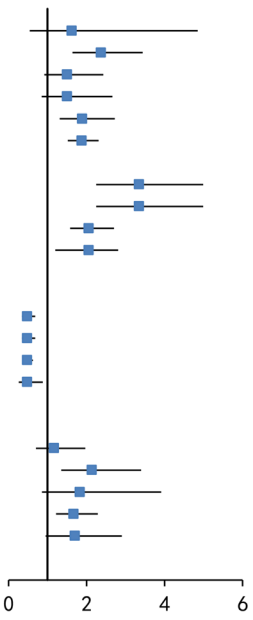


**Fig. 5** Forest plots of direct and indirect comparison for overall response rates (ORR) - I. A = Tax, C = Bev + Tax, D = Bev + Cap, G = Bev + Tax+Cap. Bev = bevacizumab, Cap = capecitabine, Tax = taxanes. OR [95%CI] = Odds ratio with 95% confidence interval, NA = not applicable

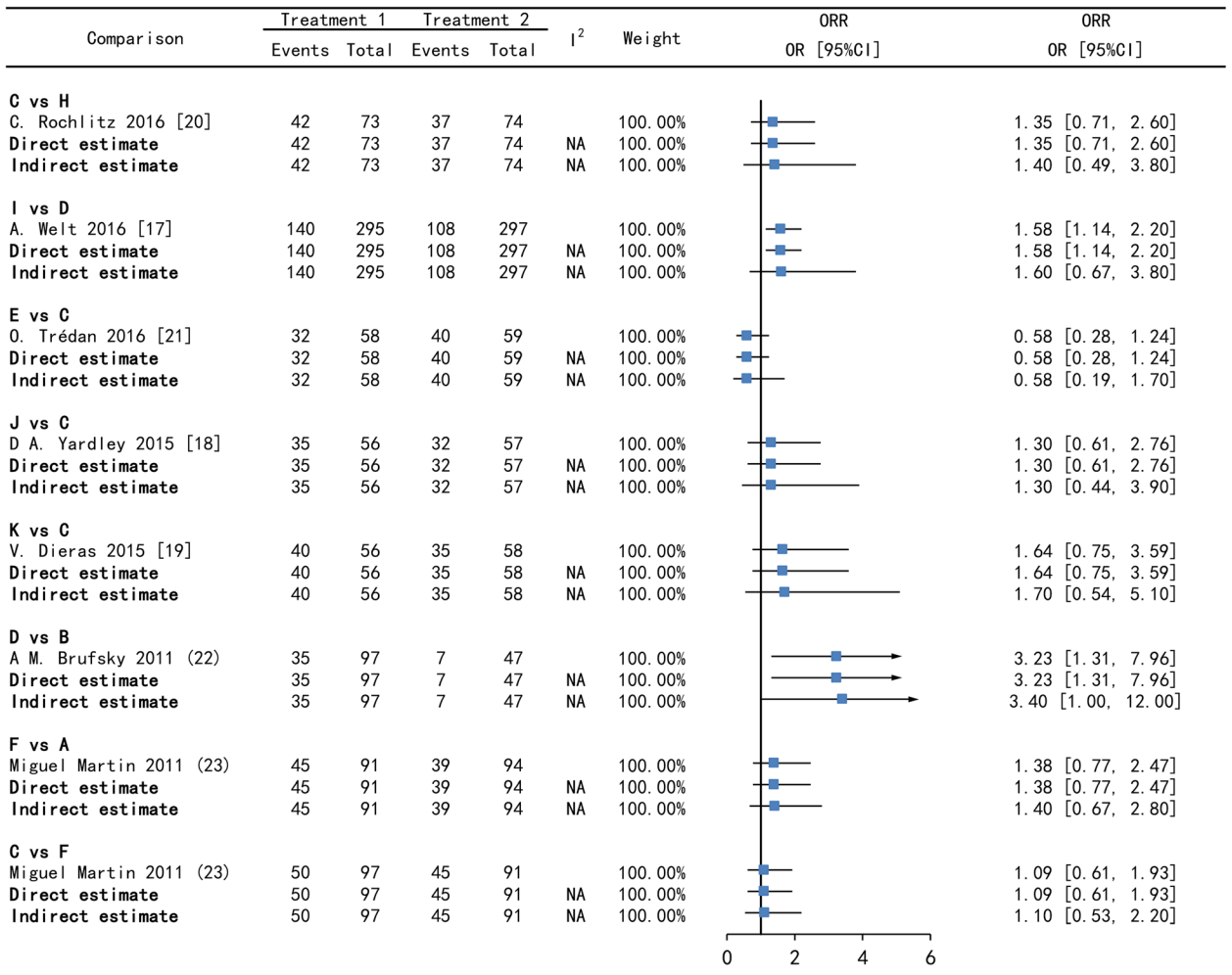


**Fig. 6** Forest plots of direct and indirect comparison for overall response rates (ORR) - II. A = Tax, B = Cap, C = Bev + Tax, D = Bev + Cap, E = Bev + Exm, F = Mot + Tax, H = Bev + Cap+Cyc, I = Bev + Cap+Vin, J = Bev + Tax+ Eve, K = Bev + Tax+Tre. Bev = bevacizumab, Cap = capecitabine, Tax = taxanes, Vin = vinorelbine, Cyc = cyclophosphamide, Exm = exemestane, Eve = everolimus, Tre = trebananib, Mot = motesanib. OR [95%CI] = Odds ratio with 95% confidence interval, NA = not applicable

evaluated the efficacy of bevacizumab-contained chemotherapy, the independent rank of bevacizumab combined with two chemotherapy agents is as flowing: Bev + Tax+-Cap>Bev + Cap+Vin>Bev + Tax+Eve>Bev + Tax+Tre>-Bev + Cap+Cyc; the rank of bevacizumab combined with chemotherapy agent: Bev + Tax>Bev + Exm>Bev + Cap (Fig. 8).

### Objective response rate

For objective response rate, sixteen studies (5689 patients) proved eligible. The results provide moderate quality evidence that Cap versus Tax (OR = 0.21, 95%CI = 0.051–0.85), Bev + Tax+Cap versus Tax (OR = 2.5, 95%CI = 1.3–4.9), Bev + Tax versus Cap (OR = 7.1, 95%CI = 1.9–28.0), Bev + Tax versus Tax (OR = 2.06, 95%CI = 1.20–2.81), Mot + Tax versus Cap (OR = 6.5, 95%CI = 1.4–31.0), Bev + Tax+Cap versus Cap (OR = 12, 95%CI = 2.8–52.0), Bev + Cap+Vin versus Cap (OR = 5.4, 95%CI = 1.3–24.0), Bev + Tax+Eve versus Cap (OR = 9.3, 95%CI = 1.7–53.0), Bev + Tax+Tre versus Cap (OR = 12, 95%CI = 2.1–69.0), Bev + Cap versus Bev + Tax (OR = 0.48, 95%CI = 0.26–0.88), Bev + Tax+Cap versus Bev + Cap (OR = 3.5, 95%CI = 1.5–8.0), Bev + Cap versus Cap (OR = 0.3, 95%CI = 0.085–0.96) and other pairwise comparisons were not statistically significant difference in Table 4. The therapeutic strategies ranking: Bev + Tax+-Tre, Bev + Tax+Cap, Bev + Tax+Eve, Bev + Tax, Mot + Tax, Bev + Cap+Vin, Bev + Cap+Cyc, Tax, Bev + Cap, Bev + Exm, and Cap. Moreover, the independent rank of bevacizumab combined with two chemotherapy agents: Bev + Tax+Tre>Bev + Tax+Cap>Bev + Tax+Eve>Bev + Cap+Vin>Bev + Cap+Cyc; the rank of bevacizumab

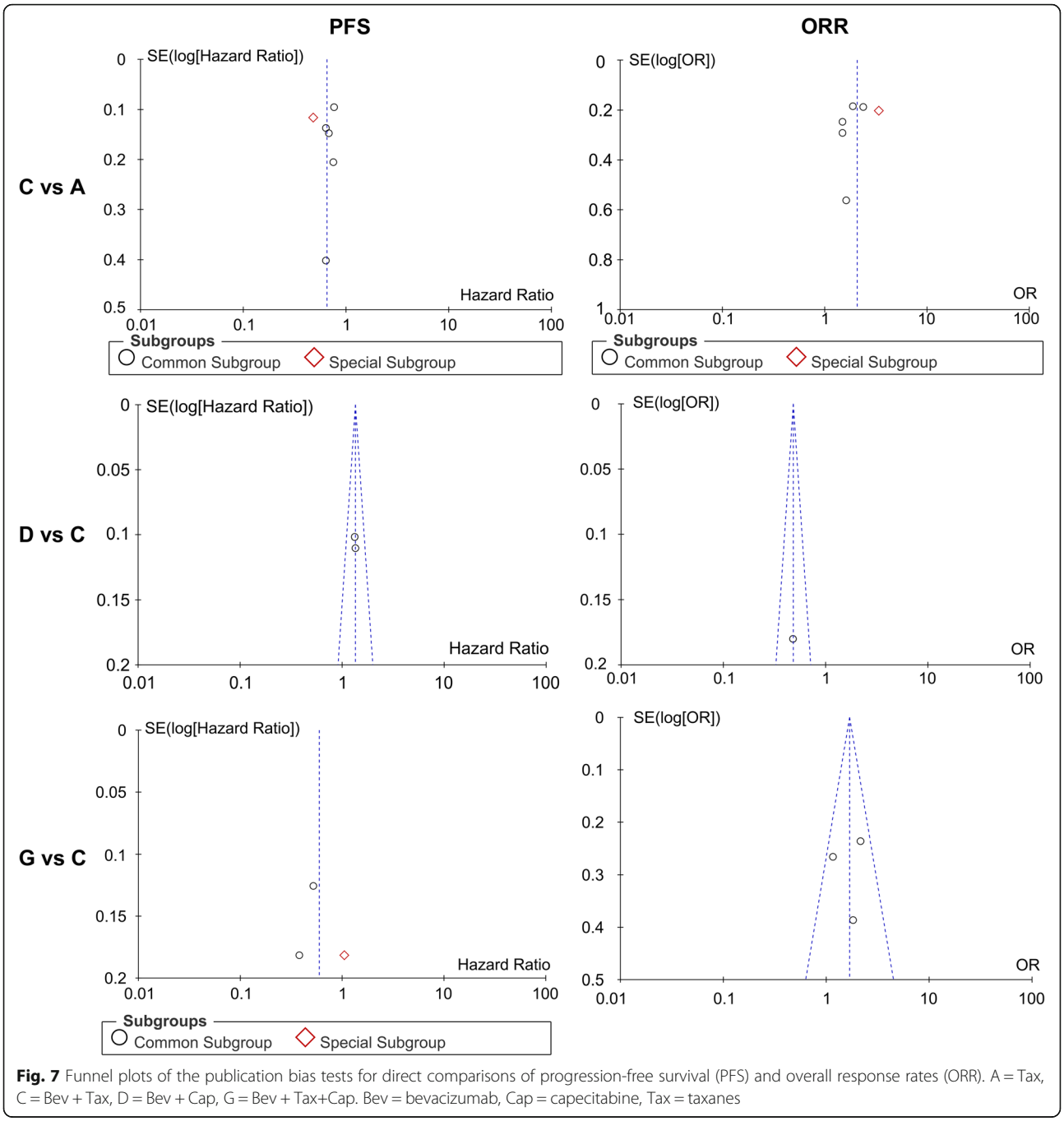


**Fig. 7** Funnel plots of the publication bias tests for direct comparisons of progression-free survival (PFS) and overall response rates (ORR). A = Tax, C = Bev + Tax, D = Bev + Cap, G = Bev + Tax+Cap. Bev = bevacizumab, Cap = capecitabine, Tax = taxanes

combined with chemotherapy agent: Bev + Tax>Bev + Cap>Bev + Exm (Fig. 9).

### Safety

Summary frequency of treatment-related grade ≧ 3 adverse events (AE), including hematologic AE (anemia, leukopenia and neutropenia) and non-hematologic AE (hypertension, haemorrhage/bleeding, thromboembolic events, neuropathy, nausea/vomiting, diarrhea, mucositis/stomatitis, edema, proteinuria, hepatobiliary disorders, hand-foot syndrome, fatigue, pain, alopecia and infection) are pooled for analysis in Table 5. We found that the toxicity of regimens significantly increases with the addition of bevacizumab or chemotherapy drugs in general, even though the adverse events of Cap and Bev + Cap+Cyc regimens are not applicable.

## Discussion

In this network meta-analysis, we included 16 RCTs enrolling 5689 patients comparing various chemotherapy

**Table 3** Indirect comparison in PFS

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **A** | 1.2 (0.46, 3.1) | **0.65 (0.48, 0.88)** | 0.87 (0.50, 1.5) | 0.65 (0.29, 1.5) | 0.91 (0.45, 1.8) | **0.38 (0.23, 0.65)** | 0.78 (0.37, 1.6) | 0.73 (0.30, 1.8) | 0.63 (0.27, 1.5) | 0.63 (0.27, 1.5) |
| 0.84 (0.33, 2.2) | **B** | 0.55 (0.22, 1.3) | 0.73 (0.34, 1.6) | 0.54 (0.17, 1.8) | 0.76 (0.24, 2.4) | **0.32 (0.12, 0.87)** | 0.66 (0.22, 2.0) | 0.61 (0.22, 1.7) | 0.53 (0.16, 1.7) | 0.53 (0.16, 1.8) |
| **1.5 (1.1, 2.1)** | 1.8 (0.75, 4.5) | **C** | 1.3 (0.83, 2.2) | 1.0 (0.47, 2.2) | 1.4 (0.67, 2.8) | **0.59 (0.39, 0.91)** | 1.2 (0.61, 2.4) | 1.1 (0.49, 2.6) | 0.97 (0.44, 2.2) | 0.98 (0.43, 2.2) |
| 1.1 (0.65, 2.0) | 1.4 (0.64, 2.9) | 0.75 (0.46, 1.2) | **D** | 0.74 (0.31, 1.8) | 1.0 (0.44, 2.5) | **0.44 (0.23, 0.83)** | 0.90 (0.38, 2.0) | 0.84 (0.43, 1.7) | 0.73 (0.28, 1.9) | 0.73 (0.28, 1.8) |
| 1.5 (0.67, 3.4) | 1.8 (0.57, 5.9) | 1.0 (0.46, 2.1) | 1.3 (0.54, 3.3) | **E** | 1.4 (0.49, 4.0) | 0.59 (0.24, 1.4) | 1.2 (0.43, 3.3) | 1.1 (0.36, 3.5) | 0.97 (0.32, 3.0) | 0.98 (0.32, 3.0) |
| 1.1 (0.55, 2.2) | 1.3 (0.42, 4.2) | 0.72 (0.35, 1.5) | 0.96 (0.41, 2.3) | 0.71 (0.25, 2.0) | **F** | **0.42 (0.18, 0.99)** | 0.86 (0.32, 2.3) | 0.81 (0.27, 2.5) | 0.70 (0.24, 2.1) | 0.70 (0.24, 2.1) |
| **2.6 (1.5, 4.4)** | **3.1 (1.2, 8.3)** | **1.7 (1.1, 2.6)** | **2.3 (1.2, 4.3)** | 1.7 (0.71, 4.1) | **2.4 (1.0, 5.4)** | **G** | 2.1 (0.90, 4.5) | 1.9 (0.75, 4.9) | 1.7 (0.67, 4.0) | 1.7 (0.66, 4.1) |
| 1.3 (0.61, 2.7) | 1.5 (0.50, 4.6) | 0.83 (0.42, 1.7) | 1.1 (0.49, 2.6) | 0.83 (0.30, 2.3) | 1.2 (0.43, 3.1) | 0.49 (0.22, 1.1) | **H** | 0.94 (0.32, 2.8) | 0.81 (0.29, 2.3) | 0.81 (0.28, 2.3) |
| 1.4 (0.55, 3.3) | 1.6 (0.59, 4.5) | 0.89 (0.38, 2.0) | 1.2 (0.60, 2.3) | 0.88 (0.28, 2.8) | 1.2 (0.41, 3.7) | 0.52 (0.20, 1.3) | 1.1 (0.36, 3.1) | **I** | 0.86 (0.27, 2.7) | 0.87 (0.26, 2.8) |
| 1.6 (0.67, 3.7) | 1.9 (0.58, 6.3) | 1.0 (0.46, 2.3) | 1.4 (0.54, 3.5) | 1.0 (0.34, 3.1) | 1.4 (0.48, 4.2) | 0.61 (0.25, 1.5) | 1.2 (0.43, 3.5) | 1.2 (0.37, 3.6) | **J** | 1.0 (0.32, 3.1) |
| 1.6 (0.66, 3.7) | 1.9 (0.57, 6.4) | 1.0 (0.46, 2.3) | 1.4 (0.55, 3.6) | 1.0 (0.34, 3.1) | 1.4 (0.48, 4.2) | 0.60 (0.24, 1.5) | 1.2 (0.43, 3.5) | 1.2 (0.36, 3.8) | 1.0 (0.32, 3.1) | **K** |

A = Tax, B = Cap, C = Bev + Tax, D = Bev + Cap, E = Bev + Exm, F = Mot + Tax, G = Bev + Tax+Cap, H = Bev + Cap+Cyc, I = Bev + Cap+Vin, J = Bev + Tax+ Eve, K = Bev + Tax+Tre
The values represent HR (95%CI), and the values in bold represent HR (95%CI) has significant statistical difference in indirect comparison
*Bev* bevacizumab, *Cap* capecitabine, *Tax* taxanes, *Vin* vinorelbine, *Cyc* cyclophosphamide, *Exm* exemestane, *Eve* everolimus, *Tre* trebananib, *Mot* motesanib

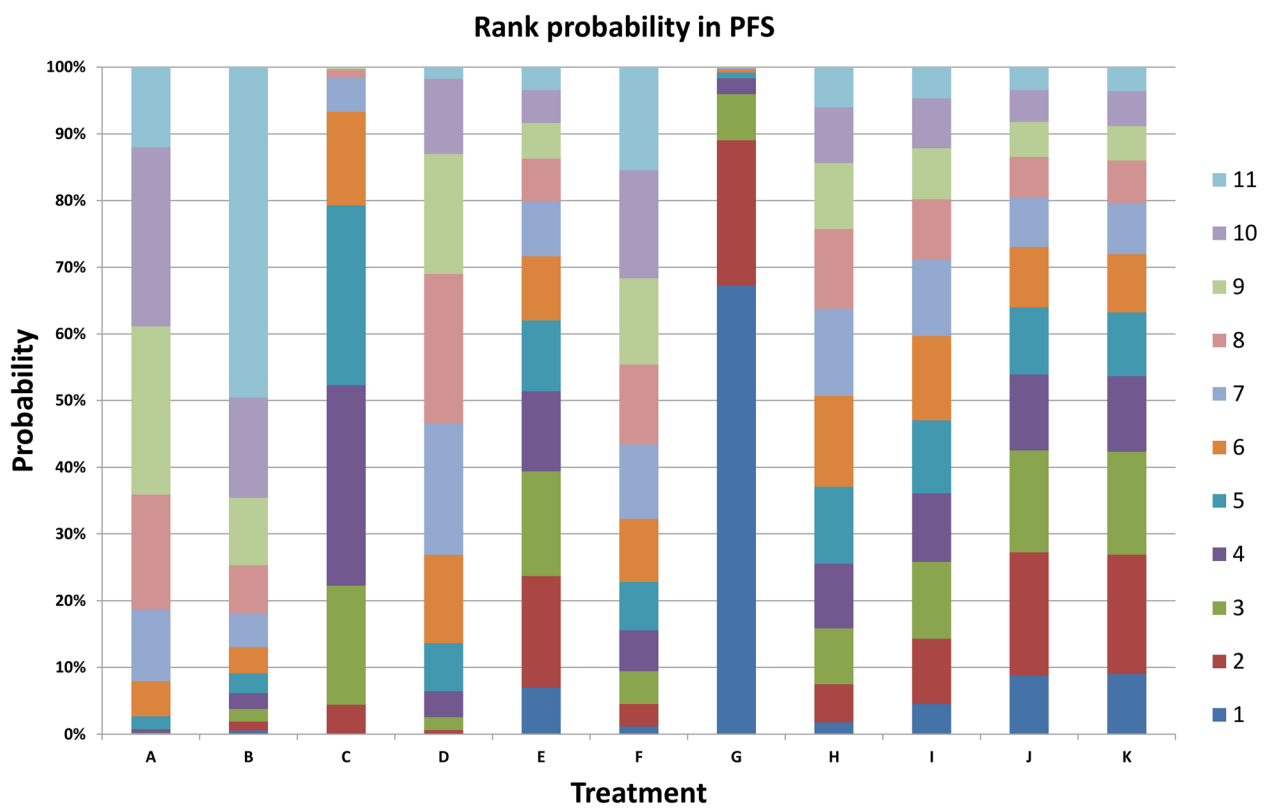


**Fig. 8** Cumulative ranking probability of progression-free survival (PFS) for the treatment of metastatic breast cancer. A = Tax, B = Cap, C = Bev + Tax, D = Bev + Cap, E = Bev + Exm, F = Mot + Tax, G = Bev + Tax+Cap, H = Bev + Cap+Cyc, I = Bev + Cap+Vin, J = Bev + Tax+Eve, K = Bev + Tax+Tre. Bev = bevacizumab, Cap = capecitabine, Tax = taxanes, Vin = vinorelbine, Cyc = cyclophosphamide, Exm = exemestane, Eve = everolimus, Tre = trebananib, Mot = motesanib. Serial number 1–11 represent probability ranking

strategies. The use of indirect comparisons within this network meta-analysis adds additional information beyond the multiple direct comparison meta-analysis that have compared Bev + Tax, Bev + Cap, Bev + Tax+-Cap with Tax, Cap and with other new chemotherapy. According to our results, it is certain that the addition of bevacizumab improved PFS and ORR compared with chemotherapy alone, which is consistent with previous studies [7, 8, 21]. Moreover, we found that more patients who received Bev + Tax had an objective response than did those who received Bev + Cap, and that Bev + Tax is superior to Bev + Cap in therapeutic strategies ranking, but there was no significant difference between Bev + Tax and Bev + Cap on PFS in HER2-negative breast cancer. Previous studies have also showed that progression-free survival with Bev + Tax is superior to that noted with Bev + Cap, but one of included RCTs has indicated that the advantage of Bev + Tax to Bev + Cap have not statistically difference on PFS [11, 12]. In addition, most included trials directly compared Bev + Tax with Tax, while few trials directly compared Bev + Cap with Cap and with Bev + Tax, which could impact our results in the indirect comparison of network meta-analysis.

The efficacy of bevacizumab combined with two chemotherapeutic agents was generally superior to bevacizumab combined with mono-chemotherapy on ORR, but there was no significant difference on PFS in patients with HER2-negative breast cancer [16–18]. In order to avoid the influence on the addition of second chemotherapy agent improves PFS and ORR compared with Bev + mono-chemotherapy alone in bevacizumab-containing regimens, the efficacy of bevacizumab combined with one or two chemotherapy agents has also been independent evaluated and ranked in this network meta-analysis. Of even greater concern is that Bev + Tax+Cap could be the best therapeutic strategy to improve PFS and ORR based on our currently evidences, which has highest-ranking in bevacizumab plus two chemotherapy agents, even the whole ranking. Besides, there were significant statistical differences compared with Bev + Cap or Bev + Tax or Cap or Tax, while several studies suggested

**Table 4** Indirect comparison in ORR

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **A** | **0.21 (0.051, 0.85)** | **2.06 (1.20, 2.81)** | 0.72 (0.35, 1.5) | 0.87 (0.28, 2.8) | 1.4 (0.67, 2.8) | **2.5 (1.3, 4.9)** | 1.1 (0.37, 3.3) | 1.1 (0.37, 3.5) | 2.0 (0.62, 6.2) | 2.5 (0.77, 8.2) |
| **4.7 (1.2, 20.0)** | **B** | **7.1 (1.9, 28.0)** | **3.4 (1.0, 12.0)** | 4.1 (0.71, 24.0) | **6.5 (1.4, 31.0)** | **12.0 (2.8, 52.0)** | 5.2 (0.96, 29.0) | **5.4 (1.3, 24.0)** | **9.3 (1.7, 53.0)** | **12.0 (2.1, 69.0)** |
| **0.49 (0.36, 0.83)** | **0.14 (0.036, 0.53)** | **C** | **0.48 (0.26, 0.88)** | 0.58 (0.19, 1.7) | 0.92 (0.45, 1.9) | 1.7 (0.95, 2.9) | 0.73 (0.26, 2.0) | 0.76 (0.26, 2.2) | 1.3 (0.44, 3.9) | 1.7 (0.54, 5.1) |
| 1.4 (0.68, 2.8) | **0.30 (0.085, 0.96)** | **2.1 (1.1, 3.9)** | **D** | 1.2 (0.34, 4.2) | 1.9 (0.74, 4.9) | **3.5 (1.5, 8.0)** | 1.5 (0.46, 5.1) | 1.6 (0.67, 3.8) | 2.7 (0.78, 9.7) | 3.5 (0.96, 12.0) |
| 1.2 (0.36, 3.6) | 0.24 (0.042, 1.4) | 1.7 (0.58, 5.2) | 0.82 (0.24, 2.9) | **E** | 1.6 (0.42, 5.9) | 2.9 (0.83, 9.9) | 1.3 (0.28, 5.6) | 1.3 (0.28, 6.1) | 2.3 (0.48, 11.0) | 2.8 (0.60, 14.0) |
| 0.72 (0.35, 1.5) | **0.15 (0.032, 0.70)** | 1.1 (0.53, 2.2) | 0.52 (0.20, 1.3) | 0.63 (0.17, 2.4) | **F** | 1.8 (0.73, 4.6) | 0.80 (0.23, 2.8) | 0.82 (0.23, 3.0) | 1.4 (0.39, 5.2) | 1.8 (0.48, 6.8) |
| **0.40 (0.20, 0.78)** | **0.085 (0.019, 0.36)** | 0.60 (0.34, 1.1) | **0.29 (0.12, 0.66)** | 0.35 (0.10, 1.2) | 0.56 (0.22, 1.4) | **G** | 0.44 (0.14, 1.4) | 0.46 (0.14, 1.5) | 0.79 (0.23, 2.7) | 0.99 (0.28, 3.5) |
| 0.91 (0.30, 2.7) | 0.19 (0.034, 1.0) | 1.4 (0.49, 3.8) | 0.65 (0.20, 2.2) | 0.79 (0.18, 3.5) | 1.3 (0.36, 4.4) | 2.3 (0.70, 7.4) | **H** | 1.0 (0.24, 4.5) | 1.8 (0.40, 8.1) | 2.2 (0.49, 10.0) |
| 0.88 (0.29, 2.7) | **0.19 (0.042, 0.80)** | 1.3 (0.46, 3.8) | 0.63 (0.27, 1.5) | 0.77 (0.16, 3.5) | 1.2 (0.34, 4.3) | 2.2 (0.66, 7.3) | 0.97 (0.22, 4.2) | **I** | 1.7 (0.37, 8.0) | 2.2 (0.47, 10.0) |
| 0.51 (0.16, 1.6) | **0.11 (0.019, 0.61)** | 0.76 (0.25, 2.3) | 0.37 (0.10, 1.3) | 0.44 (0.094, 2.1) | 0.70 (0.19, 2.6) | 1.3 (0.37, 4.4) | 0.56 (0.12, 2.5) | 0.58 (0.12, 2.7) | **J** | 1.3 (0.26, 6.1) |
| 0.40 (0.12, 1.3) | **0.085 (0.014, 0.48)** | 0.60 (0.20, 1.8) | 0.29 (0.080, 1.0) | 0.35 (0.073, 1.7) | 0.56 (0.15, 2.1) | 1.0 (0.28, 3.5) | 0.45 (0.097, 2.0) | 0.46 (0.097, 2.1) | 0.79 (0.16, 3.9) | **K** |

A = Tax, B = Cap, C = Bev + Tax, D = Bev + Cap, E = Bev + Exm, F = Mot + Tax, G = Bev + Tax+Cap, H = Bev + Cap+Cyc, I = Bev + Cap+Vin, J = Bev + Tax+ Eve, K = Bev + Tax+Tre
The values represent OR (95%CI), and the values in bold represent OR (95%CI) has significant statistical difference in indirect comparison
*Bev* bevacizumab, *Cap* capecitabine, *Tax* taxanes, *Vin* vinorelbine, *Cyc* cyclophosphamide, *Exm* exemestane, *Eve* everolimus, *Tre* trebananib, *Mot* motesanib

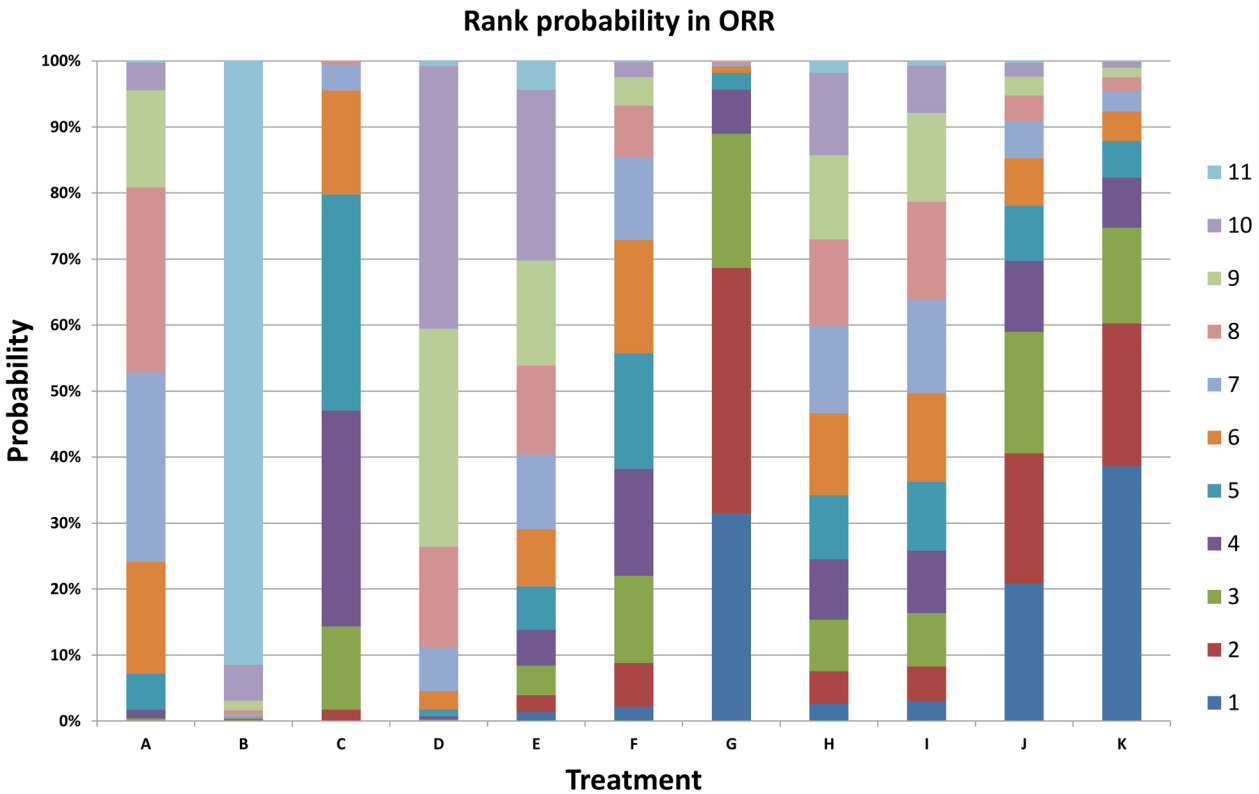


**Fig. 9** Cumulative ranking probability of overall response rate (ORR) for the treatment of metastatic breast cancer. A = Tax, B = Cap, C = Bev + Tax, D = Bev + Cap, E = Bev + Exm, F = Mot + Tax, G = Bev + Tax+Cap, H = Bev + Cap+Cyc, I = Bev + Cap+Vin, J = Bev + Tax+Eve, K = Bev + Tax+Tre. Bev = bevacizumab, Cap = capecitabine, Tax = taxanes, Vin = vinorelbine, Cyc = cyclophosphamide, Exm = exemestane, Eve = everolimus, Tre = trebananib, Mot = motesanib. Serial number 1–11 represent probability ranking

that Bev + Tax+Cap significantly improved PFS and ORR, even have manageable tolerability, compared with Bev + Tax as first-line treatment [13, 14]. However, Bev + Tax+Cap cannot be recommended as first-line chemotherapy in a phase III study, while there was no significant difference between Bev + Tax+Cap and Bev + Tax [15]. In addition, We found that two antiangiogenic agents, bevacizumab and trebananib, combined with taxanes is great potential chemotherapy strategy in our independent ranking results of bevacizumab plus two chemotherapy agents, but only the comparisons of Bev + Tax+Tre and Cap have statistical differences in HER2-negative breast cancer. Based on available evidence, Bev + Cap+Cyc might not even be a better therapeutic regimen compared with bevacizumab plus mono-chemotherapy, which is consistent with the result of previous study [19]. Also of concern, the toxicity of therapeutic drugs could inevitably increase with multidrug treatment regimens in our pooled analysis of treatment-related grade ≧ 3 adverse events, thus it is necessary that finding a balance between the efficacy and toxicity when we choose appropriate therapeutic regimens.

Several limitations of our study deserve comment. First, the included RCTs on second-line chemotherapeutic agents (such as exemestane, everolimus, trebananib and motesanib) may not be sufficient, which caused the bias of our finding. Second, overall survival (OS) was not applicable to include and evaluate the efficacy of bevacizumab-containing chemotherapy regimens in this network meta-analysis. Third, we found that the cause of heterogeneity maybe the baseline of eligible patients in direct comparison, including MBC not previously treated with chemotherapy. However, hormone receptor status may also influent on the heterogeneity and which need to be further confirmed. And previous study suggested that bevacizumab-containing regimens are superior to chemotherapy alone on pathological complete response (pCR) in triple-negative breast cancer (TNBC), which maybe different than non-TNBC [23]. Fourth, due to the inconsistencies of adverse events among the included studies, it is hard to more accurate evaluate the safety of therapeutic regimens for meta-analysis in patients with HER2-negative metastatic breast cancer.

**Table 5** Grade ≥ 3 hematological and non-hematological adverse events

| Toxicity | A | | B | | C | | D | | E | | F | | G | | H | | I | | J | | K | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Grade ≥ 3) | Tax | | Cap | | Bev + Tax | | Bev + Cap | | Bev + Exm | | Mot + Tax | | Bev + Tax+Cap | | Bev + Cap+Cyc | | Bev + Cap+Vin | | Bev + Tax+Exr | | Bev + Tax+Tre | |
| Total n | 351 | | 47 | | 1462 | | 918 | | 58 | | 92 | | 357 | | 74 | | 295 | | 55 | | 55 | |
| | $n_1/n_2$ | % | $n_1/n_2$ | % | $n_1/n_2$ | % | $n_1/n_2$ | % | $n_1/n_2$ | % | $n_1/n_2$ | % | $n_1/n_2$ | % | $n_1/n_2$ | % | $n_1/n_2$ | % | $n_1/n_2$ | % | $n_1/n_2$ | % |
| **Hematologic** | | | NA | NA | | | | | | | | | | | NA | NA | | | | | | |
| Anemia | 6/231 | 2.6 | | | 22/918 | 2.4 | 8/851 | 0.9 | 0/58 | 0.0 | | | 5/357 | 1.4 | | | | | 6/55 | 10.9 | | |
| Leukopenia | 10/231 | 4.3 | | | 84/1145 | 7.3 | 3/851 | 0.4 | 0/58 | 0.0 | | | 37/357 | 10.4 | | | 32/295 | 10.8 | | | | |
| Neutropenia | 37/262 | 14.1 | | | 267/1366 | 19.5 | 13/851 | 1.5 | 0/58 | 0.0 | | | 64/357 | 17.9 | | | 57/295 | 19.3 | 11/55 | 20.0 | 18/55 | 32.7 |
| **Non-hematologic** | | | NA | NA | | | | | | | | | | | NA | NA | | | | | | |
| Hypertension | 11/351 | 3.1 | | | 133/1462 | 9.1 | 55/851 | 6.5 | 25/58 | 43.1 | 11/92 | 12.0 | 39/357 | 10.9 | | | 9/295 | 3.1 | 2/55 | 3.6 | 18/55 | 32.7 |
| Haemorrhage/bleeding | 2/262 | 0.8 | | | 7/624 | 1.1 | 3/297 | 1.0 | 0/58 | 0.0 | | | 5/246 | 2.0 | | | 3/295 | 1.0 | 1/55 | 1.8 | | |
| Thromboembolic events | 3/262 | 1.1 | | | 17/742 | 2.3 | 18/297 | 6.1 | 1/58 | 1.7 | | | 28/357 | 7.8 | | | 31/295 | 10.5 | | | 5/55 | 9.1 |
| Neuropathy | 16/320 | 5.0 | | | 156/1448 | 10.8 | 3/851 | 0.4 | 0/58 | 0.0 | 10/92 | 10.9 | 19/357 | 5.3 | | | 11/295 | 3.7 | 6/55 | 10.9 | 20/55 | 36.4 |
| Nausea/vomiting | 7/320 | 2.2 | | | 28/956 | 2.9 | 12/574 | 2.1 | 0/58 | 0.0 | 18/92 | 19.6 | 8/155 | 5.2 | | | 19/295 | 6.4 | 3/55 | 5.5 | 4/55 | 7.3 |
| Diarrhea | 9/320 | 2.8 | | | 36/1164 | 3.1 | 29/574 | 5.1 | 0/58 | 0.0 | 3/92 | 3.3 | 21/357 | 5.9 | | | 10/295 | 3.4 | 3/55 | 5.5 | 4/55 | 7.3 |
| Mucositis/stomatitis | 2/320 | 0.6 | | | 25/763 | 3.3 | 8/297 | 2.7 | 0/58 | 0.0 | 1/92 | 1.1 | 20/357 | 5.6 | | | 8/295 | 2.7 | 8/55 | 14.5 | | |
| Edema | 6/231 | 2.6 | | | 4/420 | 1.0 | | | 0/58 | 0.0 | | | | | | | | | | | 2/55 | 3.6 |
| Proteinuria | 1/262 | 0.4 | | | 14/565 | 2.5 | 3/297 | 1.0 | | | | | 18/246 | 7.3 | | | 1/295 | 0.3 | 4/55 | 7.3 | | |
| Hepatobiliary disorders | 3/89 | 3.4 | | | 6/213 | 2.8 | | | 4/58 | 6.9 | 7/92 | 7.6 | | | | | | | | | 0/55 | 0.0 |
| Hand-foot syndrome | | | | | 4/648 | 0.6 | 157/851 | 18.4 | | | | | 107/357 | 30.0 | | | 43/295 | 14.6 | | | | |
| Fatigue | 20/320 | 6.3 | | | 59/1164 | 5.1 | 10/574 | 1.7 | 3/58 | 5.2 | 11/92 | 12.0 | 22/357 | 6.2 | | | 19/295 | 6.4 | 8/55 | 14.5 | 5/55 | 9.1 |
| Pain | 11/320 | 3.4 | | | 22/989 | 2.2 | 9/277 | 3.2 | 2/58 | 3.4 | 9/92 | 9.8 | 4/246 | 1.6 | | | | | 1/55 | 1.8 | 0/55 | 0.0 |
| Alopecia | 9/320 | 2.8 | | | 13/685 | 1.9 | 0/277 | 0.0 | 0/58 | 0.0 | 0/92 | 0.0 | | | | | | | | | 4/55 | 7.3 |
| Infection | 10/320 | 3.1 | | | 19/615 | 3.1 | 27/297 | 9.1 | | | 9/92 | 9.8 | 16/266 | 6.0 | | | 37/295 | 12.5 | | | | |

A = Tax, B = Cap, C = Bev + Tax, D = Bev + Cap, E = Bev + Exm, F = Mot + Tax, G = Bev + Tax+Cap, H = Bev + Cap+Cyc, I = Bev + Cap+Vin, J = Bev + Tax+ Eve, K = Bev + Tax+Tre

*Bev* bevacizumab, *Cap* capecitabine, *Tax* taxanes, *Vin* vinorelbine, *Cyc* cyclophosphamide, *Exm* exemestane, *Eve* everolimus, *Tre* trebananib, *Mot* motesanib, *NA* not applicable, *Total n* number of all patients with regimens, $n_1/n_2$ the number of patients with adverse reactions / total enrolled patients

## Conclusions

In summary, our network meta-analysis results showed that Bev + Tax+Cap maybe the best therapeutic regimen on PFS and ORR, which was superior to bevacizumab combined with other chemotherapy drugs in HER2-negative metastatic breast cancer. However it should be also considered that bevacizumab may add toxicity to chemotherapy and whether improve overall survival (OS) or not.

### Abbreviations

Bev: Bevacizumab; Cap: Capecitabine; CI: Confidence interval; Cyc: Cyclophosphamide; Eve: Everolimus; Exm: Exemestane; MBC: Metastatic breast cancer; Mot: Motesanib; pCR: Pathological complete response; RCTs: Randomized controlled trials; Tax: Taxanes; TNBC: Triple-negative breast cancer; Tre: Trebananib; Vin: Vinorelbine

### Acknowledgements

The authors thank Fanli Kong for her assistance in inclusion and exclusion criteria.

### Authors' contributions

All authors made substantive intellectual contributions to this study to qualify as authors. ZS conceived of the design of the study. ZS, XL and YX performed the study and analyzed the data. SL and SX prepared the manuscript. All authors read and approved the final manuscript.

### Funding

No funds were received in support of this work.

### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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Received: 28 November 2019 Accepted: 24 February 2020
Published online: 04 March 2020

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