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# Docetaxel and bevacizumab with or without trastuzumab as first-line treatment for patients with metastatic breast cancer: a meta-analysis

Z.-W. SUN[1], X.-Y. LAN[2], F.-L. KONG[1], Y.-Y. GAO[3], S. LI[2], Y.-L. XI[1]

[1]Department of Clinical Pharmacy, Dalian Municipal Central Hospital, Dalian, China
[2]Department of Neurology, Dalian Municipal Central Hospital, Dalian, China
[3]Department of Central Laboratory, Dalian Municipal Central Hospital, Dalian, China

**Abstract. – OBJECTIVE: Although bevacizumab and trastuzumab have been widely added to the standard regimen for metastatic breast cancer, the clinical outcomes remain controversial. The purpose of this study was to conduct meta-analysis to verify the clinical efficacy and safety of docetaxel and bevacizumab with or without trastuzumab as first-line treatment for patients with metastatic breast cancer (MBC).**

**MATERIALS AND METHODS: All available literature of clinical trials about docetaxel, bevacizumab, trastuzumab and metastatic breast cancer was pooled from PubMed, Embase and Cochrane library database. The meta-analysis combined the progression free survival (PFS), overall response rate (ORR) and incidence of all grades adverse events in MBC patients.**

**RESULTS: Seven clinical trials were included by two reviewers. Docetaxel and bevacizumab with trastuzumab show the pooled PFS was 16.53 months (95% CI: 13.95-19.11 months), the pooled ORR was 0.75 (95% CI: 0.69-0.80) in HER2-positive MBC patients. Docetaxel and bevacizumab show that the pooled PFS was 8.49 months (95% CI: 7.80-9.18 months), the pooled ORR was 0.51(95% CI: 0.47-0.55) in HER2-negative MBC patients.**

**CONCLUSIONS: Both for patients with HER2-positive and negative metastatic breast cancer, docetaxel and bevacizumab with or without trastuzumab as first-line treatment resulted in long survival, especially in terms of progression-free survival. Although the overall response rates are also significantly improved, it is still controversial based on the current evidence.**

*Key Words:*
Docetaxel, Bevacizumab, Trastuzumab, Metastatic breast cancer, Meta-analysis.

## Introduction

Breast cancer is the most common cancer that threatens women's health worldwide, both in terms of new cases and deaths each year[1]. Each year, it contributes 12.2% of new cases and 9.6% of deaths to the development of breast cancer worldwide. Unfortunately, 20-30% of breast cancer patients have metastasized by the time of diagnosis[2]. Metastatic breast cancer is still an incurable disease, and the main purpose of treatment is to reduce symptoms, improve quality of life and prolong survival[3]. Therefore, chemotherapy plays an important role in the treatment of breast cancer. Common chemotherapy drugs include taxol (paclitaxel, docetaxel) and anthracycline.

In the HER2-positive breast cancer subset, trastuzumab has been identified as the standard treatment for human epidermal growth factor receptor-2 (HER2) positive metastatic breast cancer (MBC) patients with significantly improved progression-free survival (PFS) and overall survival (OS) compared to chemotherapy alone[4,5]. Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody that binds and neutralizes all isoforms of VEGF, and it was the first anti-angiogenesis therapy to be approved for use in combination with chemotherapy in MBC[6,7]. Previous studies[8,9] have shown that the combination of bevacizumab, trastuzumab and docetaxel is feasible and safe, with high response rates and promising PFS in patients with HER2-positive metastatic breast cancer. However, another study[10] demonstrated that combining bevacizumab with docetaxel and trastuzumab did not significantly improve PFS in HER2-positive MBC patients.

In the HER2-negative breast cancer subset, combining bevacizumab with docetaxel has promising efficacy and acceptable toxicities in HER2-negtive MBC patients[11-13]. Compared with docetaxel alone, bevacizumab combined with

*Corresponding Author:* Zhengwu Sun, MD; e-mail: s2009unyi@hotmail.com

docetaxel significantly improved PFS, while combined drugs did not significantly impact on the safety profile in MBC[14]. Moreover, a previous study[15] indicates that no evidence of increased bevacizumab-related toxicity or reduced efficacy in MBC patients receiving first-line bevacizumab-taxane therapy.

Accordingly, we performed a systematic literature review and meta-analysis to evaluate the efficacy and safety of docetaxel and bevacizumab with or without trastuzumab as first-line treatment for patients with HER2-positive or negative metastatic breast cancer.

## Materials and Methods

### Search Strategy

A search of the PubMed, Embase and Cochrane Library was performed up to June 2021, and search strategy was constructed using medical subject headings and keywords included the terms: "docetaxel", "bevacizumab", "trastuzumab", "metastatic breast cancer". Studies published in any language were included. A manual search of the references listed in studies retrieved from the online databases and from previously published systematic reviews was also performed to identify further relevant studies.

### Assessment of Studies Quality

According to Cochrane collaboration's tool for assessing risk of bias (version 5.3), we assessed the quality of the included studies to ensure risk of biases (Table II), including prospective design, multicenter enrollment, selection bias, performance bias, attrition bias, detection bias, multivariate adjustment for potential confounders. The studies validity was arranged into four hierarchies from higher to lower, A (low), B (moderate), C (high), and D (incomplete reporting).

### Inclusion and Exclusion Criteria

We included studies that i) assess the efficacy and safety of docetaxel and bevacizumab with or without trastuzumab in HER2-positive or HER2-negtive MBC patients; ii) were published as full articles. To preserve intragroup homogeneity, we excluded that i) patients were < 18 years, pregnant; ii) types of publication were case reports, reviews, commentaries and editorials, or only reported in abstract form; and iii) trial size or study population was not clear. The above procedures of study search and selection were independently performed by two investigators (Zhengwu Sun and Xiaoyan Lan). Study eligibility was determined by all authors' consensus.

### Data Collection

Two investigators (Zhengwu Sun and Xiaoyan Lan) independently extracted the available data, with discrepancies resolved by all authors' consensus. The following data were also collected from each study: type of study, published years, country and geographical region, number of study centers, duration of treatment and number of patients and outcomes using an intention-to treat principle where missing or dropout data were considered as treated failure.

The progression free survival (PFS), overall response rate (ORR) and incidence of all grades adverse events, although not perfectly legitimate, were defined as the evaluation indexes of MBC patients.

### Statistical Analysis

Meta-analysis was carried out by pooled effect sizes (ES) of PFS, ORR and incidence of all grades adverse events in the including studies. Statistical heterogeneity tested was performed using the $X^2$ and $I^2$, and an $I^2$ value > 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. Analyses were conducted using Stata (Version 14; Stata Corp, USA) software.

## Results

### Search Results

The search identified 409 potentially relevant studies, of which 183 were included following title and abstract screening. In total, 56 studies were retained for full-text review. Initially, 45 review studies were discarded. By analyzing detail data, 4 special studies (including different treatments and patient's condition) were excluded. Finally, seven studies were identified involving 858 patients that fulfilled the inclusion criteria (Figure 1).

### 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

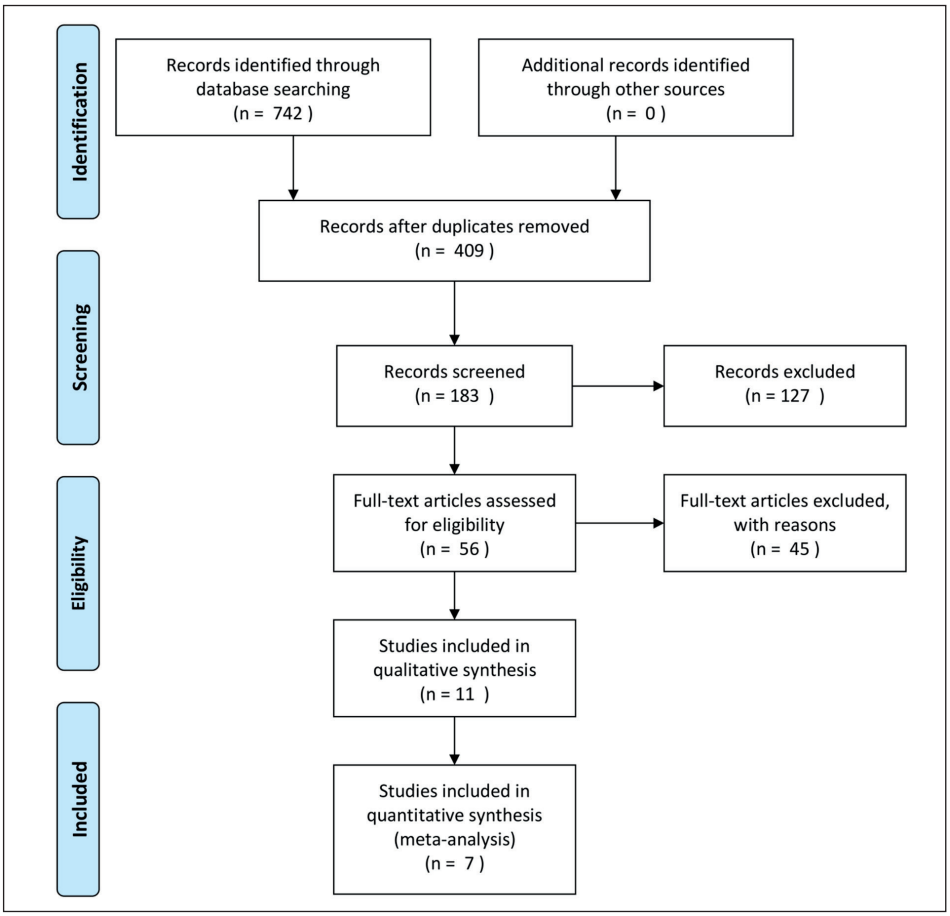


**Figure 1.** Flow diagram demonstrating inclusion/exclusion process for studies incorporate in final analyses.

basic feature descriptions of the seven studies in Table I. The mean age of patients arranged from 22 to 83 years. The dosage range of Bevacizumab, docetaxel and trastuzumab were 15 mg/kg/3 weeks, 75-105 mg/kg/3 weeks and 6 mg/kg/3 weeks respectively. Outcomes of all studies included progression free survival, overall survival, complete response, partial response, stable disease, clinical benefit response, progressive disease, nonvaluable, response duration, overall response rate, time to treatment failure. There were one retrospective study[13], two prospective studies[9,15] and four RCT studies[8,10,12,14]. Four studies came from American[8,9,12,13], whereas one study came from England,[14] one study from Italy[10] and one study from China[15].

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

### *Effect of Docetaxel and Bevacizumab with Trastuzumab in HER2-Positive MBC Patients*

For progression-free survival (PFS), docetaxel and bevacizumab with trastuzumab shows that the pooled PFS was 16.53 months (95% CI: 13.95-19.11 months) in HER2-positive MBC patients. Although one study was given higher weight in the combined analysis (Gianni L 2013), the results for progression-free survival were largely consistent across the three included studies (Figure 2A). On the other hand, docetaxel and bevacizumab with trastuzumab show that the pooled ORR (Overall response rate) was 0.75 (95% CI: 0.69-0.80) in HER2-positive MBC patients. However, it is worth noting that one study (Zhao M 2014) had a significantly lower overall response rate than the other two studies in Figure 2B.

### *Effect of Docetaxel and Bevacizumab in HER2- Negative MBC Patients*

As shown in Figure 3A, docetaxel and bevacizumab show the pooled PFS was 8.49 months

**Table I.** Demographic and baseline characteristic of included studies.

| Study | Patients | | | | | Intervention | | | Outcome | Style |
|---|---|---|---|---|---|---|---|---|---|---|
| | Year | N | Mean age | Range/ SD | MBC | Bevacizumab (mg/kg)/ 3 weeks | Docetaxel (mg/kg)/ 3 weeks | Trastuzumab (mg/kg)/ 3 weeks | | |
| Schwartzberg LS | 2014 | 21 | 52.8 | 12.6 | HER2+/ HER2- | 15 | 75 | 6 | PFS, OS, CR, PR, SD, CBR, NE, ORR | Prospective, multicenter, 2-arm study |
| Zhao M | 2014 | 26 | 54 | 38-73 | HER2+ | 15 | 75 | 6 | PFS, CR, PR, SD, CBR, PD, NE, RD, ORR | Sigle-arm RCT |
| Gianni L | 2013 | 216 | 53 | 26-82 | HER2+ | 15 | 100 | 6 | PFS, OS, CR, ORR | 2-arm RCT |
| Xu BH | 2012 | 202 | 48 | 22-74 | HER2- | 15 | 75 | None | PFS, SD, PD, NE, RD, ORR | Prospective, multicenter, sigle-arm study |
| Hurvitz SA | 2010 | 67 | 57 | 32-83 | HER2- | 15 | 75 | None | PFS, OS, CR, PR, SD, RD, ORR | Sigle-arm RCT |
| Miles DW | 2010 | 247 | 55 | 27-76 | HER2- | 15 | 100 | None | PFS, OS, RD, ORR, TTF | 3-arm RCT |
| Ramaswamy B | 2006 | 27 | 51 | 39-68 | HER2- | 15 | 105 | None | PFS, OS, CR, PR, SD, PD, NE, RD, ORR | Retrospective, sigle-arm study |

*Abbreviations:* n = the number of patients; SD = standard deviation; MBC = metastatic breast cancer; PFS = progression free survival; OS = overall survival; CR = complete response; PR = partial response; SD = stable disease; CBR = clinical benefit response; PD = progressive disease; NE = Nonvaluable; RD = Response duration; ORR = overall response rate; TTF = time to treatment failure; RCT = randomized controlled trial.

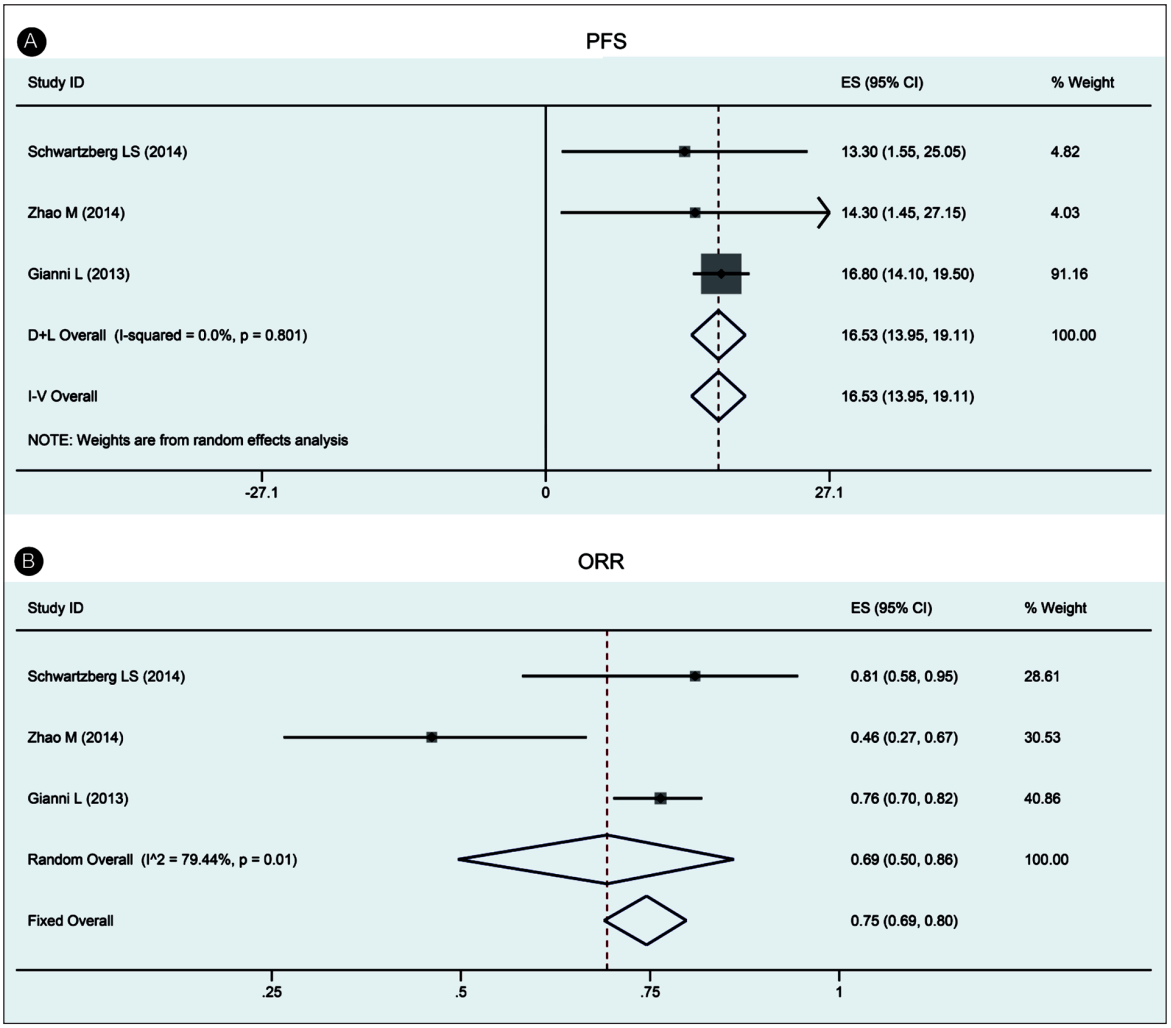


**Figure 2.** Forest plot of effect sizes (ES) of docetaxel and bevacizumab with trastuzumab for composite end points: progression free survival (PFS), overall response rate (ORR) in patients with HER2-positive metastatic breast cancer (MBC).

(95% CI: 7.80-9.18 months) in HER2-negtive MBC patients, the improvement in progression-free survival of MBC patients was significant and consistent in the combination regimen of docetaxel and bevacizumab. Besides, docetaxel and bevacizumab show that the pooled ORR was 0.51 (95% CI: 0.47-0.55) in HER2-negtive MBC patients. However, there was a high heterogeneity in the overall response rate for docetaxel and bevacizumab, which may stem from ethnic differences. In one study (Xu et al[15] 2012), all patients were from China, while the patients were from Europe and USA in the other four studies. This may affect the responsiveness and sensitivity of patients with metastatic breast cancer to docetaxel and bevacizumab (Figure 3B).

### *Safety*

Of the included studies, the adverse events of two studies[8,9] were pooled in HER-positive MBC patients, while the adverse events of three studies[9,12,15] were pooled in HER-negative MBC patients. In HER2-positive metastatic breast cancer patients, twelve kinds of adverse reactions to be pooled, the incidence of nausea, diarrhea, vomiting, fatigue, arthralgia, myalgia, epistaxis, lacrimation and mucositis close to or more than 50%. Moreover, six kinds of adverse reactions to be pooled in HER2-negtive metastatic breast cancer patients, including the incidence of hypertension, diarrhea, fatigue, epistaxis, proteinuria and insomnia. Notably, the incidence of Fatigue syndrome is the highest at 82% and 45% both in HER-positive and HER-negative MBC patients (Table III).

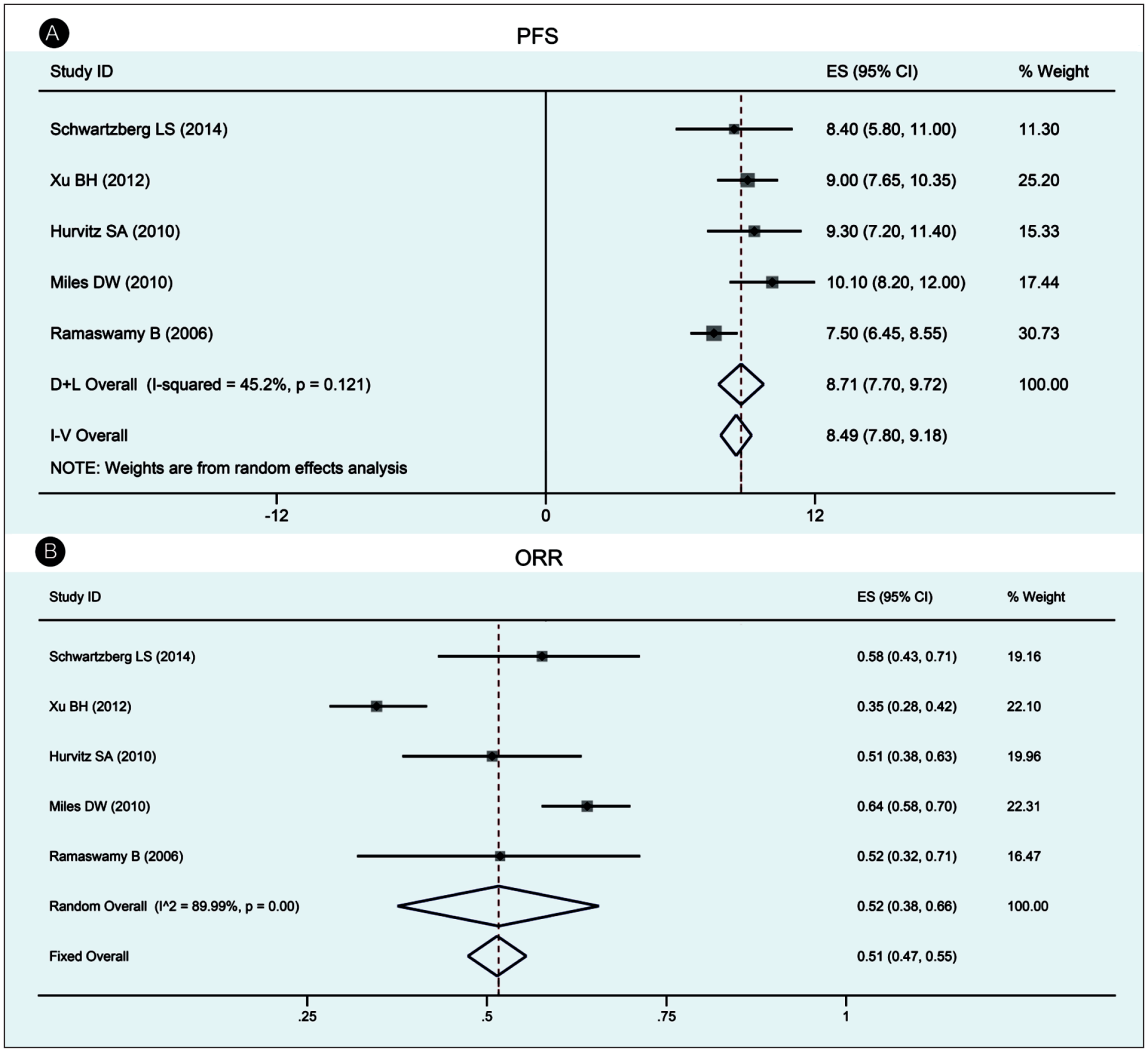


**Figure 3.** Forest plot of effect sizes (ES) of docetaxel and bevacizumab for composite end points: progression free survival (PFS), overall response rate (ORR) in patients with HER2-negtive metastatic breast cancer (MBC).

**Table II.** Internal validity of included studies.

| Study | Prospective design | Multicenter enrollment | Selection bias | Performance bias | Attrition bias | Detection bias | Multivariate adjustment for potential confounders |
|---|---|---|---|---|---|---|---|
| Schwartzberg LS (2014) | ● | ● | B | C | B | B | None reported |
| Zhao M (2014) | ● | ○ | A | B | A | B | Probably adequate |
| Gianni L (2013) | ● | ○ | A | A | B | A | Probably adequate |
| Xu BH (2012) | ● | ● | B | C | C | B | None reported |
| Hurvitz SA (2010) | ● | ○ | A | B | B | A | Probably adequate |
| Miles DW (2010) | ● | ○ | A | B | A | A | Probably adequate |
| Ramaswamy B (2006) | ○ | ○ | D | C | B | C | None reported |

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

**Table III.** Pooled adverse events in patients with HER2-positive or negative metastatic breast cancer.

| Adverse event | HER2+ | | | | HER2- | | | |
|---|---|---|---|---|---|---|---|---|
| | ES (95% CI) | Number of study | $I^2$ | *p*-value | ES (95% CI) | Number of study | $I^2$ | *p*-value |
| Hypertension | 0.32 (0.19, 0.47) | 2 | 0% | 0 | 0.16 (0.11, 0.21) | 3 | 22.18% | 0.28 |
| Nausea | 0.61 (0.46, 0.75) | 2 | 0% | 0 | - | - | - | - |
| Diarrhea | 0.59 (0.44, 0.73) | 2 | 0% | 0 | 0.17 (0.10, 0.24) | 2 | 0% | 0 |
| Constipation | 0.34 (0.21, 0.49) | 2 | 0% | 0 | - | - | - | - |
| Vomiting | 0.46 (0.31, 0.60) | 2 | 0% | 0 | - | - | - | - |
| Fatigue | 0.82 (0.69, 0.92) | 2 | 0% | 0 | 0.45 (0.36, 0.54) | 2 | 0% | 0 |
| Arthralgia | 0.60 (0.45, 0.74) | 2 | 0% | 0 | - | - | - | - |
| Myalgia | 0.50 (0.35, 0.64) | 2 | 0% | 0 | - | - | - | - |
| Rash | 0.37 (0.23, 0.52) | 2 | 0% | 0 | - | - | - | - |
| Epistaxis | 0.67 (0.52, 0.80) | 2 | 0% | 0 | 0.13 (0.07, 0.20) | 2 | 0% | 0 |
| Lacrimation | 0.48 (0.33, 0.63) | 2 | 0% | 0 | - | - | - | - |
| Mucositis | 0.47 (0.32, 0.62) | 2 | 0% | 0 | - | - | - | - |
| Proteinuria | - | - | - | - | 0.13 (0.09, 0.18) | 2 | 0% | 0 |
| Insomnia | - | - | - | - | 0.10 (0.05, 0.16) | 2 | 0% | 0 |

## Discussion

Findings from this meta-analysis suggest that first-line trastuzumab combination with docetaxel and bevacizumab therapy is effective and acceptable tolerated in patients with HER2-positive MBC cancer, while we found no evidence that bevacizumab combined with docetaxel has poorer tolerability or decreased efficacy in patients with HER2-negtive MBC cancer compared with docetaxel alone in previous studies.

Although the progression-free survival rate was consistent with previous studies and had high homogeneity in patients with HER2-positive MBC cancer, the weighting of one included study was 91.16%[10]. Thus, we need to include more large sample studies to further confirm the correctness of our existing conclusions. The pooled ORR was nearly 70%, suggesting that trastuzumab combined with bevacizumab and docetaxel has a curative effect on HER2-positive MBC cancer. However, we found that the results of two included studies[9,10] were consistent with the pooled results, while the results of the other study were much lower than the above results[8]. This is the reason for high heterogeneity. Due to the small sample size and individual differences of patients in this study, we believe that the true ORR may be more than 50%. Recent studies reported that two human epidermal growth factor receptor-added chemotherapy regimens may be more helpful in relieving patients with metastatic breast cancer. The addition of pertuzumab to trastuzumab and docetaxel significantly improved median overall survival compared with the addition of placebo[16], and also enhanced PFS and ORR of MBC patients with a predictable safety profile[17]. The incidence of most of the 12 adverse reactions included was significantly different in the two included studies[8,9]. Previous scholars[8] have shown that most adverse events occur at grade I and II, while the incidence of grade 3 and 4 is low. If more RCT are included in the future, the pooled adverse events may be more realistic and accurate, and it seems necessary to evaluate the incidence of grade III and IV.

Besides the high heterogeneity is a common problem in single-arm meta-analysis, PFS are close to the included studies in HER2-negative MBC patients, thus we believe that our final pooled PFS is reliable. According to included studies[9,12-14], ORR was concentrated in 50-60% in HER2-negative MBC patients. In a phase II single-arm clinical study, the regimen of bevacizumab added to docetaxel or paclitaxel showed significant improvement in both progression-free survival and overall survival in patients with HER2-negative metastatic breast cancer, and the overall response rates were more than half, which is also consistent with the current pooled outcomes in this study[18]. However, only one included study showed that ORR was 35% in Chinese patients[15], compared to the majority of Caucasians in other studies. Therefore, we need to include more studies to investigate the differences in chemotherapy for metastatic breast cancer that may

be due to ethnicity in future studies. The safety of bevacizumab and paclitaxel combination regimen is acceptable for patients with metastatic breast cancer. The most common serious adverse events are neutropenia, of which the ones associated with bevacizumab are thrombosis, bleeding, hypertension, and proteinuria[19-21]. In addition, the majority of included studies have shown that most adverse reactions occurred at grade I and II in HER2-negative MBC patients, while other study has shown that adverse reactions occurred at grade III[12], Under the premise of sufficient data, we need a subgroup analysis for further study.

However, our results of this present meta-analysis are limited. Firstly, more multi-centric RCT studies were required for a meta-analysis. Secondly, since the differences of adverse events exist in the included studies, only 12 adverse events were pooled in the HER2-positive MBC cancer, and only 6 adverse events were pooled in the HER2-negative MBC cancer, while two studies were included on safety profile in the majority of including studies. We only pooled the incidence of adverse events of all grades but did not pool the adverse events of grade 3 and 4. Thirdly, due to the lack of relevant data, this study cannot effectively evaluate whether patients have a longer overall survival, thus more evidence is needed to determine the overall survival rate of MBC cancer patients.

## Conclusions

In summary, this meta-analysis found that trastuzumab combined with bevacizumab and docetaxel resulted in long progression-free survival and high response rates in patients with HER2-positive MBC cancer, while bevacizumab combined with docetaxel had a reliable efficacy and lower incidence of adverse events in patients with HER2-negative MBC cancer. Due to the limitations of the quality of the included studies, more high-quality large-sample studies are needed to verify this study.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### Funding

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### Authors' Contribution

ZS and XL designed the meta-analysis; ZS and XL searched the literature; FK, YG and SL analyzed the literature; ZS and XL wrote the manuscript; ZS edited the manuscript.

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