

## Review Article

# Efficacy and safety of nanoparticle albumin-bound paclitaxel for treating metastatic breast cancer: a meta-analysis

Jia Zhu<sup>1\*</sup>, Li-Ping Yan<sup>2,5\*</sup>, Jie Wu<sup>3\*</sup>, Feng-Feng Wang<sup>1</sup>, Chang-Gan Mo<sup>4</sup>, Jian-Lun Liu<sup>1</sup>

<sup>1</sup>Department of Breast Surgery, The Affiliated Tumor Hospital of Guangxi Medical University, Nanning 530021, Guangxi, People's Republic of China; <sup>2</sup>The Third Department of Breast Surgery, The Third People's Hospital of Nanchang, Nanchang 330009, Jiangxi, People's Republic of China; <sup>3</sup>The Second Department of Chemotherapy, Affiliated Ruikang Hospital of Guangxi University of Chinese Medicine, Nanning 530011, Guangxi, People's Republic of China; <sup>4</sup>Department of Cardiology, The People's Hospital of Hechi, Hechi 547000, Guangxi, People's Republic of China; <sup>5</sup>The Third Department of Breast Surgery, Breast Specialist Hospital of Jiangxi, Nanchang 330009, Jiangxi, People's Republic of China. \*Co-first authors.

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**Abstract:** Objective: Clinical trials have reported conflicting results about the efficacy and toxicity of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) for treating metastatic breast cancer. This meta-analysis was performed to gain a clearer picture of the efficacy and safety of this drug. Methods: We systematically searched PubMed, Chinese National Knowledge Infrastructure (CNKI), Ovid, EMBASE and Cochrane literature databases for randomized controlled trials (RCTs) of nab-paclitaxel to treat metastatic breast cancer. Data on overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and incidence of adverse effects were meta-analyzed to yield pooled odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CI). Potential heterogeneity was calculated using the Q statistic and I<sup>2</sup> value. Results: The meta-analysis included six RCTs involving 1614 patients. Nab-paclitaxel was associated with significantly higher ORR than were control drug treatments (OR 2.46, 95% CI 1.92 to 3.14, P < 0.00001). It was also associated with higher PFS than were control drug treatments (HR 0.83, 95% CI 0.73 to 0.94, P = 0.003). However, OS was similar for nab-paclitaxel and control treatments (HR 0.87, 95% CI 0.71 to 1.05, P = 0.14). Analysis of the six studies showed that nab-paclitaxel was associated with significantly higher risk of grade 3 sensory neuropathy than were control drug treatments (OR 1.82, 95% CI 1.21 to 2.74, P = 0.004). Conclusions: These findings suggest that nab-paclitaxel is associated with significantly higher ORR but also greater risk of toxicity than are other drug treatments for metastatic breast cancer.

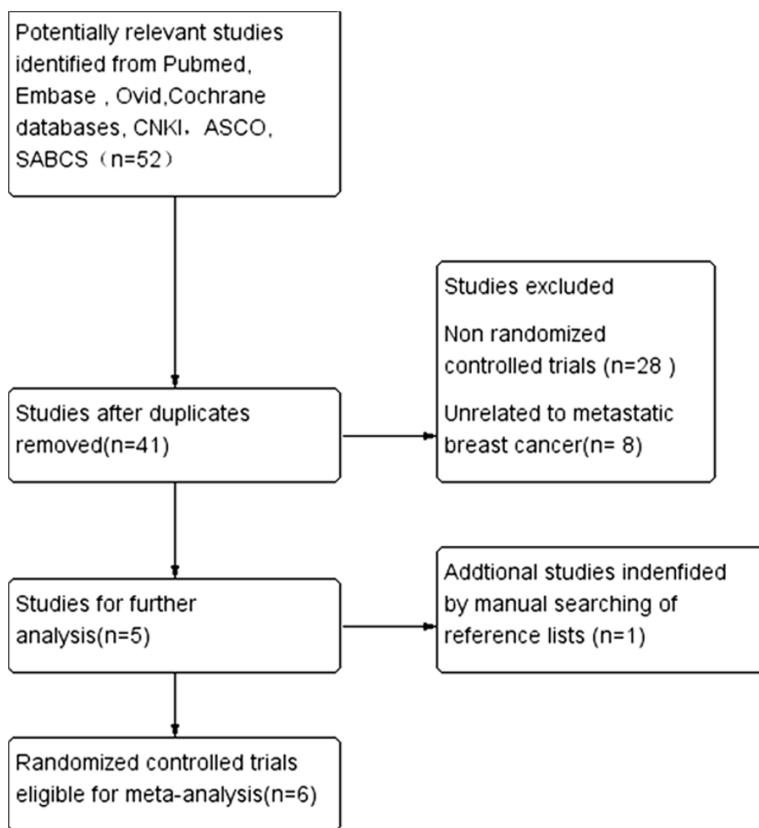
**Keywords:** Nab-paclitaxel, metastatic breast cancer, meta-analysis, toxicity

## Introduction

Management of metastatic breast cancer remains an important challenge for clinicians, who seek to provide palliative therapy to ameliorate symptoms, improve quality of life, prolong survival, and delay disease progression [1]. The class of compounds called taxanes has become an important treatment option for advanced or recurrent breast cancer [2], with the taxane paclitaxel widely used as combination therapy [3] or monotherapy to treat metastatic breast cancer [4]. Normally paclitaxel is formulated with the solvents ethanol and polyethylated castor oil, both of which present disadvantages. Ethanol is insoluble in water, while polyethylated castor oil can cause severe aller-

gic reactions, peripheral neuropathy, and hematological toxicity [5, 6]. In addition, polyethylated castor oil micelles can accumulate in erythrocytes, trapping the paclitaxel there as well, reducing the bioavailability and hence efficacy of the drug [7, 8].

To avoid these solvent-associated problems, paclitaxel has been formulated together with albumin and 130-nm nanoparticles to give nanoparticle albumin-bound paclitaxel (nab-paclitaxel or Abraxane; Abraxis BioScience, Los Angeles, CA, USA). Using albumin, the body's natural carrier of hydrophobic molecules, increases the distribution of paclitaxel into tumor cells, eliminating the need for synthetic solvents that may cause toxic effects.



**Figure 1.** Flowchart of study selection.

This novel formulation shown greater overall response rate (ORR) and progression-free survival (PFS) in a randomized phase III trial [9] and a phase II trial [10] comparing nab-paclitaxel (260 mg/m<sup>2</sup>, delivered intravenously over 30 min, no premedication) with solvent-based paclitaxel (175 mg/m<sup>2</sup>, delivered intravenously over 3 h, with premedication). In these studies, nab-paclitaxel was associated with significantly lower rates of grade 4 neutropenia and grade 3 sensory neuropathy than was solvent-based paclitaxel. These two clinical trials suggested that, although nab-paclitaxel therapy required higher doses of the drug, it nevertheless showed significantly lower toxicity, it did not require premedication, and the entire dose could be infused over a much shorter time.

These clear advantages of nab-paclitaxel have not been observed in all studies. For example, a randomized controlled trial [11] showed that nab-paclitaxel was not superior to solvent-based paclitaxel in terms of progression-free survival and hemotoxicity. Therefore it is important to gain a clearer picture of the safety and

efficacy of nab-paclitaxel as this novel therapy is adopted by more medical centers around the world.

In the present study, meta-analysis of randomized controlled trials and clinical trials was performed to evaluate the safety and efficacy of nab-paclitaxel compared to other drug treatments for metastatic breast cancer, such as solvent-based paclitaxel. The following outcomes were compared for the two types of therapy: ORR, PFS, overall survival (OS), and incidence of adverse events.

## Materials and methods

### Literature search strategy

The following literature databases were systematically searched, without language restrictions, through 1 April 2013: PubMed, Ovid, EMBASE, the Chinese National Knowledge Infrastructure (CNKI), and the Cochrane Database. The following keywords were used: “nanoparticle albumin-bound paclitaxel” or “nab-paclitaxel” or “ABI-007” or “Abraxane®”, and all these keywords in combination with “breast cancer/carcinoma/neoplasms” and “metastatic” or “advanced” and “randomized”. In addition, the reference lists of relevant articles were hand-searched, as were abstracts and proceedings from meetings of the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium (SABCS).

### Inclusion criteria and exclusion criteria

To be included in our meta-analysis, studies had to satisfy the following conditions: (1) participants were non-pregnant, non-lactating females aged 18 or older with recurrent or metastatic breast cancer diagnosed histologically or cytologically; (2) participants did not show clinical evidence of brain metastases or serious concurrent illness; (3) the design was a randomized controlled trial (RCT); and (4) sufficient

**Table 1.** Summary of all studies included in the meta-analysis

Study	Sample size	Trial design	Nap-paclitaxel arm (s)	Nap-paclitaxel dose	Control arm	Control dose
Gradishar et al. (2005)	454	Phase III randomized controlled	NP (229)	260 mg/m <sup>2</sup> q3w	P (225)	175 mg/m <sup>2</sup> q3w
Rugo et al. (2012)	554	Phase III randomized controlled	NP+B (271)	NP 150 mg/m <sup>2</sup> q1w +B (dose not reported)	P+B (283)	P 90 mg/m <sup>2</sup> q1w +B (dose not reported)
Guan et al. (2009)	210	Phase II randomized controlled	NP (104)	260 mg/m <sup>2</sup> q3w	P (106)	175 mg/m <sup>2</sup> q3w
Hong et al. (2012)	75	Phase III randomized controlled	NP (37)	150 mg/m <sup>2</sup> ; d1, d8, d15 q28day	P (38)	85 mg/m <sup>2</sup> ; d1, d8, d15 q28day
Gradishar et al. (2009, 2012)	300	Phase II randomized controlled	Arm A: NP (76) Arm B: NP (76) Arm C: NP (74)	Arm A: 300 mg/m <sup>2</sup> q3w Arm B: 100 mg/m <sup>2</sup> weekly Arm C: 150 mg/m <sup>2</sup>	Arm D: Doc (74)	100 mg/m <sup>2</sup> q3w
Zhao et al. (2008)	21	Phase III randomized controlled	NP (9)	260 mg/m <sup>2</sup> q3w	P (12)	175 mg/m <sup>2</sup> q3w

Abbreviations: B, bevacizumab; Doc, docetaxel; NP, nap-paclitaxel; P, solvent-based paclitaxel.

data were reported to allow estimation of odds ratios (ORs) or hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Exclusion criteria included: (1) the study unrelated to metastatic breast cancer; (2) the design was not a randomized controlled trial (RCT); (3) repeated publications.

#### Data extraction and quality assessment

Three reviewers (Jia Zhu, Li-Ping Yan, Jie Wu) independently extracted data from included studies. Discrepancies in the collected data were discussed and resolved by a third reviewer (Jian-Lun Liu). The following data were extracted: first author's last name, year of publication; the number, ethnicity, and median age of patients; and data on ORR, PFS and adverse events.

The methodological quality of each trial was evaluated using the following Cochrane criteria: random sequence generation, allocation concealment, participant blinding, blinding to outcome assessment, completeness of outcome data, selective reporting, and other biases.

#### Statistical analysis

All data analysis was carried out using RevMan 5.2 software (Cochrane Collaboration). The primary efficacy measures were ORR and incidence of adverse events. These were calculated as ORs with 95% CIs. The secondary efficacy measures were PFS and OS, for which HRs were calculated together with the 95% CIs. If the trials did not report this information directly, appropriate data, such as the *P*-value from the log-rank test, were extracted in order to esti-

mate the log HR and its variance. The HR and its variance were calculated for each included trial using the methods of Tierney and Parmar [12, 13], PFS and OS data were extracted from survival curves, and Kaplan-Meier curve data were extracted using the Engauge Digitizer version 4.1 (<http://digitizer.sourceforge.net/>). Statistical significance of pooled ORs and the logarithm of HR was assessed using the Z-test, with *P* < 0.05 defined as significant.

Heterogeneity between studies was evaluated using the chi squared-based Q-test recommended by the Cochrane Collaboration. If *P* > 0.1, the fixed-effects model was used; if *P* < 0.1, the random-effects model was applied. Meta-analyses for which *I*<sup>2</sup> > 50% were considered to have essential heterogeneity [14].

## Results

#### Literature search

Systematic review of literature databases turned up 52 potentially relevant studies involving nab-paclitaxel, but 45 were excluded based on review of titles and abstracts as being irrelevant or failing to satisfy the inclusion criteria. The remaining 6 articles were read in full and found to fulfill the inclusion criteria, so they were included in the meta-analysis. Six of the studies were RCTs involving 1614 patients (Figure 1).

Basic characteristics of the included studies are listed in Table 1. Key details about each study and its participants are highlighted as following. One Phase II RCT [10] involved Chinese

	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
Gradishar et al. (2005)	+	+	+	+	+	+	?
Gradishar et al. (2012)	+	+	+	+	+	+	?
Guan et al. (2009)	+	-	?	+	+	+	?
Hong et al. (2012)	+	?	?	+	?	+	?
Rugo et al. (2012)	+	+	+	+	?	+	?
Zhao et al. (2008)	+	+	+	+	?	-	?

**Figure 2.** Risk of bias summary.

patients ranging in age from 18 to 70 with an Eastern Collaborative Oncology Group (ECOG) performance status of  $\leq 1$ . One Phase III RCT [9] involved Caucasian participants aged 18 or older with an ECOG performance status  $> 2$ . In these two trials, nab-paclitaxel (260 mg/m<sup>2</sup>, q3w) was compared with solvent-based paclitaxel (175 mg/m<sup>2</sup>, q3w). The primary endpoint was ORR; secondary endpoints were PFS and OS. In a Phase III RCT [11], nab-paclitaxel (150 mg/m<sup>2</sup>, q1w) was compared with solvent-based paclitaxel (90 mg/m<sup>2</sup>, q1w), with both formulations delivered in combination with bevacizumab. Bevacizumab dosing was not reported for either treatment arm. The primary endpoint was PFS. Another Phase III RCT [15] compared nab-paclitaxel (150 mg/m<sup>2</sup>; d1, d8, d15, q28day) with solvent-based paclitaxel (85 mg/m<sup>2</sup>; d1, d8, d15, q28day). The primary end-

points were rates of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Two RCTs [16] and [17] were duplicate publications involving the same set of patients with previously untreated metastatic breast cancer who received nab-paclitaxel (300 mg/m<sup>2</sup>, q3w; 100 mg/m<sup>2</sup> or 150 mg/m<sup>2</sup> weekly) or docetaxel (100 mg/m<sup>2</sup>, q3w). The primary outcome was PFS in one study [16], and OS in the other [17]. One RCT [18] involved Chinese patients ranging in age from 18 to 70 with an Eastern Collaborative Oncology Group (ECOG) performance status of  $\leq 1$ , nab-paclitaxel (260 mg/m<sup>2</sup>, q3w) was compared with solvent-based paclitaxel (175 mg/m<sup>2</sup>, q3w). The primary endpoints were rates of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). (**Table 1**)

The included studies generally showed low risk of bias (**Figures 2, 3**). Cochrane's risk of bias tool was used to assess the individual risk of bias in each study [19]. The criteria of quality assessment were sequence generation of allocation, allocation concealment, blinding of participants, personnel and outcome assessment, incomplete outcome data, selective reporting and other bias. The risk of bias in each eligible trial was independently assessed.

#### Meta-analysis of ORR

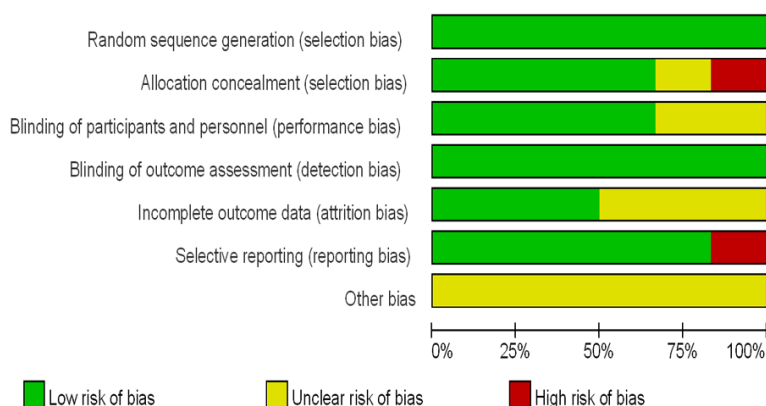
Meta-analysis of the six included studies, showed that ORR was significantly higher for nab-paclitaxel comparing with control drug treatments (OR 2.46, 95% CI 1.92 to 3.14,  $P < 0.00001$ ). These studies showed a lack of heterogeneity for ORR ( $I^2 = 27\%$ ,  $P = 0.22$ ; **Figure 4**), suggesting that these results are robust.

#### Meta-analysis of OS

Among the six studies, OS was found to be similar for nab-paclitaxel and control treatments (HR 0.87, 95% CI 0.71 to 1.05,  $P = 0.14$ ;  $I^2 = 0\%$ ,  $P = 0.51$  for heterogeneity) (**Figure 5**).

#### Meta-analysis of PFS

Among the six studies, nab-paclitaxel was associated with significantly better PFS than were control treatments (HR 0.83, 95% CI 0.73 to 0.94,  $P = 0.003$ ;  $I^2 = 45\%$ ,  $P = 0.11$  for heterogeneity) (**Figure 6**).



**Figure 3.** Risk of bias graph.

## Meta-analysis of adverse events

Meta-analysis of the six studies showed that nab-paclitaxel was associated with significantly higher risk of grade 3 sensory neuropathy than were control treatments (OR 1.82, 95% CI 1.21 to 2.74,  $P = 0.0004$ ;  $I^2 = 24\%$ ,  $P = 0.25$  for heterogeneity) (**Figure 7**). Whether nab-paclitaxel was associated with significantly higher or lower rates of neutropenia was not possible to meta-analyze because of the significant heterogeneity among studies for grade 3 neutropenia ( $I^2 = 93\%$ ,  $P = 0.23$ ) and grade 4 neutropenia ( $I^2 = 89\%$ ,  $P = 0.004$ ) (**Figures 8, 9**).

## Discussion

Nab-paclitaxel is a novel formulation of albumin-bound paclitaxel that eliminates the need for synthetic solvents with potentially toxic effects [20]. The albumin carries paclitaxel and other drugs directly into tumor cells by the gp60 receptor-mediated pathway, increasing the anti-tumor activity of those drugs while also reducing their toxicity [21]. Our meta-analysis of six trials involving 1614 patients suggests that nab-paclitaxel is associated with significantly higher ORR and PFS than are solvent-based paclitaxel or docetaxel. At the same time, nab-paclitaxel and control treatments are associated with similar OS, while nab-paclitaxel is associated with significantly higher grade 3 sensory neuropathy than are control treatments.

We undertook this meta-analysis in an effort to resolve contradictory findings in the literature. Retrospective studies [22, 23] reported that

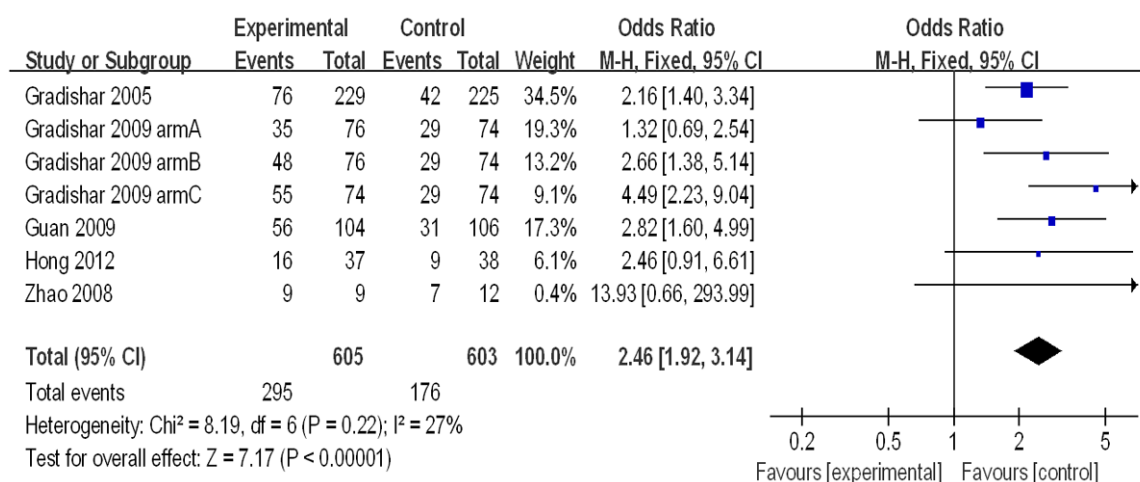
most patients treated with nab-paclitaxel for metastatic breast cancer experienced some clinical benefit, and patients showing therapeutic response lived significantly longer than those who did not. A randomized phase III trial [9] and a randomized phase II trial [10] involving patients with metastatic breast cancer showed that nab-paclitaxel was associated with higher response rates, longer time to tumor progression and significantly lower toxicity than was

standard paclitaxel. Conversely a recent Phase III trial presented at the 2012 annual meeting of the American Society of Clinical Oncology [11] reported that nab-paclitaxel did not show higher PFS than paclitaxel, while at the same time showing greater toxicity. Drawing from a larger sample size than any of these studies on their own, the present meta-analysis suggests that nab-paclitaxel offers some benefit in terms of ORR and PFS, but not in terms of OS. At the same time, the meta-analysis suggests that nab-paclitaxel is associated with significantly greater risk of grade 3 sensory neuropathy than are other drug treatments. This suggests that the potential clinical benefits of nab-paclitaxel should be weighed against the increased risk of toxicity.

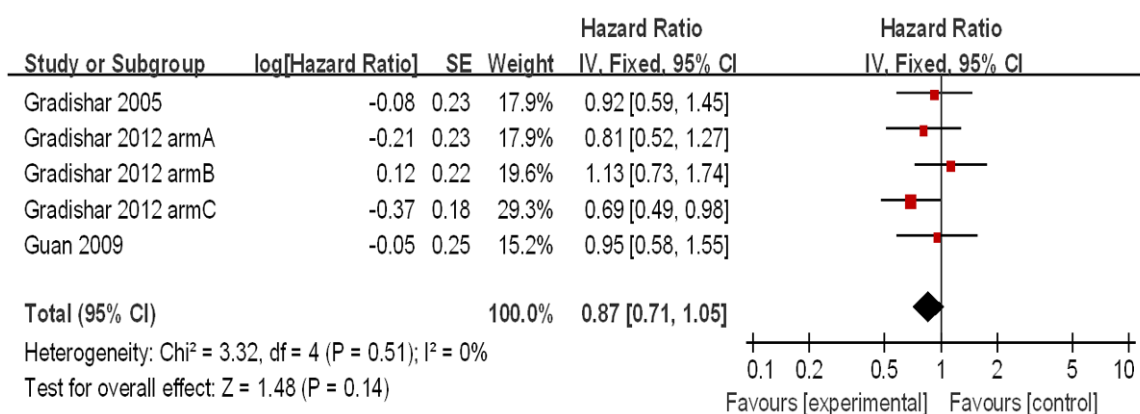
But it should be noted that there are potential reasons for this meta-analysis results. To begin with, nab-paclitaxel, administered as a colloidal suspension of 130 nanometer particles, deliver paclitaxel to tumors by biologically interacting with albumin receptors that mediate drug transport, resulting in a higher cumulative doses of paclitaxel than the standard paclitaxel. In addition, in the included trial, the doses of nab-paclitaxel in nab-paclitaxel arms were higher than other paclitaxel arms. Compared with the standard paclitaxel, higher cumulative concentrations in tumors and higher doses nab-paclitaxel used in the chemotherapeutic agents may benefit in ORR and PFS while at the same time showing greater toxicity of grade 3 sensory neuropathy. This meta-analysis suggests that nab-paclitaxel not benefit in terms of OS, there are potential reasons for this, as only six studies were included, and no OS was showed in the



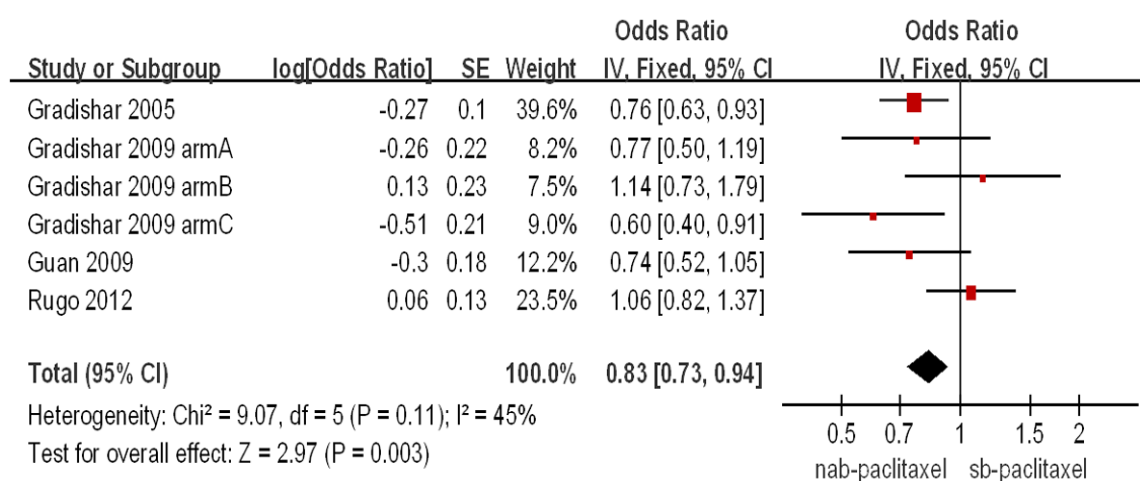
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**Figure 4.** Forest plot comparing overall response rate with nab-paclitaxel to that with control drug treatments.



**Figure 5.** Forest plot comparing overall survival with nab-paclitaxel to that with control drug treatments.

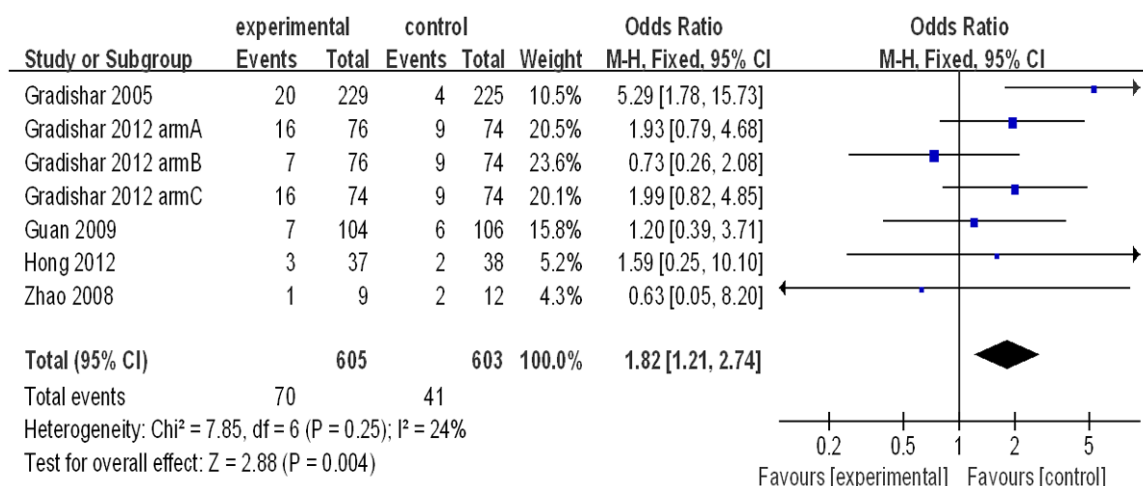


**Figure 6.** Forest plot comparing progression-free survival with nab-paclitaxel to that with control drug treatments.

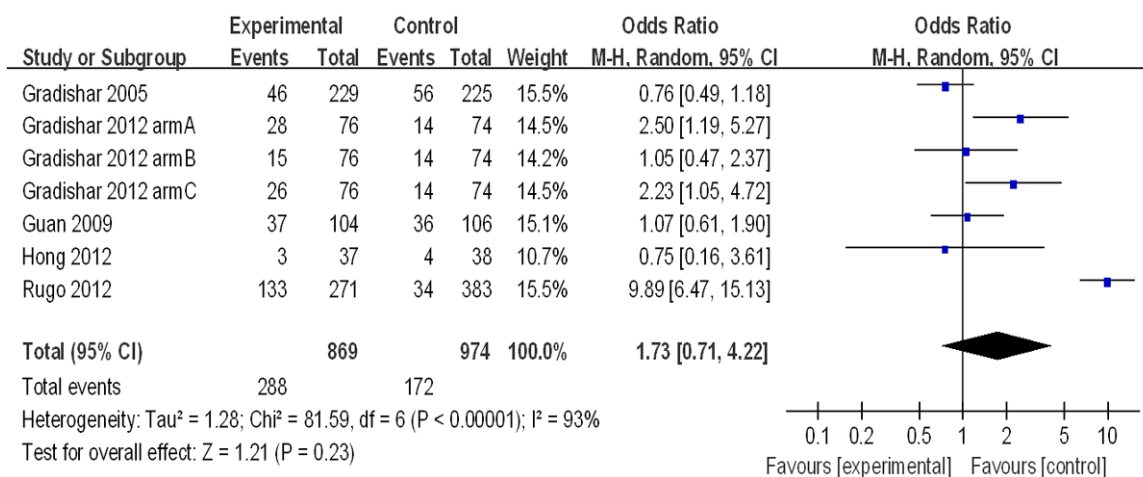
Phase III trial study from (Rugo et al.) [11], (Hong et al.) [15] and (Zhao et al.) [18].

Incomplete data, may cause the error of the results.

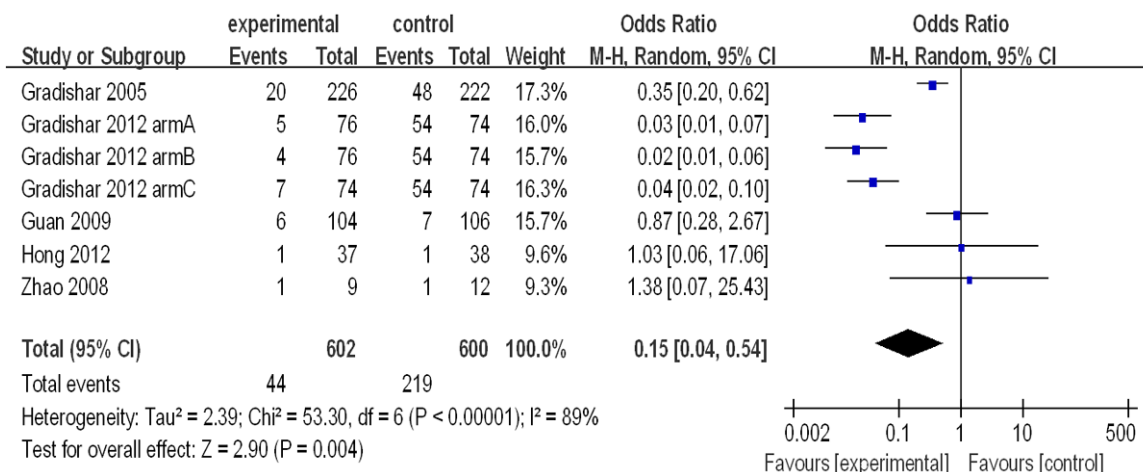
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**Figure 7.** Forest plot comparing the incidence of grade 3 sensory neuropathy observed with nab-paclitaxel to that observed with control drug treatments.



**Figure 8.** Forest plot comparing the incidence of grade 3 neutropenia observed with nab-paclitaxel to that observed with control drug treatments.



**Figure 9.** Forest plot comparing the incidence of grade 4 neutropenia observed with nab-paclitaxel to that observed with control drug treatments.

Our observation that nab-paclitaxel is associated with better ORR and PFS but not OS may reflect the relatively small numbers of patients in each included trial. They seem unlikely to reflect heterogeneity between studies, given the relatively low  $I^2$  values determined for ORR and OS. We were unable to compare the frequencies of grade 3 or grade 4 neutropenia associated with nab-paclitaxel or control drug therapies because of the high heterogeneity detected between studies. This heterogeneity is likely to reflect differences in the chemotherapeutic agents, doses and schedules used.

The conclusions of our meta-analysis are limited by issues with the individual studies. First, only six studies were included, all of which were relatively small and most of which reported inadequate information about blinding or allocation concealment, raising the possibility of bias. Second, the trials showed substantial heterogeneity for some of the outcomes examined, probably reflecting differences in nab-paclitaxel dose regimens and in the nature and dose of control therapy. Third, we had to extract HRs and CIs for PFS and OS from survival curves in some studies that did not directly report these data. This may have introduced error into our analysis.

With these limitations in mind, we suggest that, based on our meta-analysis, nab-paclitaxel is associated with better ORR and PFS than are other drug therapies commonly used to treat metastatic breast cancer. On the other hand, nab-paclitaxel does not improve OS, and it is associated with significantly greater risk of grade 3 sensory neuropathy. These findings suggest that future studies should examine ways to reduce the toxicity of nab-paclitaxel and improve OS, and more high-quality RCTs are required to evaluate the efficacy and safety of nab-paclitaxel versus with control drug treatments in patients with metastatic breast cancer.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Jian-Lun Liu, Breast Surgery Tumor Hospital, Guangxi Medical University, Nanning 530021, Guangxi, People's Republic of China. Tel: +86-0771-5308635; Fax: +86-0771-5308635; E-mail: 15579163593@163.com

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