Original Article

Efficacy and safety of nanoparticle-albumin-bound paclitaxel compared with conventional taxanes in women with breast cancer: a systematic review and meta-analysis

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Background: Long-term benefit of nanoparticle-albumin-bound paclitaxel (Nab-P) over conventional taxanes in breast cancer patients is still controversial. We conducted a systematic review of studies to identify the optimal taxanes for selection in clinical practice.

Methods: We enrolled studies if they enrolled adults (age ≥18) with breast cancer, compared Nab-P (at any dose) to conventional paclitaxel or docetaxel, provided information on survival data, the response rate, or adverse events, were randomized controlled trials, case-control studies, or cohort studies, and were published in English (including those published online, ahead of the print publication). Cochrane Collaboration tool and Newcastle-Ottawa scale were used for bias-risk assessment. Grading of recommendations assessment, development, and evaluation approach were adopted for the quality of evidence evaluation. The outcomes included the overall response rate, pathological complete response rate, progression-free survival, overall survival, allergic reaction, leukopenia, neutropenia, and sensory neuropathy.

Results: A total of 20 eligible clinical studies comprising 11,046 patients were included in the analysis. No significant publication bias was observed based on a visual inspection of the funnel plots for progressionfree survival (PFS), and overall survival (OS). Compared to the conventional taxanes group (n=2,743), the Nab-P group (n=1,680) had a significantly higher ORR (RR =1.21, 95% CI: 1.07–1.37; P=0.003) and pCR (RR =1.33, 95% CI: 1.17–1.51; P<0.001). The Nab-P group also had a lower risk of disease progression and death than the conventional taxanes group (HR =0.89, P=0.269). Additionally, the Nab-P group had fewer treatment-related allergic reactions (RR =0.74, 95% CI: 0.59–0.93; P=0.009) and less grade ≥4 neutropenia (RR =0.39, 95% CI: 0.20–0.77; P=0.007) than the conventional taxanes group. The incidence of any-grade of neutropenia and sensory neuropathy were significantly higher in the Nab-P group than the conventional taxanes group (P=0.009 and P<0.001, respectively).

Discussion: The Nab-P in all stages of breast cancer patients had significantly better efficacy and tolerance than the conventional taxanes. Moreover, preventive strategies for reducing the incidence of Nab-P induced sensory neuropathy should be explored in future studies.

Keywords: Breast cancer; nanoparticle-albumin-bound paclitaxel (Nab-P); taxanes; meta-analysis

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Introduction

According to the *World Cancer Report 2020*, breast cancer has surpassed lung cancer to become the most common malignant tumor in women (1). However, the decline of breast cancer mortality may be partly related to developments in chemotherapy (2). Taxanes are considered the cornerstone drugs in many cancers, including ovarian cancer, lung cancer, pancreatic cancer, and breast cancer. In China, approved taxanes include paclitaxel, docetaxel, liposomal paclitaxel, and nanoparticle-albumin-bound paclitaxel (Nab-P). Notably, the water solubility of conventional taxanes, including paclitaxel and docetaxel, is extremely poor, which makes intravenous administration challenging (3). Additionally, conventional taxanes have poor selectivity for the site of action, weak targeting, poor drug delivery efficiency, and low tissue availability, and the cosolvents can also cause various adverse reactions, including allergic reactions, neurotoxicity (4,5), and even drug resistance (6,7). Additionally, the tiny particles formed in the blood circulation encapsulate the effective drugs, hindering the effects and limiting the extensive application of conventional paclitaxel.

Following the continuous development and application of new formulations of paclitaxel, Nab-P was first approved by the United States (US) Food and Drug Administration (FDA) in 2005 for the treatment of advanced breast cancer. In 2009, Nab-P was approved for marketing in China, and at the same time, the 1st nanotechnology drug delivery application for breast cancer was approved by the FDA. This novel nano-drug delivery system comprises albumin, which is a carrier of natural fat-soluble molecules. The characteristics of hydrophobic albumin molecules, via the transcellular albumin-binding glycoprotein (GP60) pathway, and the secreted protein acidic rich in cysteine (SPARC) pathway in the extracellular matrix of tumors, are used to increase the concentration of the extra-tumor drug. This novel delivery system also increases the speed at which paclitaxel enters tumor cells and allows for the effective redistribution of the drug. Taken together, these design features avoid the problems and toxicity associated with solvents (8).

Nab-P has shown better efficacy and safety than conventional taxanes in early studies but the superiority of Nab-P has failed to be verified in a phase III study (9). Further more, the conclusions of toxicity profiles comparison between Nab-P and conventional taxanes are inconsistent in previous meta-analysis studies (10,11). Thus, we conducted a meta-analysis of the therapeutic outcomes and safety of Nab-P and conventional taxanes in breast cancer to gather more information for reference in clinical practice. We present the following article in accordance with the PRISMA reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-690/rc) (12).

Methods

Protocol and guidance

The protocol was registered in PROSPERO (CRD42020190984).

Search strategy

The PubMed, Web of Science, Embase, Scopus, and the Cochrane Library databases were searched to retrieve eligible studies from their inception to December 31, 2020. The Medical Subject Heading (MeSH) terms of breast neoplasms, Nab-P, and corresponding keywords were used. The search strategy is detailed in Appendix 1. To maximize the search for relevant articles, reference lists from the eligible articles and systematic reviews were also checked.

Inclusion criteria

Studies were considered eligible if they enrolled adults (age ≥18) with breast cancer, compared Nab-P (at any dose) to conventional paclitaxel or docetaxel, provided information on survival data, the response rate, or adverse events (Aes), were randomized controlled trials (RCTs), case-control studies (CCSs), or cohort studies (CSs), and were published in English (including those published online, ahead of the print publication).

Exclusion criteria

Studies were excluded if they were case reports, case series, single-arm clinical trials, animal studies, gray literature (including meeting abstracts), did not contain hazard ratios (HRs) or odd ratios (Ors) with their 95% confidence intervals (95% Cis), included any neoplasm other than breast cancer, and had been reported in multiple publications.

Outcomes

The efficacy outcomes included the overall response rate

(ORR), pathologic complete response (pCR), progression-free survival (PFS), and overall survival (OS). The safety outcomes included any grade Aes and grade 3/4 Aes.

Study selection

The study selection was performed independently by 2 authors; any discrepancies were reviewed by a 3rd author and resolved by consensus. The study selection steps were as follows: (I) 1 author removed duplicate articles; (II) 2 independent authors screened all the titles and abstracts and reached a consensus with each other; and (III) the full texts were obtained, and the articles were further screened to identify eligible studies. Any disagreements were resolved by consensus.

Data extraction

The data collection was performed independently by 2 authors, who used a standard data extraction form to collect the data from the included studies. The following data were extracted: the first author's last name, year of publication, study design, race of patients, number of patients, treatment lines, study region, study treatment (name, dosage, schedule, and combination drug if any), efficacy outcomes (i.e., PFS, OS, ORR, and pCR), and AE outcomes. When a study mentioned an outcome of interest without estimates, the data were obtained by calculation and transformation. If a study only stated the survival curve, the curve was imported into Engauge Digitizer to obtain the original data by drawing the outline of the curve and deriving the data to calculate the HR and the CI of the curve according to a previously describe method (13).

Assessment of risk of bias and quality of evidence

The risk of bias for each included RCT was assessed using the Cochrane Collaboration tool (14). The risk of bias for each included CCS or CS was assessed by the Newcastle-Ottawa scale (15). The quality of evidence for the outcomes was assessed using the grading of recommendations assessment, development, and evaluation (GRADE) approach (16).

Statistical analysis

Data synthesis

We performed the statistical analyses using the "meta" package in R (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria). We input the outcome data of each included study in the meta-analysis (17). The pooled HRs and RRs were reported with 95% Cis; all tests were 2-sided, and a probability level of 0.05 was used to determine statistical significance. Heterogeneity among the studies was assessed using the I^2 statistic. If significant heterogeneity was not present (I^2<50%), a fixed-effects model was used to pool the outcomes, and otherwise, a random-effects model was used. Publication bias was assessed by funnel plots and eggers test

Subgroup analysis

Subgroup analyses were performed to examine the interactions and explain the heterogeneity according to lines of treatment (1st-line or 2nd-line), treatment frequency [every week (QW) or every 3 weeks (Q3W)], the control drug (paclitaxel or docetaxel), the combination drug (with or without), race of patients (Asian or Western), and tumor stage (early or advanced) when the relevant data were available.

Sensitivity analyses

We conducted sensitivity analyses by excluding trials with high or unknown risks of bias, excluding the largest trials, using random-effect models, and excluding trials with male patients.

Results

Characteristics of the included studies

A total of 4,340 articles were initially retrieved. Next, the titles and abstracts of the articles were carefully read, and any duplicate and irrelevant articles were excluded. After reading the full text of the articles, and based on the aforementioned inclusion and exclusion criteria, 20 studies (22 articles, including 2 studies that had reported the outcomes of interest in separate articles) were ultimately included in the meta-analysis (9,17-37). *Figure 1* shows the screening process. The characteristics of the included studies are shown in *Table 1*.

Quality evaluation of the included studies

The quality of the 20 included studies was evaluated according to the study type. In this meta-analysis, 2 quality evaluation scales were used; that is, the Cochrane risk of

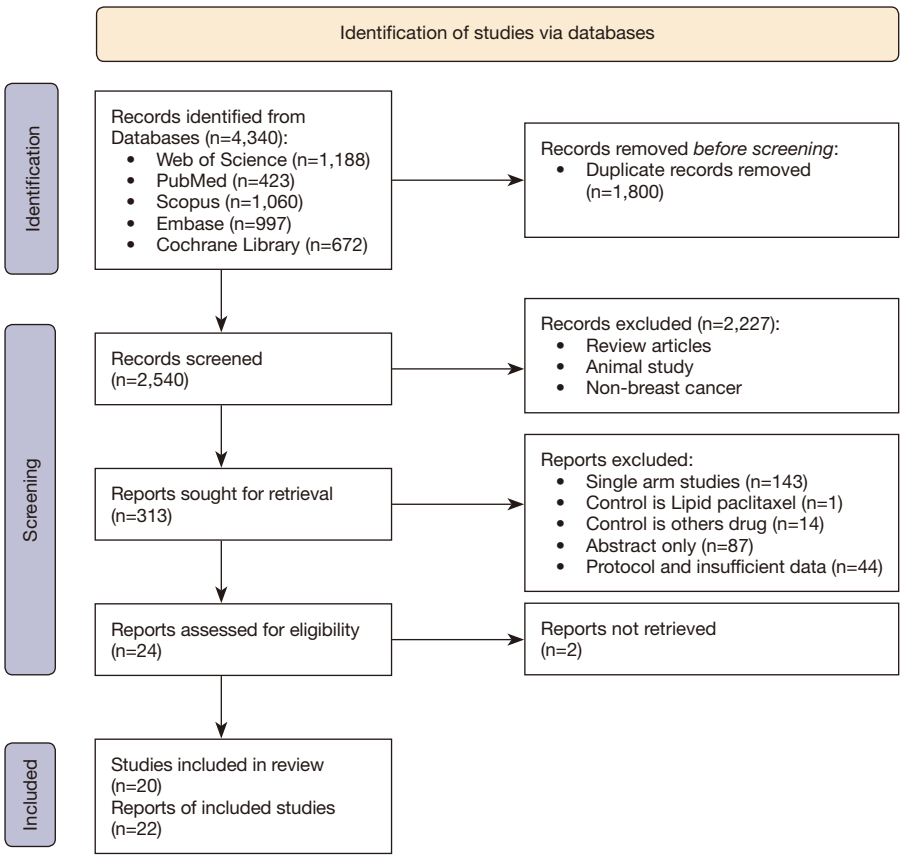

Figure 1 Flow chart of the screening process.

bias assessment form for the 14 included RCTs and the Newcastle-Ottawa scale (NOS) for the 6 included CCSs and CSs. The included studies were found to have moderate risks of bias (see Appendix 2).

Outcome indicators of the included literature

As Appendix 3 shows, the indicators extracted from the included articles included PFS, OS, ORR, pCR, and other indicators related to the research objectives. Additionally, data on adverse outcomes, such as allergy, leukopenia, neurotoxicity, and neutropenia, were extracted.

Meta-analysis of therapeutic efficacy

ORR

The ORRs were available in 11 studies (9,18-21,24-26,28,31,35,36). The heterogeneity test results for those studies were I^2=68% (P<0.01); thus, a random-effects model was used for the analysis. The results showed that the ORR of the Nab-P group was 21% higher than that of the control group (RR =1.21, 95% CI: 1.07–1.37, and P=0.003, see *Figure 2A* for further details). The meta-regression analysis showed that the dosage of the drug affected the combined effect size. The heterogeneity among the studies was not due to the region of the study, number of doses, controls, study design, or tumor type (see Appendix 4). In the subgroup analyses, the ORRs of the patients in the Nab-P groups who received 2 treatment lines, had a treatment frequency of Q3W, received the single-administration treatment mode, and were Asian were significantly higher than those of the control groups (see Appendix 5).

pCR

The pCRs after the neoadjuvant treatment of Nab-P and solvent-based paclitaxel of early breast cancer patients were available in 7 studies (17,23,25,28,30,32,33,36). The heterogeneity test results for those studies were I^2=8% (P=0.37); thus a fixed-effects model was used for the analysis. The results showed that the pCR of the

Table 1 Characteristics of the included studies

Author	Publication year	Country	Research type	Sample size	Cancer type	Triple-negative breast cancer	Dosage and frequency	Control
Gradishar	2005	Russia, USA, UK	RCT	454	Metastatic	Not mentioned	260Q3W/175Q3W	sb-pc
Davidson	2008	–	RCT	351	Metastatic	Not mentioned	260Q3W/175Q3W	sb-pc
Gradishar	2009	Russia, USA	RCT	148	Metastatic	Not mentioned	100QW, 150QW, 300Q3W/100Q3W	doc
Guan	2009	China	RCT	210	Metastatic	Not mentioned	260Q3W/175Q3W	sb-pc
Pippen	2011	–	RCT	197	Early	Not mentioned	260Q3W/175Q3W	sb-pc
Zhang	2012	China	RCT	52	Not mentioned	Not mentioned	260/175	sb-pc
Gradishar	2012	Russia, USA	RCT	148	Metastatic	Not mentioned	100QW, 150QW, 300Q3W/100Q3W	doc
Rugo	2015	USA	RCT	554	Metastatic	Not mentioned	150QW/90QW	sb-pc
Huang	2015	China	RCT	120	Advanced	Not mentioned	125QW/80QW	sb-pc
Untch	2016	Germany	RCT	1,206	Primary	Not mentioned	125QW/80QW	sb-pc
Tamura	2017	Japan	RCT	197	Metastatic	Not mentioned	150QW/73Q3W	doc
Cortes	2018	Russia, USA, UK	RCT	454	Metastatic	Not mentioned	260Q3W/175Q3W	sb-pc
Gianni	2018	Spain, Australia, Singapore	RCT	672	Not mentioned	Not mentioned	125QW/90QW	sb-pc
Mahtan	2018	USA	OS	925	Metastatic	Not mentioned	–	sb-pc
Kuwayama	2018	Japan	RCT	152	Early	Not mentioned	100QW/75Q3W	doc
Ciruelos	2019	Spain	RCT	20	Not mentioned	Not mentioned	100QW, 150QW, 150Q2W/80QW	sb-pc
Xie	2019	China	OS	162	Early	Not mentioned	260Q2W/175Q2W	sb-pc
Untch	2019	Germany	RCT	1,206	Primary	Not mentioned	125QW/80QW	sb-pc
Luhn	2019	USA	OS	200	Not mentioned	Triple-negative breast cancer	–	sb-pc
Bachelot	2019	France	OS	1,436	Metastatic	Not mentioned	–	doc
Yang	2019	China	OS	50	Not mentioned	Not mentioned	260Q3W/175Q3W	sb-pc
Han	2020	China	OS	95	Advanced	Not mentioned	260Q3W/175Q3W	sb-pc

RCT, randomized controlled trials; Q3W, every 3 weeks; QW, every week; sb-pc, solvent-based paclitaxel; doc, docetaxel; OS, observational study.

neoadjuvant treatment was 33% higher in the Nab-P breast cancer group than the control group (RR =1.33, 95% CI: 1.17–1.51; P<0.001). Thus, Nab-P had some advantages in the treatment of early breast cancer (see *Figure 2B* for further details).

PFS

Data on the PFS of patients with breast cancer in the Nab-P and conventional taxanes groups were available in 6 studies (9,20,21,26,27,35). The heterogeneity test results for those studies were I^2=77% (P<0.01); thus, a random-effects model was used for the analysis. The results showed that the risk of disease progression or death was 11% lower in the Nab-P treatment group than the control group (HR =0.89, 95% CI: 0.73–1.09; P=0.269; see *Figure 2C*). The meta-regression analysis showed that the region of study, dosage, number of doses, controls, and study design did not cause heterogeneity among the studies (see Appendix 6). In

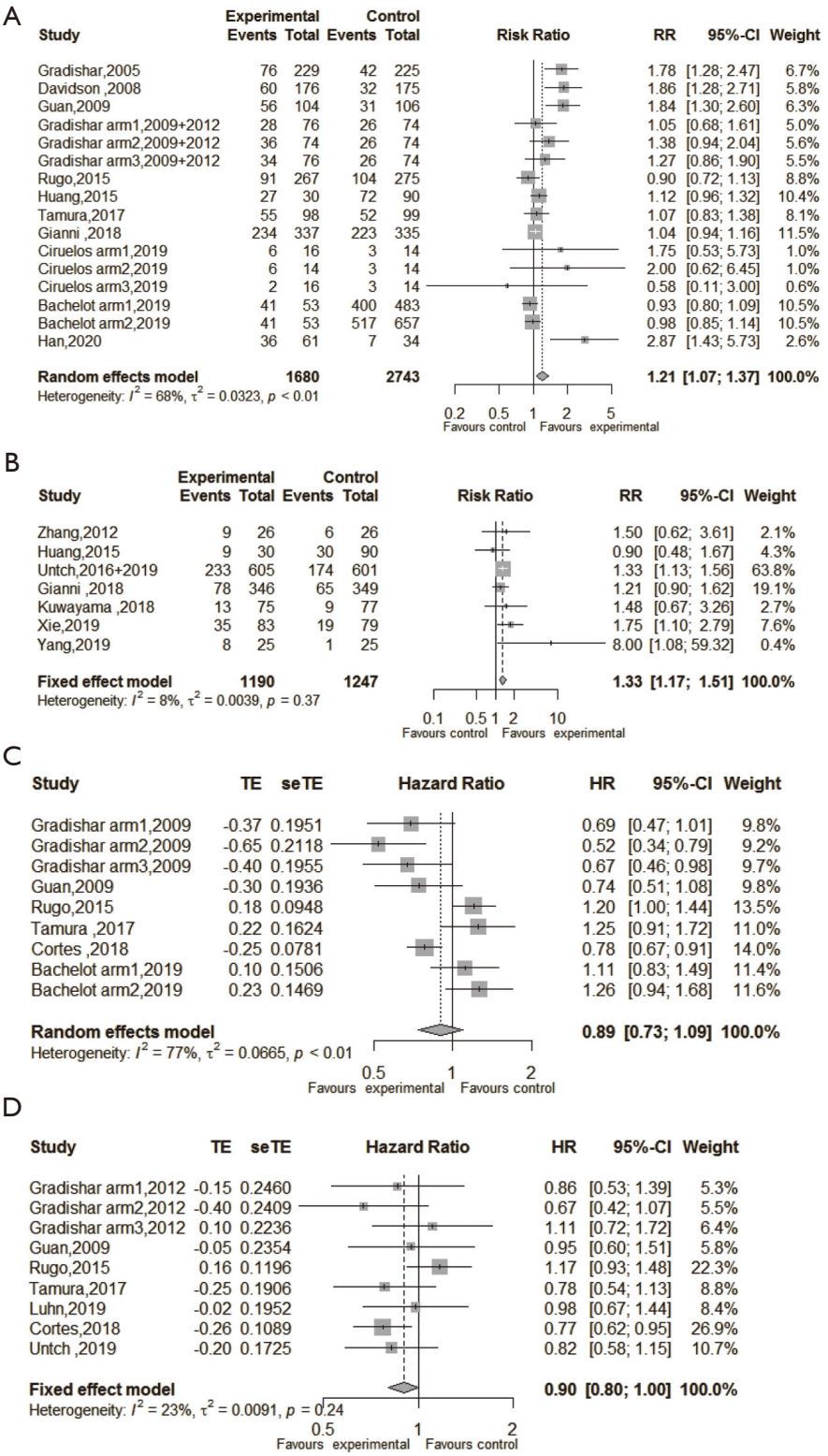

Figure 2 Forest plot of the (A) ORR; (B) pCR; (C) PFS; and (D) OS of Nab-P and solvent-based paclitaxel/docetaxel in the treatment of breast cancer. ORR, overall response rate; pCR, pathological complete response rate; PFS, progression-free survival; OS, overall survival; TE, Log (hazard ratio); SE, standard error.

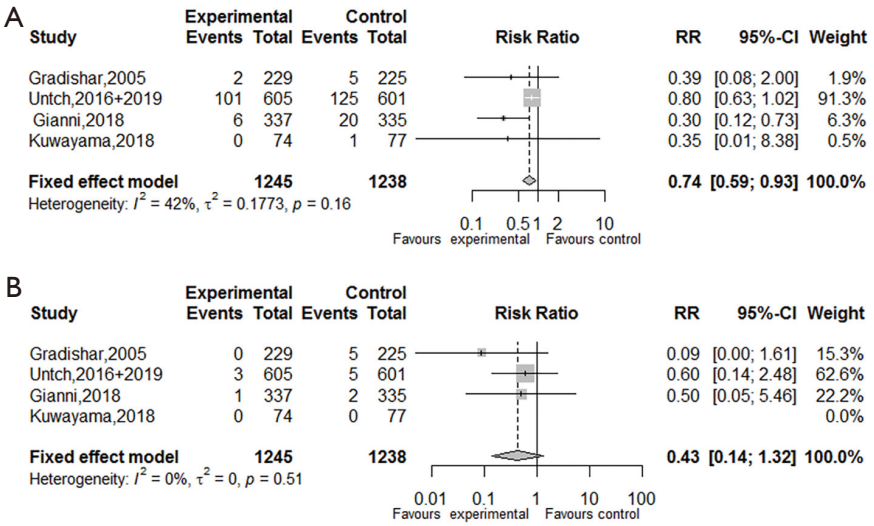

Figure 3 Forest plots of the incidences of allergic reaction of any grade (A) and grade ≥3 (B) in patients with breast cancer receiving Nab-P and solvent-based paclitaxel/docetaxel treatments.

the subgroup analysis, the risk of disease progression or death of the patients in the Nab-P groups who received 2 treatment lines and had a treatment frequency of Q3W was significantly lower than that of patients in the control groups. No significant difference was found between the 2 groups in terms of race (Western or Asian). Additionally, different administration modes (single or combination) had the opposite effect on PFS between the 2 groups (see Appendix 7).

OS

Data on patients' OS after Nab-P and conventional taxanes treatments for breast cancer were available in 7 studies (9,21,24,26,27,33,34). The heterogeneity test results were I^2=23% (P=0.24); thus, a fixed-effects model was applied. The results indicated that the risk of death among breast cancer patients in the Nab-P treatment group was 10% less than that of patients in the control group, but no significant difference was found between the groups (P=0.478; see *Figure 2D* for further details). In the subgroup analysis, the risk of death of patients in the Nab-P groups who received two treatment lines, had a treatment frequency of Q3W, and received a single-administration treatment mode was significantly lower than that of patients in the control groups. No significant difference was reported in the subgroups as stratified by race, control group, or disease stage (see Appendix 8).

Meta-analysis of drug safety

Allergic reactions

Data on the incidence of allergic reactions were available in 4 studies (17,18,20,30,33). The pooled results showed that the risk of allergic reactions of any grade in the Nab-P group were 26% lower than those of patients in the control group (RR =0.74, 95% CI: 0.59–0.93; P=0.009). The risk of grade ≥3 allergic reactions in the Nab-P group was 57% lower than that in the control group, but no significant difference was found between the 2 groups (RR =0.43, 95% CI: 0.14–1.32; P=0.14, see *Figure 3* for further details).

Leukopenia

Data on the incidence of leukopenia were available in 9 studies (9,21,25,26,28,30,31,33,37). No significant difference in the risk of leukopenia of any grade was found between the 2 treatment groups (RR =1.00, 95% CI: 0.93–1.08; P=0.991, see *Figure 4A* for further details). Compared to the conventional taxanes group, the risk of grade ≥3 leukopenia in patients with breast cancer in response to Nab-P treatment was increased by 1% (RR =1.01, 95% CI: 0.93–1.08; P=0.955, see *Figure 4B* for further details), but the difference was not significant. Compared to docetaxel treatment, the risk of grade ≥3 leukopenia in the Nab-P treatment group was significantly decreased by 35% (RR =0.65, 95% CI: 0.55–0.77; P<0.001). However, no significant difference was observed in the risk of grade

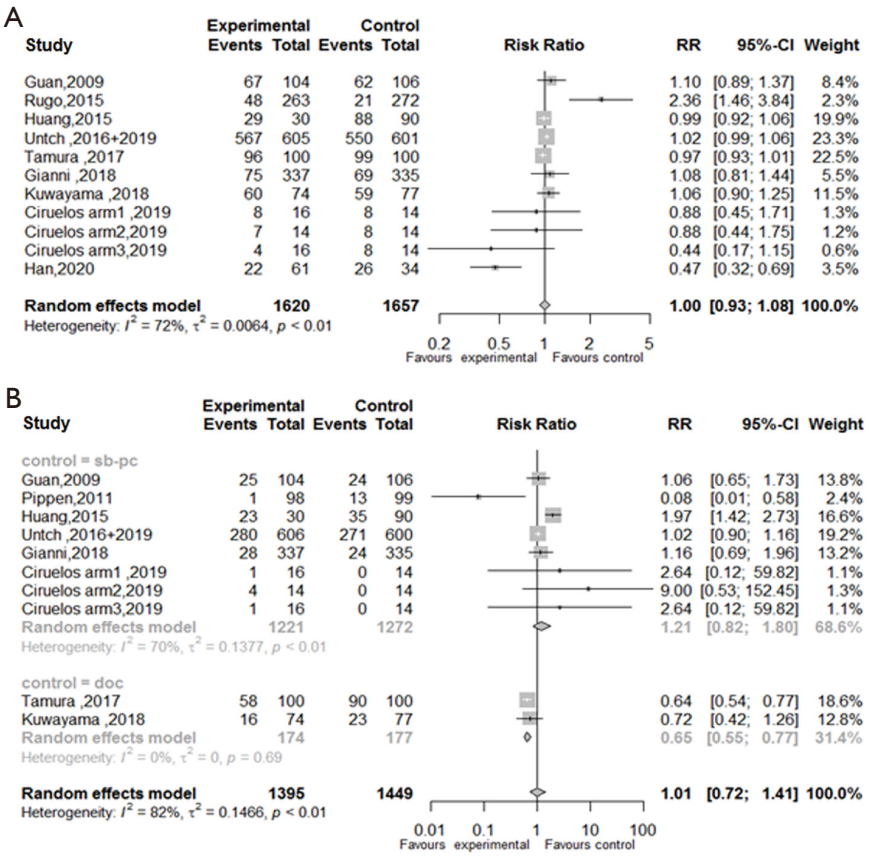

Figure 4 Forest plots of the incidences of leukopenia of any grade (A) and grade ≥ 3 (B) in patients with breast cancer receiving Nab-P and solvent-based paclitaxel/docetaxel treatments.

≥3 leukopenia between the conventional solvent-based paclitaxel group and Nab-P group (RR =1.21, 95% CI: 0.82–1.80; P>0.05, see *Figure 4B*).

Neutropenia

Data on the incidence of neutropenia were available in 13 studies (9,17,20,21,23-26,28-31,33,35,36). The risk of neutropenia of any grade in the Nab-P group was 8% higher than that of the conventional taxanes group (RR =1.08, 95% CI: 1.02–1.14; P=0.009, see *Figure 5A*). Compared to docetaxel treatment, the risk of grade ≥3 neutropenia in the Nab-P treatment group was significantly decreased by 46% [RR =0.54 (0.37, 0.79)], but no significant difference in the risk of grade ≥3 neutropenia was found between the conventional solvent-based paclitaxel treatment and the Nab-P treatment groups (see *Figure 5B* for further details). The risk of grade ≥ 4 neutropenia in the Nab-P group was significantly lower than that of the conventional taxanes group [RR =0.39 (0.20, 0.77); P=0.007; see *Figure 5C* for further details].

Sensory neuropathy

Data on the incidence of sensory neuropathy were available in 12 studies (9,17,20,21,24-26,28-33,35). The risk of sensory neuropathy was 21% higher in the Nab-P group than the conventional taxanes group [RR =1.21 (1.10, 1.33); P<0.001; see *Figure 6* for further details].

Publication bias and sensitivity analysis

No significant publication bias was observed based on a visual inspection of the funnel plots for PFS and OS (see Appendix 9). A sensitivity analysis of the primary outcome indicators was conducted by excluding each study, one by one. Our results showed that each study had a negligible effect on the outcomes, which was not changed as a result of eliminating a specific study; thus, the results of this meta-analysis were relatively stable (see Appendix 10).

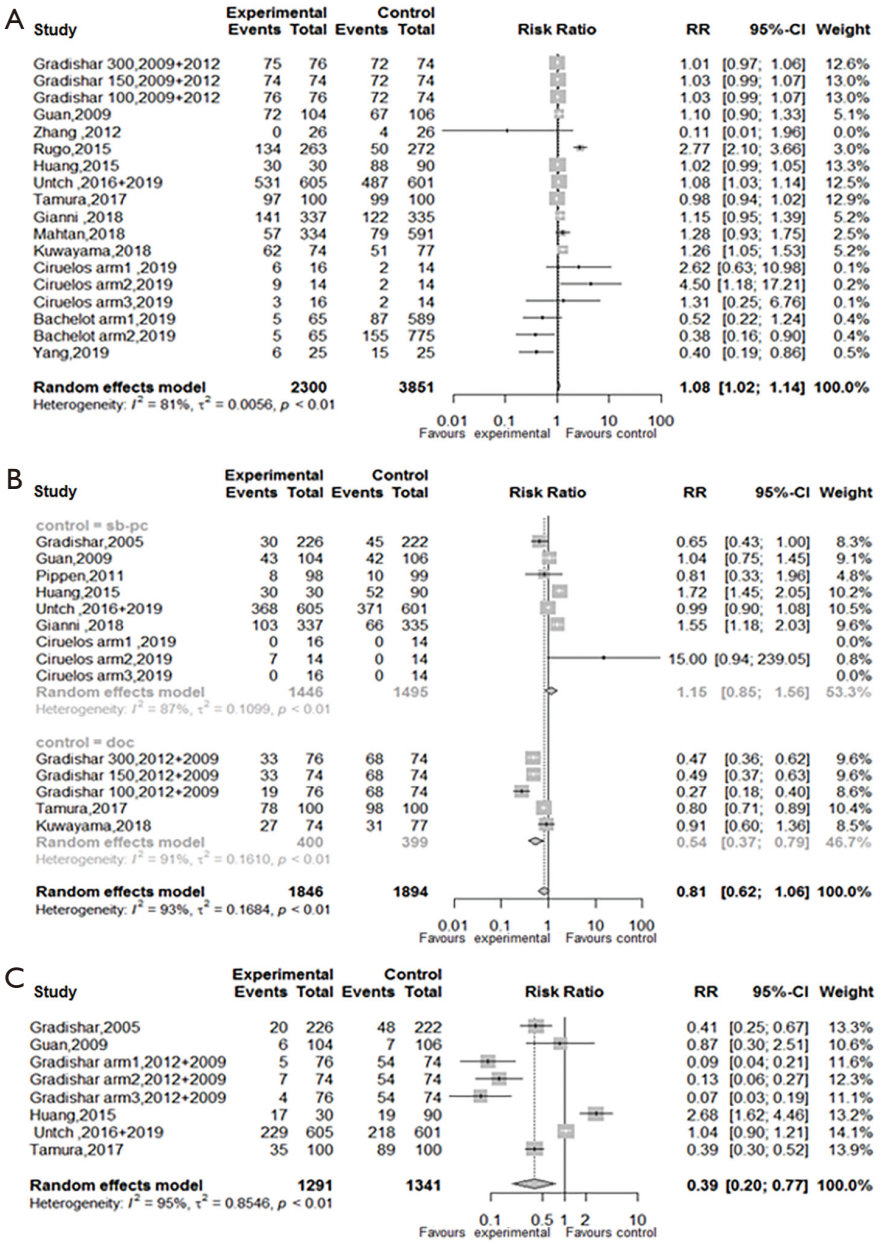

Figure 5 Forest plot of the incidences of neutropenia of any grade (A) grade ≥3 (B) grade ≥4 (C) in patients with breast cancer receiving Nab-P and solvent-based paclitaxel/docetaxel treatments.

Discussion

Albumin is an endogenous protein that does not have an opsonizing effect. A previous study demonstrated that albumin could be used as a drug carrier to prepare nanoparticles and reduce the affinity of nanoparticles to macrophages (38), thereby prolonging the circulating period and improving the targeted efficacy of the drug. The results of this meta-analysis showed that the pCRs and ORRs of breast cancer patients treated with Nab-P were better than those of breast cancer patients treated with solvent paclitaxel. This is likely because the nano-drug delivery system binds paclitaxel to albumin, thereby reducing the dose of paclitaxel and the need for toxic solvents, such as polyoxyethylene castor oil (39). The albumin transport pathway (gp60-caveolin-SPARC) may facilitate the

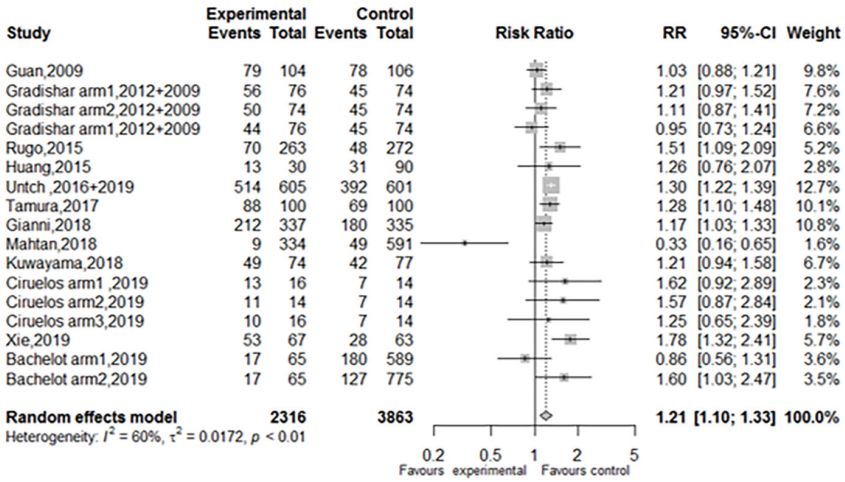

Figure 6 Forest plot of the incidence of sensory neuropathy in patients with breast cancer receiving Nab-P and solvent-based paclitaxel/docetaxel treatments.

transportation of Nab-P (40). We found that the application of Nab-P in late lines of treatment had better effects than conventional taxanes on all indicators of therapeutic efficacy in patients with advanced breast cancer. This may be due less interference of anti-tumor therapies n the late-line group than front-line group, which usually involves monotherapy rather than combination therapy. Our results provide further evidence that Nab-P has more beneficial effects in breast cancer treatment than conventional taxanes.

Additionally, in the advanced setting, patients treated with Q3W Nab-P benefited more than those with QW Nab-P in the ORR, PFS and OS when compared with conventional taxanes. It may be that the patients who received Q3W dosing also received corresponding preventive and supportive therapy (e.g., granulocyte-colony stimulating factor) to ensure full-dosage chemotherapy and the entire course of treatment. Thus, patients' compliance with Q3W Nab-P is expected to be better than their compliance with a weekly regimen. We also compared the efficacy of Nab-P and conventional taxane treatment under different modes of administration in relation to the ORR, PFS, and OS of patients with advanced breast cancer. Our results demonstrated that Nab-P monotherapy had more beneficial effects on the ORR, PFS, and OS of patients, which may be because the combination of drugs dilute the efficacy of Nab-P, which in turn resulted in findings of non-significant differences in comparisons of Nab-P to conventional taxanes. Additionally, while combination therapy may improve short-term curative effects, it may also increase the risk of toxicity, which could in turn result in a failure to complete the entire course of chemotherapy. Thus, in later-line treatments, Nab-P monotherapy may be better than conventional taxanes for patients with advanced breast cancer.

The adverse reactions caused by Nab-P and conventional taxanes in the treatment of breast cancer were also explored. We found that there was no significant difference between the 2 treatments in relation to allergic reactions and leukopenia. However, the incidences of peripheral neurotoxicity and neutropenia caused by Nab-P were significantly higher than those caused by conventional taxanes. The relative higher dosage of paclitaxel in Nab-P compared to those of standard paclitaxel in the control groups may be the major cause of higher incidence of treatment related adverse events Additionally, the administration time of Nab-P was decreased to 30 minutes due to the removal of organic solvents, which is another reason for the increase in allergic reactions and neurotoxicity. In addition to the solvent, the dose of each injection, time of administration, treatment duration, and cumulative dose are also known to influence the occurrence of peripheral neuropathy (41).

This study had several limitations. First, the included RCTs provided little information on the risk assessment items, and thus we were unable to properly evaluate the quality of the studies. However, in sensitivity analyses, no significant changes were found after excluding studies of high and unknown quality. Second, the sample sizes of the included studies were relatively small in relation certain outcomes; thus, further research needs to be conducted

using large sample-sized studies to extend findings on these outcomes. Finally, since we have not enrolled non-English language literature databases that the language bias might exist.

In conclusion, the pCR rate and the response rate was significantly higher in patients treated with neoadjuvant nab-paclitaxel than those with conventional taxanes. The PFS and OS of advanced breast cancer patients were comparable between the groups; however, Nab-P produced fewer side effects than conventional taxanes, including allergic reactions, which suggests that Nab-P has a unique mechanism of action and offers considerable advantages in the treatment of breast cancer. Nab-P has promising efficacy and tolerance in the treatment of advanced breast cancer patients, and it is expected to be widely used in breast cancer patients.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist Available at https://apm.amegroups.com/article/view/10.21037/apm-22-690/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-690/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Appendix 1

Search strategy

We used PubMed, Web of Science, Embase, Scopus, and the Cochrane Library to identify papers on albumin-bound paclitaxel treated for breast cancer from inception to December 31, 2020.

Search words:
1. breast neoplasm, breast cancer, mammary cancer, breast carcinoma
2. albumin bound paclitaxel, nab-paclitaxel, abraxane, ABI 007

We used the following combinations of search terms:
1. Pubmed:
((("breast neoplasm"[Title/Abstract] OR "breast cancer"[Title/Abstract]) OR "mammary cancer"[Title/Abstract]) OR "breast carcinoma"[Title/Abstract]) AND ((("albumin bound paclitaxel"[Title/Abstract] OR "nab-paclitaxel"[Title/Abstract]) OR "abraxane"[Title/Abstract]) OR "abi 007"[Title/Abstract])

2. Web of science:
TS =("breast neoplasm" OR "breast cancer" OR "mammary cancer" OR "breast carcinoma") AND TS =("albumin bound paclitaxel" OR nab-paclitaxel OR abraxane OR "ABI 007")

3. Scopus:
(TITLE-ABS-KEY ("breast neoplasm" OR "breast cancer" OR "mammary cancer" OR "breast carcinoma") AND TITLE-ABS-KEY ("albumin bound paclitaxel" OR nab-paclitaxel OR abraxane OR "ABI 007"))
4. Embase:

#1'breast neoplasm':ti,ab,kw OR 'breast cancer':ti,ab,kw OR 'mammary cancer':ti,ab,kw OR 'breast carcinoma':ti,ab,kw
#2 'albumin bound paclitaxel':ti,ab,kw OR 'nab paclitaxel':ti,ab,kw OR abraxane:ti,ab,kw OR 'abi 007':ti,ab,kw
#1 AND #2

5. Cochrane library:
#1 ("breast neoplasm" OR "breast cancer" OR "mammary cancer" OR "breast carcinoma"):ti,ab,kw
#2 ("albumin bound paclitaxel" OR nab-paclitaxel OR abraxane OR "ABI 007"):ti,ab,kw
#1 AND #2

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Appendix 2

Cochrane risk assessment form of the randomized controlled trials included in the meta-analysis

Author	Selection bias		Implementation bias	Measurement bias	Follow-up bias (lost to follow-up)	Report bias (selective report)	Other bias
	Randomized sequence generation	Allocation concealment	Participants blinded	Outcome-rater blinded			
Gradishar *et al.*, 2005 (18)	Randomized but with no specific description of the method	Unknown	Unknown	Unknown	Unknown	Unknown	None
Davidson *et al.*, 2008 (19)	Randomized	Randomly allocated	Unknown	Unknown	Unknown	Unknown	None
Gradishar *et al.*, 2009 (20)	Randomized	Unknown	Unknown	Blinded	Lost to follow-up	Unknown	None
Guan *et al.*, 2009 (21)	Randomized but with no specific description of the method	Unknown	Unknown	Unknown	Unknown	Unknown	None
Pippen *et al.*, 2011 (22)	Randomized but with no specific description of the method	Unknown	Unknown	Unknown	Unknown	Unknown	None
Zhang *et al.*, 2012 (23)	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	None
Gradishar *et al.*, 2012 (24)	Randomized	Unknown	Unknown	Blinded	Lost to follow-up	Unknown	None
Rugo *et al.*, 2015 (9)	Randomized but with no specific description of the method	Unknown	Unknown	Unknown	Lost to follow-up	Unknown	None
Huang *et al.*, 2015 (25)	Randomized but with no specific description of the method	Unknown	Unknown	Unknown	Unknown	Unknown	None
Untch *et al.*, 2016 (17)	Randomized	Unknown	Unblinded	Blinded	Unknown	Unknown	None
Tamura *et al.*, 2017 (26)	Randomized	Randomly allocated	Unknown	Unknown	Unknown	Unknown	None
Cortes *et al.*, 2018 (27)	Randomized but with no specific description of the method	Unknown	Unknown	Unknown	Unknown	Unknown	None
Gianni *et al.*, 2018 (28)	Randomized but with no specific description of the method	Unknown	Unknown	Unknown	Unknown	Unknown	None
Kuwayama *et al.*, 2018 (30)	Randomized but with no specific description of the method	Unknown	Unknown	Unknown	Unknown	Unknown	None
Ciruelos *et al.*, 2019 (31)	Randomized	Unknown	Blinded: with no specified description	Blinded: with no specified description	No loss to follow-up	Unknown	None
Untch *et al.*, 2019 (33)	Randomized	Unknown	Unblinded	Blinded	Unknown	Unknown	None

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Newcastle-Ottawa scale (NOS) of the Cohort study included in the meta-analysis

Author	Selection of the study population				Comparability between groups	Outcome measurement			Score
	Representativeness of the exposure group	Selection method of the non-exposure group	Determination of exposure factors	Indication of no initial outcome		With/without sufficient evaluation of the results	Sufficient follow-up time	Adequate follow-up	
Mahtani *et al.*, 2018 (29)	Good	Not described	File record	Yes	Comparable	File	With	Not described	7
Xie *et al.*, 2019 (32)	Good	The same population	File record	Yes	Comparable	Phone	Without	20% lost to follow-up	7
Luhn *et al.*, 2019 (34)	Good	The same population	File record	Yes	Comparable	File	With	Completed	9
Bachelot *et al.*, 2019 (35)	Good	The same population	File record	Yes	Comparable	Not described	With	Completed	8
Yang *et al.*, 2019 (36)	Good	The same population	File record	Unknown	Comparable	File	Without	Not described	6
Han and Wang, 2020 (37)	Good	The same population	File record	Unknown	Comparable	Not described	Not described	Not described	5

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Appendix 3

Extracted efficacy indicators from the included literature

Author	PFS (HR: 95% CI)	OS (HR: 95% CI)	ORR (event.e, n.e/event.c, n.c)	pCR (event.e, n.e/event.c, n.c)
Gradishar, 2005	0.78 (0.67–0.91)	0.77 (0.62–0.95)	76, 229/42, 225	/
Davidson, 2008	/	/	60, 176/32, 175	/
Guan, 2009	0.74 (0.506–1.081)	0.95 (0.6–1.51)	56, 104/31, 106	/
Zhang, 2012	/	/	/	9, 26/6, 26
*Gradishar arm 1, 2009 + 2012	/	0.86 (0.53–1.39)	28, 76/26, 74,	/
*Gradishar arm 2, 2009 + 2012			36, 74/26/74	
*Gradishar arm 3, 2009 + 2012			34, 76/26, 74	
Rugo, 2015	1.2 (1–1.45)	1.17 (0.92–1.47)	91, 267/104, 275	/
Huang, 2015	/	/	27, 30/72, 90	9, 30/30, 90
Tamura, 2017	1.25 (0.91–1.72)	0.78 (0.54–1.14)	/	/
Cortes, 2018	/	0.77 (0.62–0.95)	/	/
Gianni, 2018	/	/	234, 337/223, 335	78, 346/65, 349
Kuwayama, 2018	/	/	/	13, 75/9, 77
+Ciruelos arm 1, 2019	/	/	6, 16/3, 14	/
+Ciruelos arm 2, 2019			6, 14/3, 14	
+Ciruelos arm 2, 2019			2, 16/3, 14	
Xie, 2019	/	/	/	35, 83/19, 79
Untch, 2016 + 2019	/	/	/	233, 605/174, 601
Luhn, 2019	/	0.98 (0.67–1.44)	/	/
#Bachelot arm 1, 2019	1.26 (0.95–1.69)	/	41, 53/400, 483	/
#Bachelot arm 2, 2019			41, 53/517, 657	
Yang, 2019	/	/	/	8, 25/1, 25
Han, 2020	/	/	36, 61/7, 34	/

*: doc test group, arm 1: 300 mg/m^2, arm 2: 150 mg/m^2, arm 3: 100 mg/m^2, +: sb-pc test group, arm 1: 100 mg/m^2 QW, arm 2: 150 mg/m^2 QW, arm 3: 150 mg/m^2 Q2W, #: arm1: doc control group, arm 2: sb-pc control group, event.e: Sample size of the endpoint event in the experimental group. n.e: Sample size of the test group; event.c: Sample size of the endpoint event in the control group n.c: Sample size of the control group.

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Extracted safety indicators from the included literature

Author	Allergic reactions		Leukopenia		Neutropenia			Neurotoxicity
	Overall (event.e, n.e/ event.c, n.c)	grade ≥ 3 (event.e, n.e/ event.c, n.c)	Overall (event.e, n.e/ event.c, n.c)	grade ≥ 3 (event.e, n.e/ event.c, n.c)	Overall (event.e, n.e/ event.c, n.c)	grade ≥ 3 (event.e, n.e/ event.c, n.c)	grade ≥ 4 (event.e, n.e/ event.c, n.c)	Overall (event.e, n.e/event.c, n.c)
Gradishar, 2005	2, 229/5, 225	0, 229/5, 225	/	/		30, 226/45, 222	20, 226/48, 222	/
Guan, 2009	/	/	67, 104/62, 106	25, 10/24, 106	72, 104/67, 106	43, 104/42, 106	6, 104/7, 106	79, 104/78, 106
Pippen, 2011	/	/	1, 98/13, 99	/		/	/	/
Zhang, 2012	/	/	/	/	0, 26/4, 26	/	/	/
*Gradishar arm 1, 2009 + 2012	/	/	/	/	75, 76/72, 74,	33, 76/68, 74	5.76/54, 74,	56, 76/45, 74
*Gradishar arm 2, 2009 + 2012					74, 74/72, 74,	33, 74/68, 74	7.74/54, 74,	50, 74/45, 74
*Gradishar arm 3, 2009 + 2012					76, 76/72, 74,	19, 76/68, 74	4.76/54, 74,	44, 76/45, 74
Rugo, 2015	/	/	48, 263/21, 272	/	134, 263/50, 272	/	/	70, 263/48, 272
Huang, 2015	/	/	29, 30/88, 90	23, 30/35, 90	30, 30/88, 90	30, 30/52, 90	17, 30/19, 90	13, 30/31, 90
Tamura, 2017	/	/	96, 100/99, 100	58, 100/90, 100	97, 100/99, 100	78, 100/98, 100	35, 100/89, 100	88, 100/69, 100
Gianni, 2018	6, 337/20, 335	1, 337/2, 335	75, 337/69, 335	28, 337/24, 335	141, 337/122, 335	103, 337/66, 335	/	212, 337/180, 335
Mahtan, 2018	/	/	/	/	57, 334/79, 591	/	/	9, 334/49, 591
Kuwayama, 2018	0, 74/1, 77	0, 74/0, 77	/	60, 74/59, 77	62, 74/51, 77	21, 74/31, 77	/	49, 74/42, 77
+Ciruelos arm 1, 2019	/	/	8, 16/8, 14	1, 16/0, 14	6, 16/2, 14	0, 16/0, 14	/	13, 16/7, 14
+Ciruelos arm 2, 2019			7, 14/8, 14	4, 14/0, 14	9, 14/2, 14	7, 14/0, 14		11, 14/7, 14
+Ciruelos arm 3, 2019			4, 16/8, 14	1, 16/0, 14	3, 16/2, 14	0, 16/0, 14		10, 16/7, 14
Xie, 2019	/	/	0, 16/1, 14	/	/	/	/	53, 67/28, 63
Untch, 2016 + 2019	101, 605/125, 601	3, 605/5, 601	567, 605/550, 601	280, 606/271, 600	531, 605/487, 601	368, 605/371, 601	229, 605/218, 601	514, 605/392, 601
#Bachelot arm 1, 2019	/	/	/	/	5, 65/87, 589,	/	/	17, 65/180, 589
#Bachelot arm 2, 2019					5, 65/155, 755			17, 65/127, 775
Yang, 2019	/	/	/	/	6, 25/15, 25	/	/	/
Han, 2020	/	/	/	22, 61/26, 34	/	/	/	/

*: doc test group, arm 1: 300 mg/m^2, arm 2: 150 mg/m^2, arm 3: 100 mg/m^2; +: sb-pc test group, arm 1: 100 mg/m^2 QW, arm 2: 150 mg/m^2 QW, arm 3: 150 mg/m^2 Q2W; #: arm 1: doc control group, arm 2: sb-pc control group; event.e: Sample size of the endpoint event in the experimental group; n.e: Sample size of the test group; event.c: Sample size of the endpoint event in the control group; n.c: Sample size of the control group.

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Appendix 4

Meta-regression analysis of ORR

Controlling factor	I^2 (%)	P
Region of study	60.39	Asian 0.210 Europe 0.055 Complex 0.075
Dosage	42.31	0.003
Number of doses	19.24	Q3W 0.068 QW 0.256 Q2W
Control group	69.59	sb-pc 0.3528
Research design	68.73	RCT 0.974
Tumor type	69.22	0.441

ORR, objective response rate.

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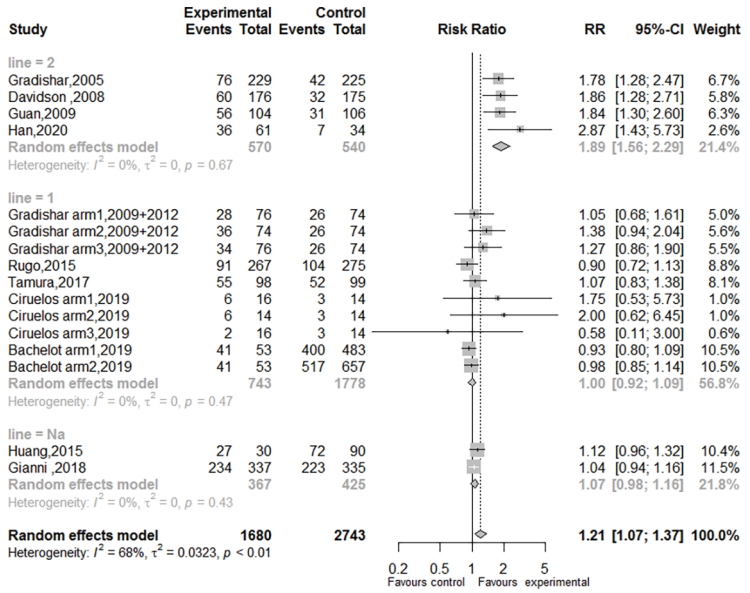
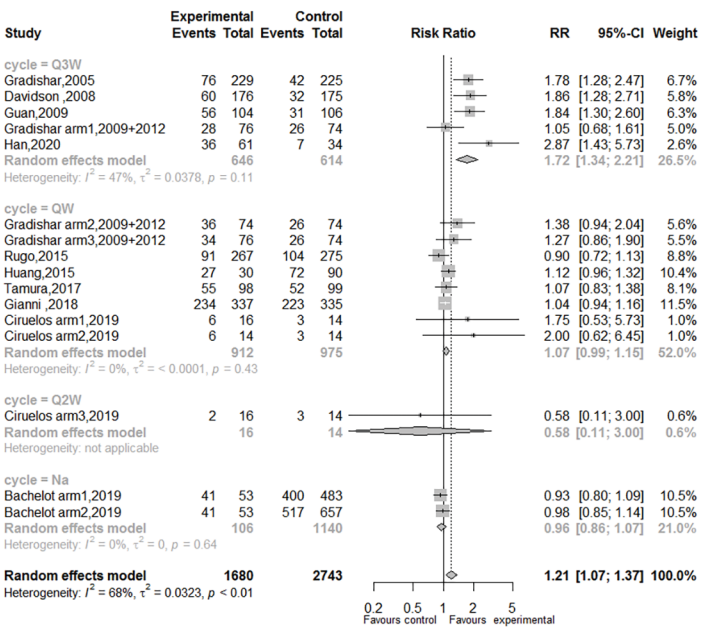
Appendix 5

Subgroup analysis of objective response rate by treatment lines.



Subgroup analysis of objective response rate by treatment frequency.



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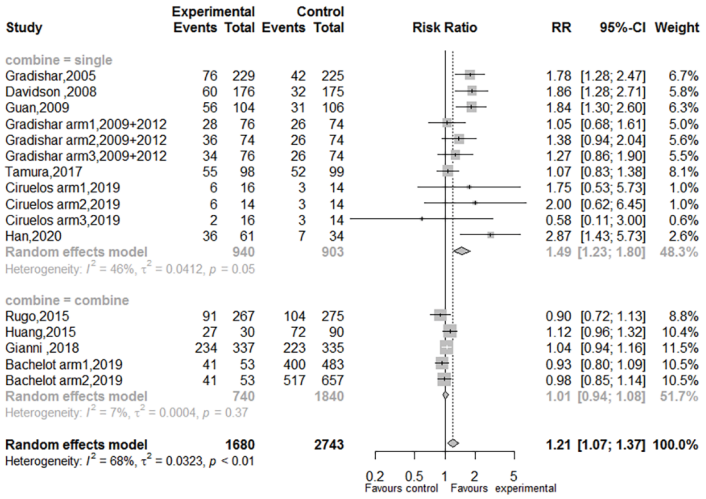
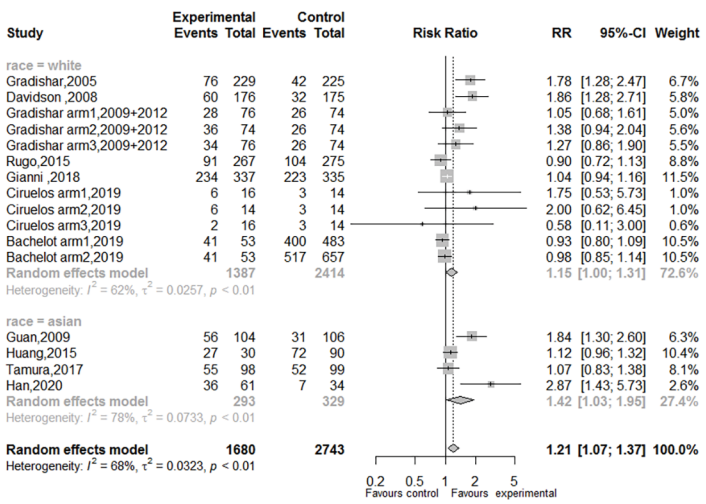
Subgroup analysis of objective response rate by treatment mode.



Subgroup analysis of objective response rate by ethical groups.



Appendix 6

Meta-regression analysis of PFS

Controlling factor	I^2 (%)	P
Region of study	79.88	Europe 0.668
Dosage	77.24	0.589
Number of doses	69.96	Q3W 0.068 QW 0.256
Control	80.13	Sb-pc 0.615
Research design	75.51	RCT 0.119

PFS, progress free survival.

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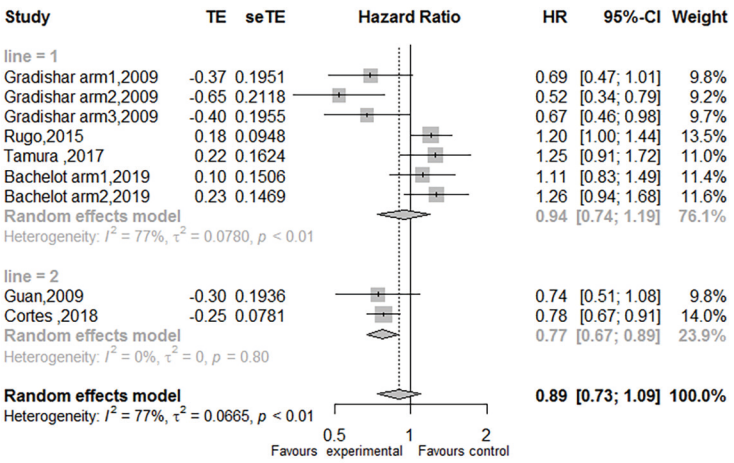
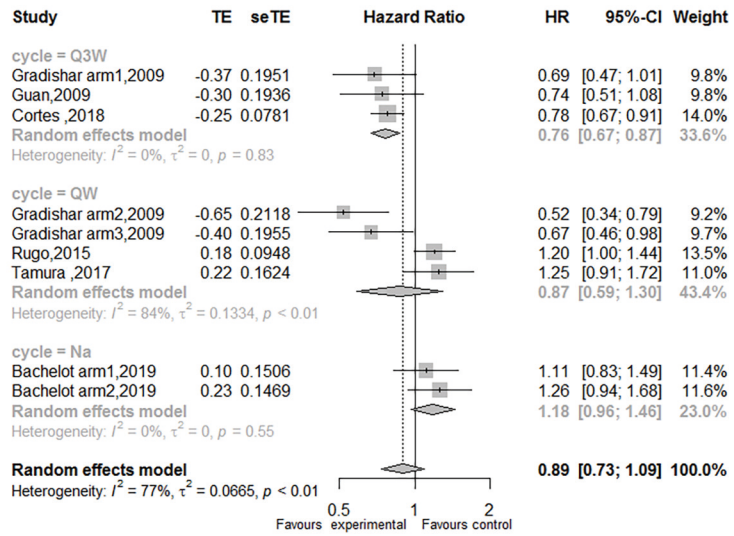
Appendix 7

Subgroup analysis of progress free survival. by treatment lines.

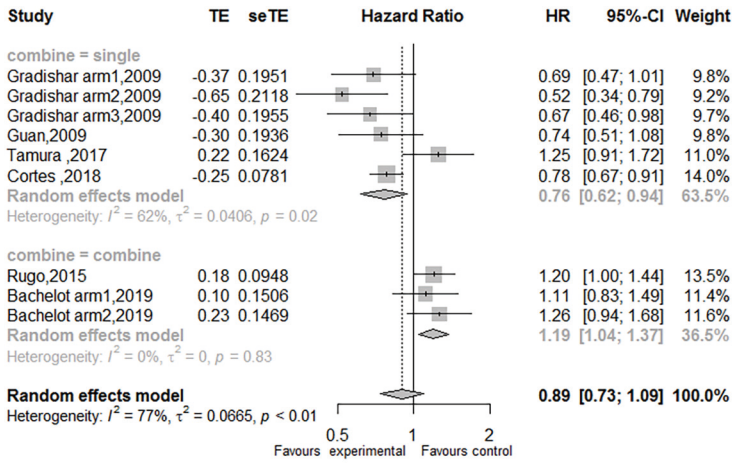


Subgroup analysis of progress free survival by treatment frequency.

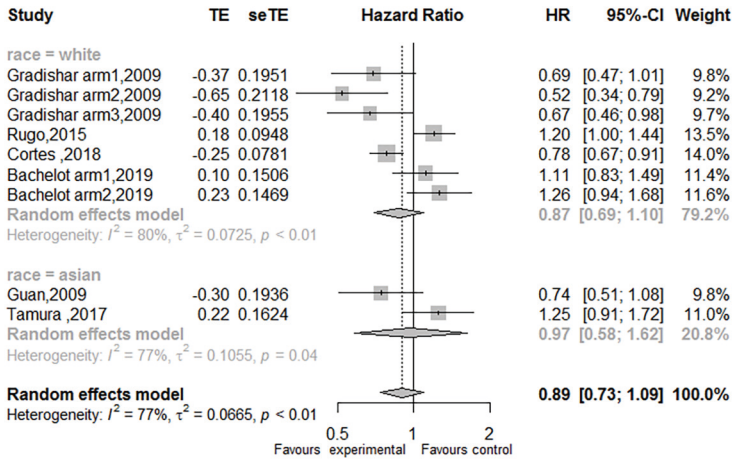


https://dx.doi.org/10.21037/apm-22-690

Subgroup analysis of progress free survival by treatment mode.



Subgroup analysis of progress free survival by race.



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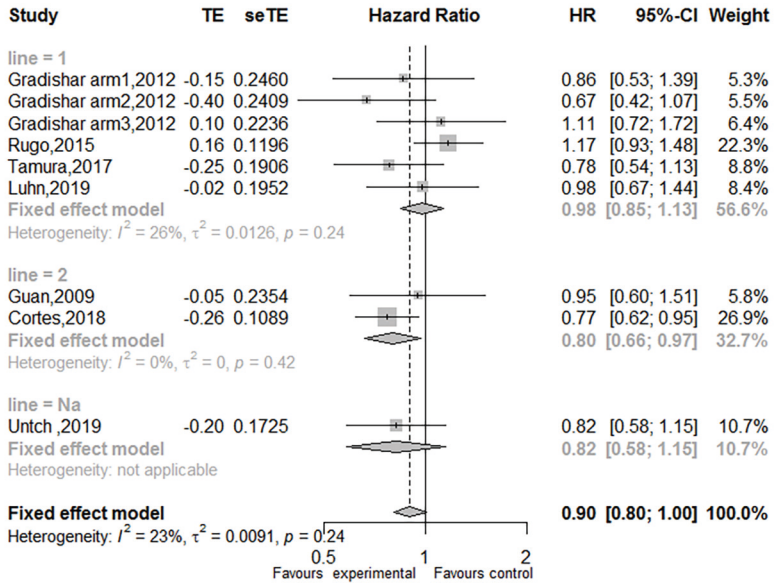
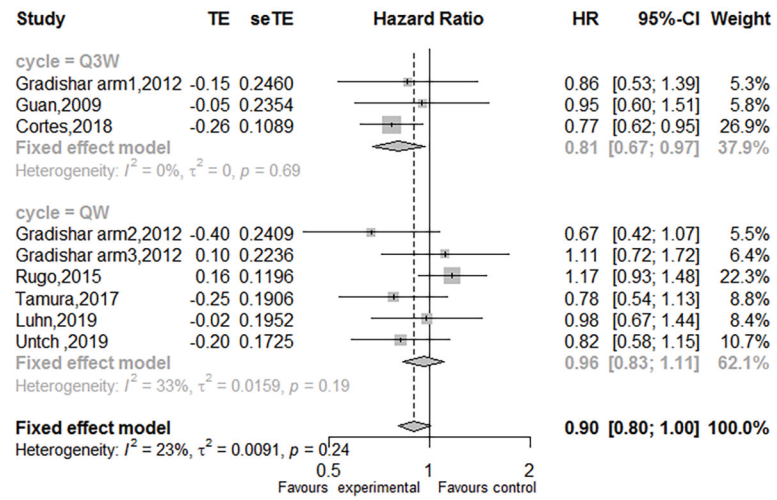
Appendix 8

Subgroup analysis of overall survival by treatment lines.

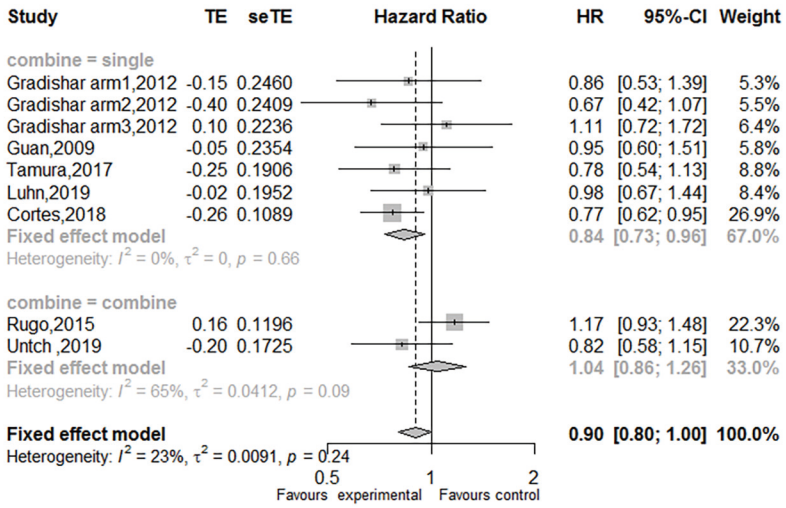


Subgroup analysis of overall survival by treatment frequency.

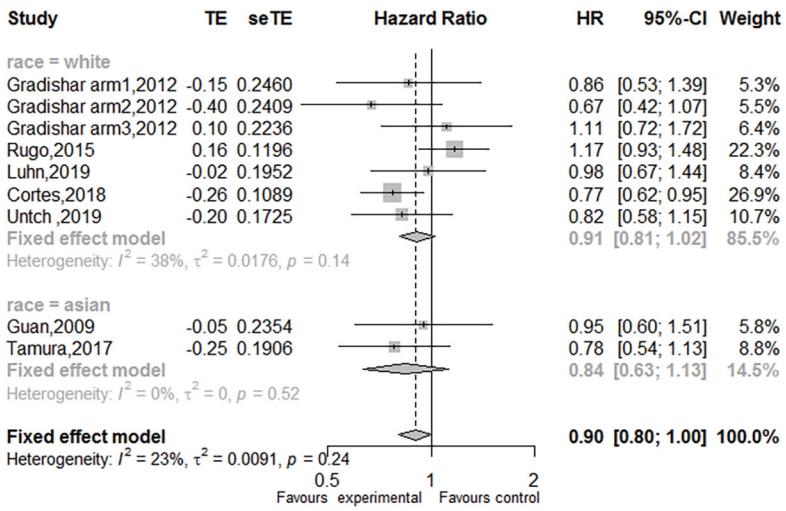


https://dx.doi.org/10.21037/apm-22-690

Subgroup analysis of overall survival by treatment mode.

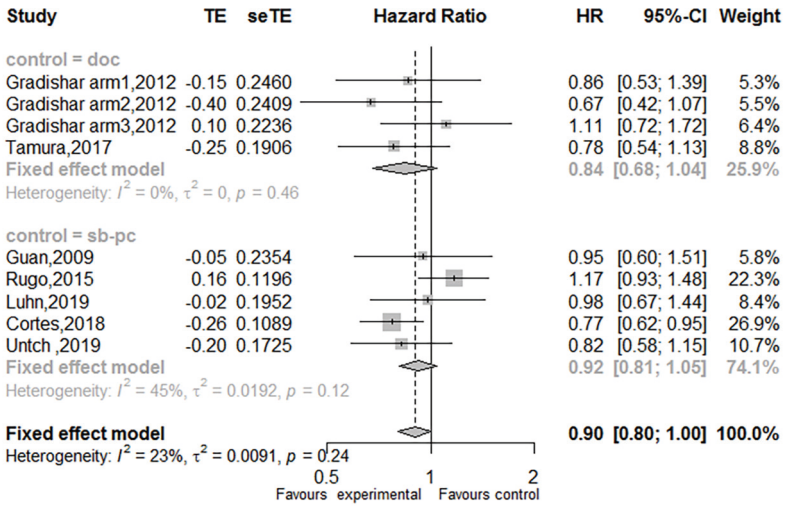


Subgroup analysis of overall survival by race.

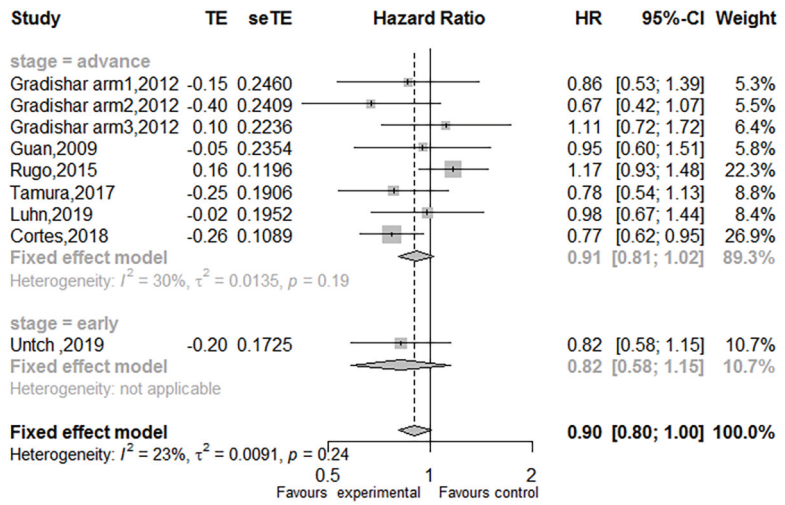


https://dx.doi.org/10.21037/apm-22-690

Subgroup analysis of overall survival by different control groups.

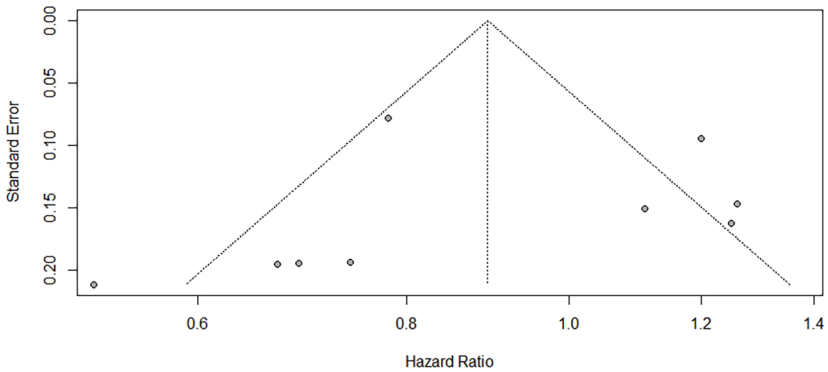


Subgroup analysis of overall survival by different control groups.



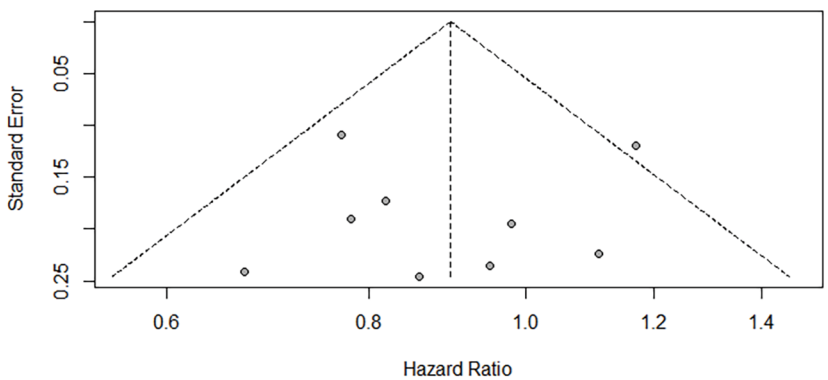
https://dx.doi.org/10.21037/apm-22-690

Appendix 9



Funnel plots of progress free survival of patients with breast cancer receiving Nab-P and solvent paclitaxel/docetaxel treatments.

Egger's test for PFS: P=0.581



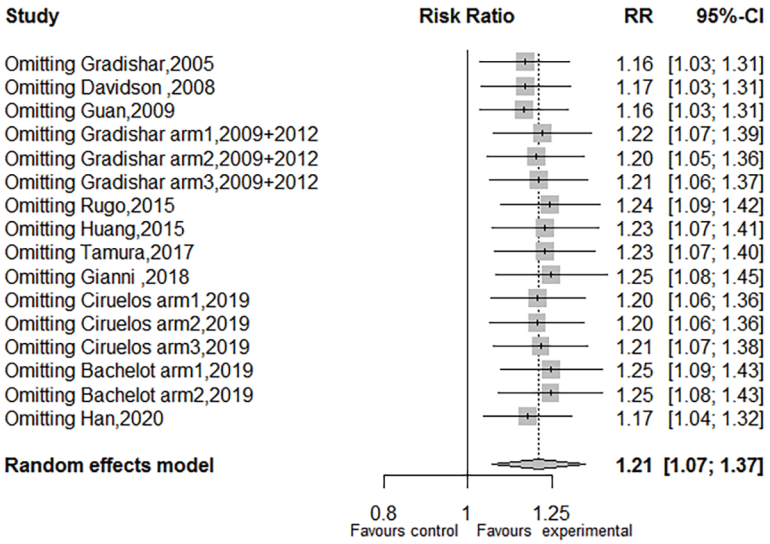
Funnel plots of OS of patients with breast cancer receiving Nab-P and solvent paclitaxel/docetaxel treatments.

Egger's test for PFS: P=0.782

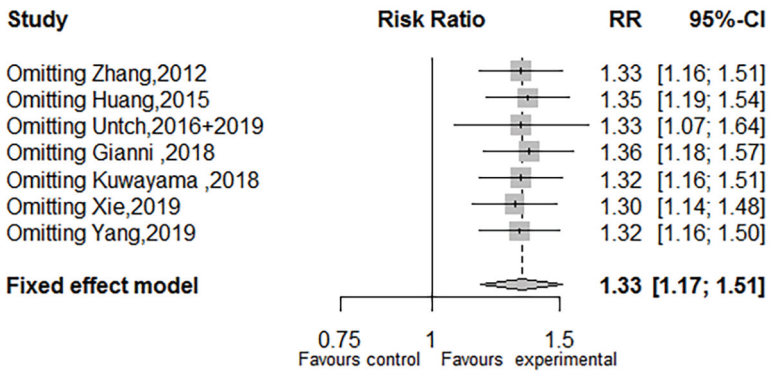
https://dx.doi.org/10.21037/apm-22-690

Appendix 10

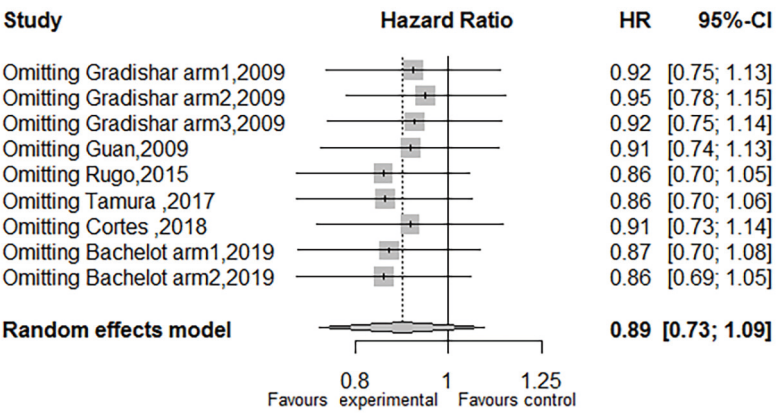
Sensitivity analysis of objective response rate



Sensitivity analysis of pathological complete response

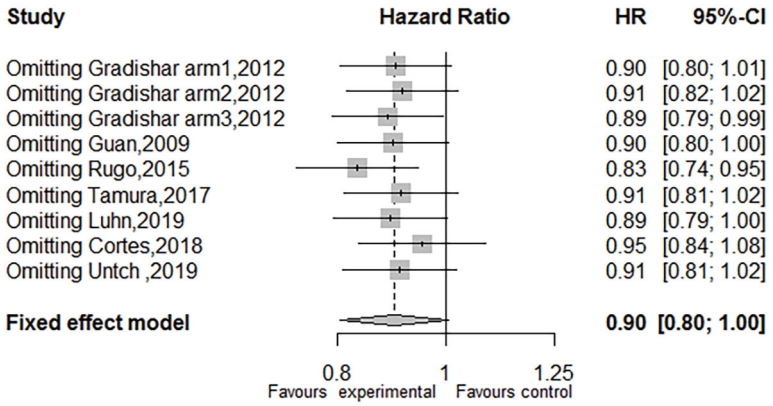


Sensitivity analysis of progress free survival



https://dx.doi.org/10.21037/apm-22-690

Sensitivity analysis of overall survival.



https://dx.doi.org/10.21037/apm-22-690