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Meta-analysis

Meta-analysis of Clinical Efficacy and Safety of Pertuzumab and Trastuzumab Combined Therapy in HER-2 Positive Breast Cancer

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Abstract

Objective: To systematically evaluate the clinical efficacy and safety of pertuzumab and trastuzumab combined therapy in human epidermal growth factor receptor 2 (HER-2) positive breast cancer through a meta-analysis.

Methods: English databases including PubMed, Embase, and the Cochrane Central Register of Controlled Trials, as well as Chinese databases including China National Knowledge Infrastructure, Wanfang Database, and the Chinese Biomedical Literature Service System (Sinomed), were searched for randomized controlled trials (RCTs) comparing pertuzumab and trastuzumab combined therapy (experimental group) with trastuzumab alone (control group) for the treatment of HER-2 positive breast cancer. The literature search time was from the establishment of the database to July 2022. Two reviewers independently screened the literature, extracted data, and assessed the quality of the literature. Meta-analysis was performed using Review Manager 5.4 software.

Results: A total of 9 RCTs involving 7199 patients were included in the meta-analysis. The results of the effectiveness indicators showed that the risk of tumor progression in HER-2 positive breast cancer patients receiving dual-targeted therapy was significantly lower than that in patients receiving trastuzumab alone [Hazard ratios (HR) = 0.68, 95% confidence intervals (CI) (0.58, 0.79), $P<0.00001$]; the overall survival (OS) of HER-2 positive breast cancer patients receiving dual-targeted therapy was significantly longer than that of patients receiving trastuzumab alone [HR=0.73, 95% CI (0.59, 0.88), $P<0.0009$]. In terms of safety, there was no statistical difference in the incidence of severe adverse events and ≥3 grade neutropenia between the experimental and control groups ($P>0.05$), but the incidence of ≥3 grade diarrhea in the experimental group was significantly higher than that in the control group [relative risks = 2.44, 95% CI (1.95, 2.99), $P<0.00001$].

Conclusion: The combined therapy of pertuzumab and trastuzumab has significant clinical efficacy in HER-2 positive breast cancer patients, and its application can further improve patients' progression-free survival and OS. However, it also increases the risk of adverse reactions to a certain extent.

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Therefore, in clinical practice, it is necessary to strengthen the monitoring and protection of relevant adverse reactions in patients.

Keywords: pertuzumab, trastuzumab, HER-2 positive breast cancer, clinical efficacy, safety, meta-analysis

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1 INTRODUCTION

Breast cancer is a common malignant tumor in clinical practice. In recent years, the incidence of this disease has been increasing and gradually becoming younger[1]. According to related research[2], breast cancer accounts for about 25.1% of all cancers in women worldwide, and approximately 14.7% of patients with breast cancer die. Another study[3] pointed out that 24.4% to 31.8% of breast cancer patients have human epidermal growth factor receptor 2 (HER-2) gene amplification or overexpression, which can make breast cancer cells more aggressive, and thus HER-2-positive patients have a worse prognosis than HER-2-negative patients. Trastuzumab is a molecular targeted drug targeting HER-2[4]. It can downregulate HER-2 expression and accelerate the degradation and absorption of HER-2 receptor protein, achieving the effect of inhibiting tumor angiogenesis. Currently, trastuzumab has been clinically applied to the treatment of various malignant tumors including breast cancer. Some studies[5] have confirmed that the use of trastuzumab can significantly improve the survival rate of HER-2-positive breast cancer patients. However, other studies[6] have shown that as the patient's condition progresses and metastasizes, trastuzumab's ability to control the disease is limited, and some studies[7] have found that trastuzumab has certain cardiotoxicity and drug resistance. With the advancement of technology, a new generation of anti-HER-2 targeted therapy drugs - pertuzumab, was launched in the United States in June 2012, and its therapeutic effect in advanced breast cancer patients was significant[8]. Pertuzumab was launched in China in December 2018. However, because the drug had a high early selling price and was not covered by medical insurance, its clinical use was relatively low until January 2020, when China officially included it in the medical insurance drug list and significantly reduced its price, which finally led to its widespread use. This move also truly promoted the standardization of HER-2-positive breast cancer treatment in China. Studies by scholars such as Wuerstlein[9] have shown that compared with trastuzumab + chemotherapy, the dual anti-HER2 treatment regimen of pertuzumab + trastuzumab + chemotherapy can further increase the overall pathological complete remission rate of patients. The ASCO guidelines[10] also recommend adding adjuvant pertuzumab treatment to the trastuzumab-based combination chemotherapy for high-risk, early HER-2-positive breast cancer patients. However, because research on the combination use of pertuzumab is still relatively rare, the safety of pertuzumab combination therapy in clinical practice is in question. Therefore, this study uses a systematic review and meta-analysis method to compare the efficacy and safety of pertuzumab combined with trastuzumab and trastuzumab monotherapy in the treatment of HER-2-positive breast cancer, aiming to provide corresponding scientific evidence for clinical drug selection.

2 DATA AND METHODS

2.1 Inclusion and Exclusion Criteria for Literature

The included literature must meet the following criteria: (1) randomized controlled trials (RCTs) that compare the combined use of pertuzumab and trastuzumab for the treatment of HER-2 positive breast cancer with trastuzumab monotherapy; (2) the patients included in the literature are all adults; (3) the Eastern Cooperative Oncology Group performance status of the patients in the included literature is 0 or 1; (4) the left ventricular ejection fraction of the patients in the included literature is ≥50%; (5) the intervention measures are as follows: pertuzumab and trastuzumab dual targeting combined use compared with trastuzumab monotherapy, without limiting the dose and course of the drug; (6) the outcome indicators include clinical efficacy indicators [progression-free survival (PFS), overall survival (OS)] and safety indicators [serious adverse events (SAE), ≥Grade 3 adverse reactions, ≥Grade 3 adverse reactions mainly include neutropenia, diarrhea].

The following literature will be excluded: (1) literature such as reviews, cohort studies, animal experiments, case studies, basic research, cross-sectional studies, case reports, etc.; (2) literature with outcome indicators that do not meet the inclusion criteria; (3) literature that cannot obtain the full text; (3) literature with data that cannot be extracted, incomplete original data provided, and data that cannot be obtained through inquiry; (4)

literature with a sample size of <15; (5) literature with only abstracts and no full text, duplicate publications, or incomplete data.

2.2 Literature Search Strategy

Firstly, we formulated a search strategy based on the "PICOS principle" in the Cochrane Handbook for Systematic Reviews. The literature databases searched mainly included Chinese and English databases. The English databases searched were PubMed, Embase, and the Cochrane Central Register of Controlled Trials. The Chinese databases searched were China National Knowledge Infrastructure, Wanfang Database, and China Biomedical Literature Service System (Sinomed). The search period was limited from the establishment of the databases to July 2022.

Different keywords were used for the Chinese and English databases. Free words and subject terms were used to search the English databases with keywords such as "Breast Cancer", "Breast Neoplasm(s)", "Breast Tumor(s)", "Mammary Neoplasm(s)", "Mammary Cancer(s)", "Trastuzumab", "Herceptin", "Pertuzumab", and "Perjeta". The search strategy was determined after multiple preliminary searches. The Chinese databases were searched using keywords such as "HER-2 阳性乳腺癌 "、" 乳腺癌 "、" 帕妥珠单抗 "、" 曲妥珠单抗 "、" 帕妥珠单抗联合曲妥珠单抗 "、" 帕妥珠单抗安全性 "、" 曲妥珠单抗安全性 " and " 随机对照试验 ".

2.3 Quality Evaluation and Data Extraction

According to the inclusion criteria for literature, two trained researchers independently screened the literature. The initial screening was mainly based on the title and abstract, and the literature that met the inclusion criteria was searched and read in full text. If necessary, the original authors were contacted to avoid missing data. If the evaluation results of the literature were inconsistent, a third party was invited to participate in the discussion and resolve the issue. The methodological quality of the included studies was evaluated using the Cochrane Collaboration's risk of bias assessment tool for RCTs, including six aspects: randomization method, allocation concealment, blinding, completeness of outcome data, selective reporting of study results, and other sources of bias. The methodological quality evaluation results were divided into three risk levels: low risk of bias, high risk of bias, and unclear, and each risk level corresponded to specific items in the Cochrane risk of bias assessment criteria. The Cochrane score was independently completed by two evaluators, and a third party was invited to discuss and decide if the results were inconsistent. The data extraction items included patient baseline information, the groups allocated by randomization and the number of cases in each group, age, intervention measures, outcome indicators (mainly clinical efficacy indicators such as PFS and OS, and safety indicators such as SAE and ≥Grade 3 adverse reactions).

2.4 Statistical Analysis

Meta-analysis was conducted using RevMan 5.4 software. Hazard ratios (HR) were used as the effect measure for survival data, while relative risks (RR) were used for dichotomous outcome data. Point estimates and 95% confidence intervals (CI) were calculated for each effect size, and the $I2$ statistic was used to assess heterogeneity among the included studies. When there was statistical homogeneity among the studies (P>0.1, I^2<50%), a fixed-effect model was used for the meta-analysis. When statistical heterogeneity was present (P<0.1, I^2>50%), the sources of heterogeneity were investigated. If there was clinical and methodological heterogeneity but no statistical heterogeneity between two study groups, a random-effects model was used for the meta-analysis. If there was significant clinical heterogeneity, subgroup analysis or sensitivity analysis was used. Descriptive analysis was used to explain any differences that could not be explained by heterogeneity. The significance level for meta-analysis was set at α=0.05.

3 RESULTS

3.1 Literature Search Process and Results

A total of 657 articles were obtained from the database search. Firstly, 96 duplicate articles were removed using NoteExpress. Secondly, 479 articles were excluded based on their titles, abstracts, and full texts, which were reviews, case reports, animal experiments, or meta-analyses. Finally, 82 articles were screened by reading the full text based on inclusion and exclusion criteria, and 9 articles were included in the meta-analysis. A total of 7,199 patients were included, with 3,590 in the experimental group and 3,609 in the control group (Figure 1).

3.2 General Characteristics of the Included Studies

General Characteristics of the Included Studies (Table 1).

3.3 Methodological Quality Assessment of the Included Studies

The methodological quality of the nine included studies was evaluated using the methods provided by RevMan 5.4 software. All studies indicated that randomization was used for grouping, and four studies used double-blinding. There were no clinical trial dropouts, and two studies reported complete outcome data. The baseline levels of the included literature were comparable. Based on the evaluation of the risk of bias in the literature, the overall quality of the literature was generally fair. The risk of bias in the included studies is

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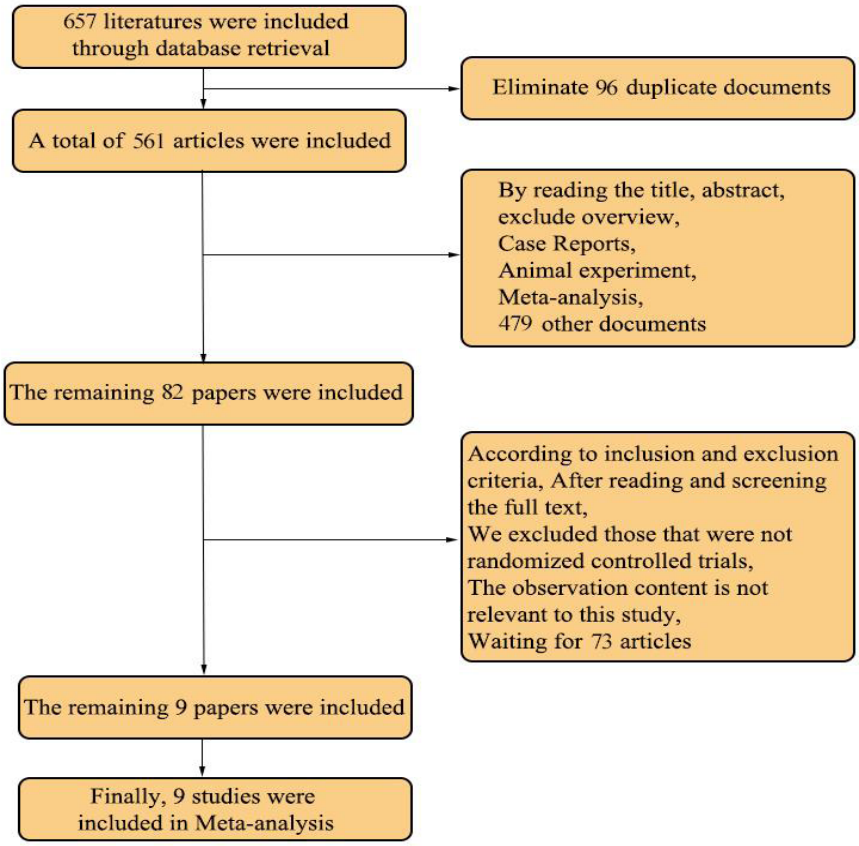

Figure 1. Flow chart of literature search.

Table 1. General Characteristics of the Included Studies

Author	Year of Publication	Sample Size	Age	Intervention Program		Outcome Measures
		Test/Control	Test/Control	Test	Control	
Xu et al.[11]	2020	122/121	51(26-74)/ 53 (25-71)	Pertuzumab 840mg, iv, then 420mg, q3w + trastuzumab 8mg/kg, iv, then 6mg/kg, q3w + docetaxel 75mg/m^2, q3w	Placebo + trastuzumab 6mg/kg, iv, q3w + docetaxel 75mg/m^2, q3w	PFS, OS, SEA, ≥Grade 3 adverse reactions
Arpino et al.[12]	2017	129/129	60.9±10.85/ 62.3±11.54	Pertuzumab 840mg, iv, followed by 420mg, q3w + trastuzumab 8mg/kg, iv, followed by 6mg/kg, q3w + anastrozole 1mg, qd or letrozole 2.5mg, qd + docetaxel	Trastuzumab 8mg/kg, iv, followed by 6mg/kg, q3w + anastrozole 1mg, qd or letrozole 2.5mg, qd + docetaxel	PFS, OS, SAE, ≥Grade 3 adverse reactions
Gianni et al.[13]	2016	107/107	49.6±10.05/ 50.9±8.94	Pertuzumab 840mg, iv, followed by 420mg, q3w + trastuzumab 8mg/kg, iv followed by 6mg/kg, q3w + docetaxel	Trastuzumab 8mg/kg, iv, then 6mg/kg, q3w + docetaxel	PFS, SAE, ≥Grade 3 adverse reactions
Huang et al.[14]	2022	38/38	56.50±5.74/ 56.02±5.76	EC regimen for 4 cycles, q3w continuous THP	EC regimen for 4 cycles, q3w continuous TH	SAE
Minckwitz et al.[15]	2017	2400/2404	51.7±10.9/ 51.4±10.7	Pertuzumab 840mg, iv, followed by 420mg, q3w + trastuzumab 8mg/kg, iv followed by 6mg/kg, q3w + chemotherapy	Placebo + trastuzumab 8mg/kg, iv, followed by 6mg/kg, q3w + chemotherapy	SAE, ≥Grade 3 adverse reactions

Swain et al.[16]	2020	402/406	53.4±10.94/ 53.5±11.35	Pertuzumab 420mg, iv, q3w + trastuzumab 6mg/kg, iv, q3w + docetaxel	Placebo + trastuzumab 6mg/kg, iv, q3w + docetaxel	PFS, SAE, ≥Grade 3 adverse reactions
Lin et al.[17]	2022	35/51	76±4/75±4	Pertuzumab 840mg, iv, then 420mg, q3w + vinorelbine tartrate 25-30mg/m^2, iv, day 1, 8, 15 + trastuzumab 8mg/kg, iv, Then 6mg/kg, q3w	Vinorelbine tartrate 25-30mg/m^2, iv, on days 1, 8, 15 + trastuzumab 8mg/kg, iv, then 6mg/kg, q3w	PFS, ≥Grade 3 adverse reactions
Urruticoechea et al.[18]	2017	228/224	53.0±11.21/ 55.1±10.10	Pertuzumab 840mg, iv, followed by 420mg, q3w + trastuzumab 8mg/kg, iv, followed by 6mg/kg, q3w + capecitabine 1000mg/m^2, po, bid, q3w	Trastuzumab 8mg/kg, iv, then 6mg/kg, q3w + capecitabine 1250mg/m^2, po, bid, q3w	PFS, OS, SAE
Rimawi et al.[19]	2018	129/129	59(35-87)/ 61(31-89)	Pertuzumab 840mg, iv, followed by 420mg, q3w + trastuzumab 8mg/kg, iv followed by 6mg/kg, q3w + anastrozole 1mg, qd or letrozole 2.5mg + docetaxel, iv, q3w or paclitaxel, qw	Trastuzumab 8mg/kg, iv, followed by 6mg/kg, q3w + anastrozole 1mg, qd or letrozole 2.5mg + docetaxel, iv, q3w or paclitaxel, qw	PFS, SAE, ≥Grade 3 adverse reactions

shown in Figures 2 and 3.

3.4 Outcome Indicator Meta-analysis

3.4.1 PFS

Seven studies reported PFS, and there was no statistical heterogeneity among the studies (P=0.33, I^2=12%). The experimental group included a total of 1,152 patients, while the control group included 1,167 patients. The fixed-effects model meta-analysis results showed that HER-2-positive breast cancer patients receiving dual-targeted therapy had a significantly lower risk of tumor progression than those receiving trastuzumab alone, with statistical significance [HR=0.68, 95% CI (0.58, 0.79), P<0.00001], as shown in Figure 4.

3.4.2 OS

Three studies reported OS, with no statistically significant heterogeneity among the studies (P=0.13, I^2=49%). The experimental group had a total of 479 cases, while the control group had 474 cases. The meta-analysis results of the fixed-effects model showed that the OS of HER-2 positive breast cancer patients receiving dual-targeted therapy was significantly longer than that of patients receiving only trastuzumab treatment, with statistically significant difference [HR=0.73, 95% CI (0.59, 0.88), P<0.0009], as shown in Figure 5.

3.4.3 SEA

Eight studies reported the incidence of SEA, and there was statistical heterogeneity among the studies (P=0.02, I^2=67%). The experimental group included 3521 patients, and the control group included 3532 patients. The random-effects model meta-analysis showed that there was no significant difference in the incidence of SEA events between the two groups [RR=1.18, 95% CI (0.98, 1.39), P=0.07]. This result suggests that dual-target therapy does not increase the risk of SEA events in patients, as shown in Figure 6.

3.4.4 Grade ≥3 Adverse Events

Neutropenia and diarrhea are common adverse events of trastuzumab and pertuzumab. Seven studies reported the incidence of neutropenia and diarrhea, with a total of 3289 patients in the trial group and 3328 patients in the control group. For neutropenia, there was no significant heterogeneity among the 7 studies (P=0.15, I^2=44%), and the fixed-effects model meta-analysis showed no significant difference in the incidence of neutropenia between HER-2 positive breast cancer patients receiving dual-target therapy and those receiving trastuzumab alone [RR=1.03, 95% CI (0.92, 1.13), P=0.73], as shown in Figure 7A. For diarrhea, there was no significant heterogeneity among the 7 studies (P=0.34, I^2=10%), and the fixed-effects model meta-analysis showed that the incidence of diarrhea was higher in HER-2 positive breast cancer patients receiving dual-target therapy compared to those receiving trastuzumab alone, with a significant difference [RR=2.44, 95% CI (1.95, 2.99), P<0.00001], as shown in Figure 7B.

4 DISCUSSION

Breast cancer ranks second among female malignant

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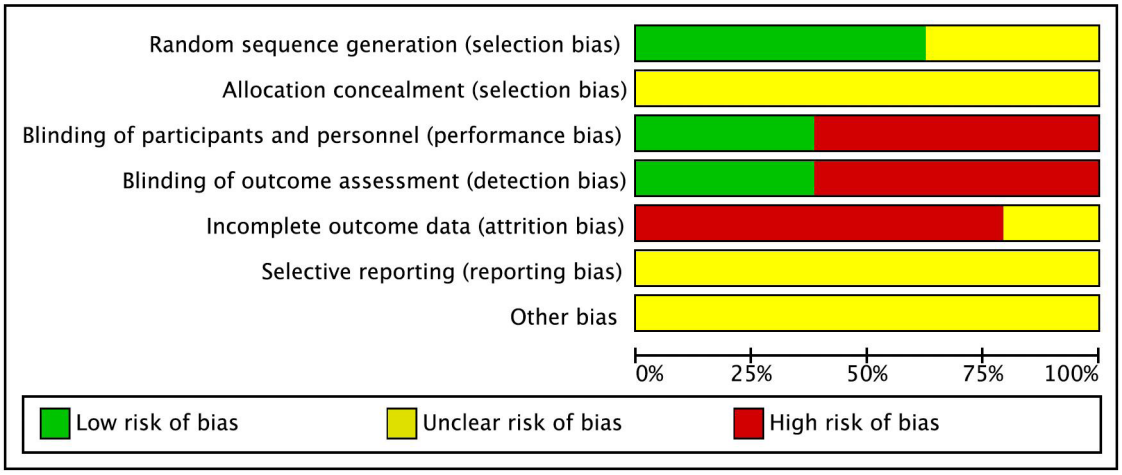

Figure 2. Risk of bias graph for included studies.

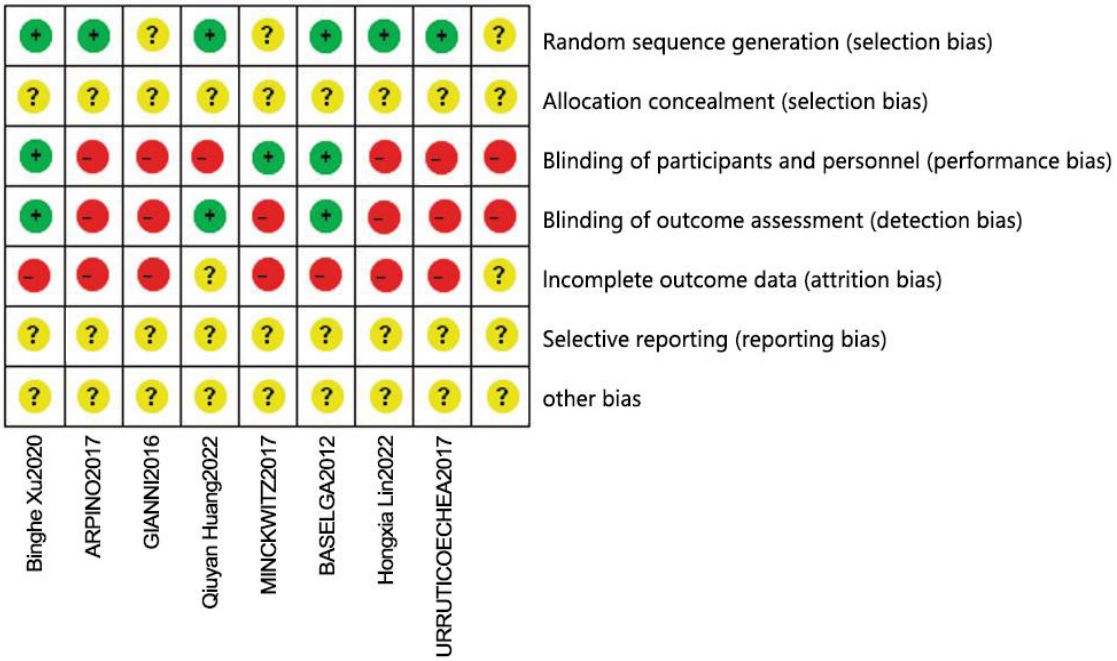

Figure 3. Summary of Bias Risk in Included Studies.

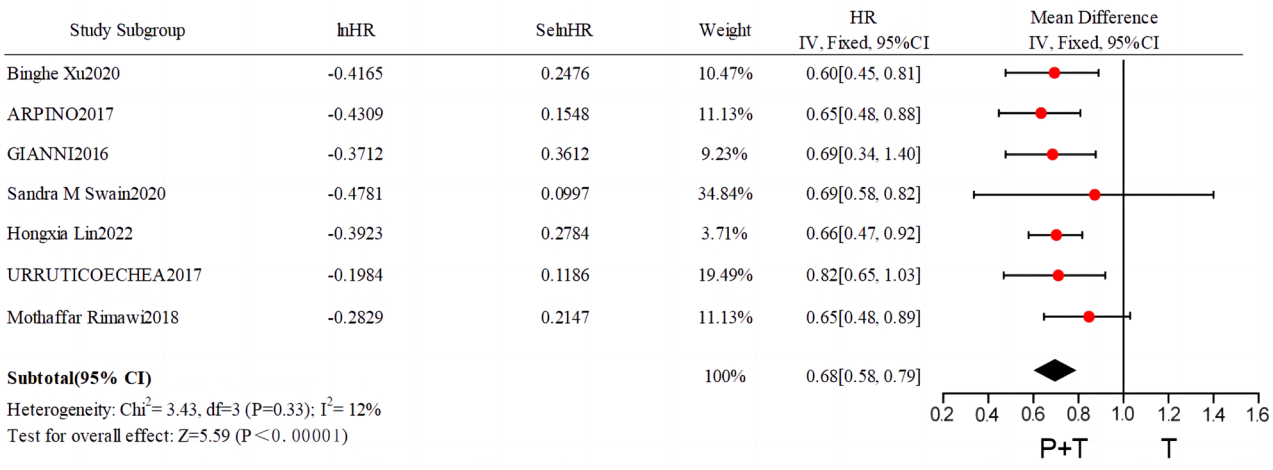

Figure 4. Forest plot of meta-analysis comparing PFS between the two groups.

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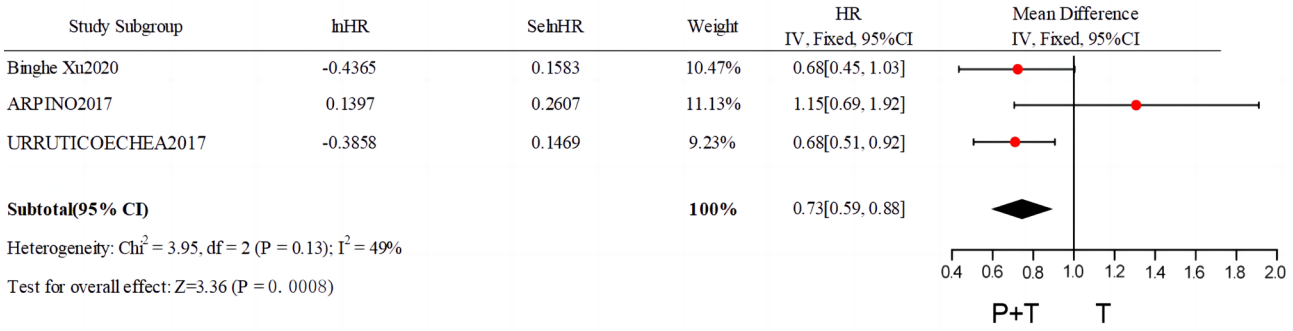

Figure 5. Forest plot of meta-analysis comparing OS between the two groups.

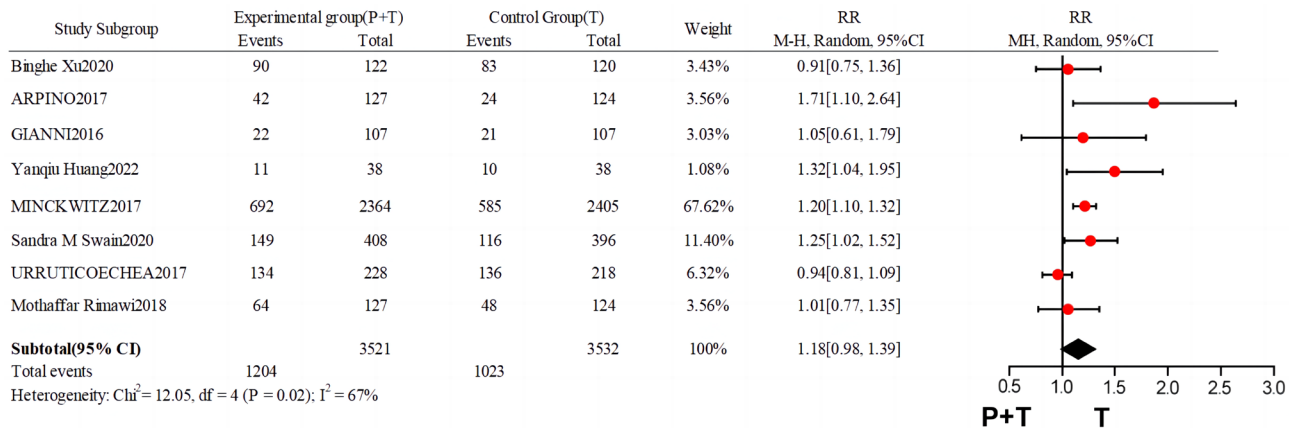

Figure 6. Forest plot of the meta-analysis comparing the incidence of SEA between the two groups.

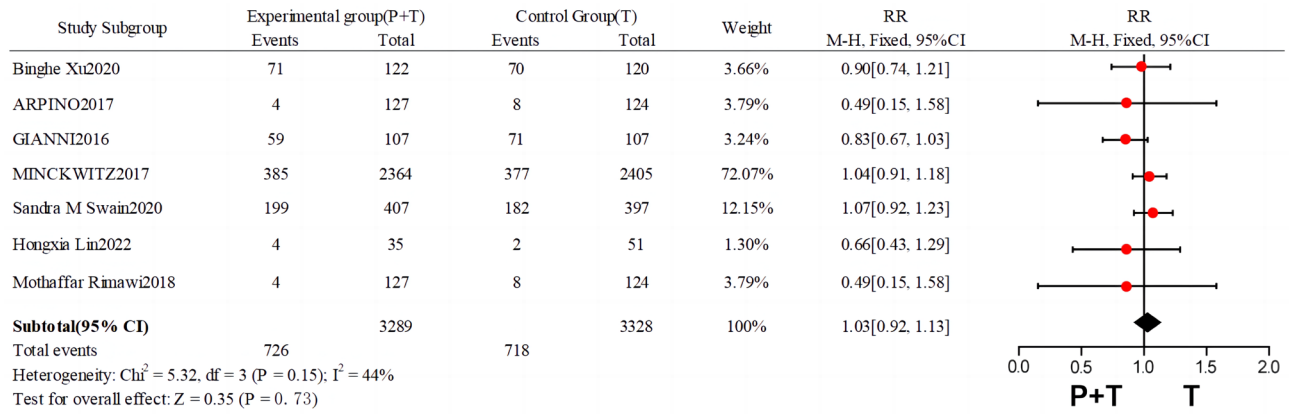

Figure 7A. Forest plot of meta-analysis comparing the incidence of neutropenia between the two groups.

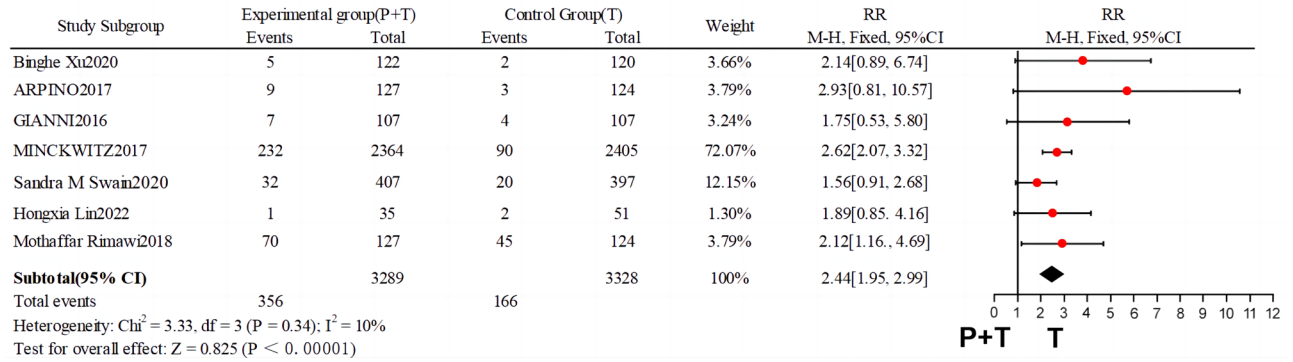

Figure 7B. Forest plot for meta-analysis comparing diarrhea between the two groups.

tumors[20]. With the continuous in-depth research on the disease and the continuous optimization of treatment in recent years, the treatment of breast cancer has gradually developed in the direction of combining various methods such as local treatment and targeted therapy[21]. Currently, surgery is still one of the most effective methods for treating breast cancer, which can effectively prolong the survival of patients. Patients who undergo surgical treatment usually receive additional chemotherapy after surgery, the purpose of which is to further consolidate and enhance the therapeutic effect[22]. Related studies[23] have shown that epidermal growth factor receptor can promote tumor cell proliferation, adhesion, maturation, etc. HER-2 is a common receptor, which can trigger downstream intracellular proliferation pathways and achieve the effect of inhibiting cancer cells by promoting their apoptosis, growth arrest, etc[24]. The overexpression of HER-2 plays a significant role in the pathogenesis of breast cancer. The HER family of receptors consists of four transmembrane tyrosine kinase receptors on the surface of normal cells, including HER-1, HER-3, and HER-4, in addition to HER-2[25]. Unlike other HER receptors, HER-2 does not require specific ligand activation and can undergo ligand-independent dimerization at any time, while the other receptors exist in an inactive state on the plasma membrane and can only be activated when bound to a ligand[26]. HER receptors can activate multiple cell pathways through dimerization, which in turn trigger gene transcription and activate cell proliferation and differentiation pathways to promote cell growth and differentiation[27].

In HER-2-positive breast cancer, HER-2 not only homodimerizes with other HER-2 receptors but also heterodimerizes with other HER-2 receptors[28]. Trastuzumab can only bind to subdomain IV of HER-2 extracellular domain and inhibit ligand-independent signal transduction. However, there is still a possibility of heterodimerization between HER-2 and HER-3, so trastuzumab cannot completely inhibit all tumor growth stimulation signals[29]. Pertuzumab can bind to subdomain II of HER-2 and inhibit heterodimerization between HER-2 and HER-3 through ligand-induced mechanism[30]. In theory, the two have complementary effects, and the combination of the two targeted drugs can provide more effective signal transduction blockade than the use of a single drug. Monoclonal antibodies have become the standard method for cancer drug therapy. Currently, in addition to developing new monoclonal antibodies, international researchers are also actively exploring combinations of monoclonal antibodies. Monoclonal antibodies usually only target a single signaling pathway, and tumors can overcome blockade by translocation, so the blockade effect of monoclonal antibodies is limited[31]. By combining monoclonal antibodies, it is possible to simultaneously block two or more signaling pathways, thereby producing cumulative or synergistic effects on tumor growth. However, not all combined antibodies have the expected synergistic effect. Currently, most clinical studies of monoclonal antibody combination therapy are still in the early stages. It is expected that in the near future, more monoclonal antibody combination therapies will be included in the standard treatment of corresponding tumors.

A meta-analysis study[32] including seven different treatment schemes for HER2-positive breast cancer concluded that the combination of pertuzumab, trastuzumab, and chemotherapy is the most effective method for treating patients. Our study supports this previous conclusion. In terms of PFS, patients receiving dual-targeted therapy for HER2-positive breast cancer had significantly lower tumor progression risks than those receiving only trastuzumab treatment. In terms of OS, patients receiving dual-targeted therapy had significantly longer survival periods than those receiving only trastuzumab treatment. In terms of the risk of SAE, there was no statistically significant difference in the incidence of SAE between patients receiving dual-targeted therapy and those receiving only trastuzumab treatment, indicating that dual-targeted therapy does not increase the risk of SAE. In terms of grade 3 or higher adverse reactions, there was no statistically significant difference in the incidence of neutropenia between patients receiving dual-targeted therapy and those receiving only trastuzumab treatment, but the incidence of diarrhea was higher in patients receiving dual-targeted therapy. The combined effect heterogeneity of the analysis results was low, and the results remained unchanged after changing the model, indicating that this study's results are robust and reliable. A study[33] predicted that the research focus for HER2-positive breast cancer patients in the future will mainly involve reducing toxicity and application costs rather than improving targeted therapy's effectiveness. Scholars like Hurvitz[34] have also confirmed the significant correlation between pertuzumab and various adverse reactions. Therefore, the adverse reactions of patients receiving dual-targeted therapy for HER2-positive breast cancer require clinical attention.

This study still has many shortcomings, such as: (1) this study did not adopt uniform inclusion and exclusion criteria and efficacy judgment standards for each study; (2) although this study conducted extensive searches, potential publication bias risks cannot be completely ruled out; (3) this study was limited by the lack of original data, which prevented the analysis of regional differences, among other factors.

5 CONCLUSION

In summary, the clinical efficacy of the combination

of pertuzumab and trastuzumab in treating HER2-positive breast cancer patients is significant, and the use of this combination can further improve patients' PFS and OS levels. However, it also increases the risk of adverse reactions to a certain extent. Therefore, in clinical practice, monitoring and prevention of related adverse reactions in patients should be strengthened.

Acknowledgements
Not applicable.

Conflicts of Interest
The authors declared no conflict of interest.

Author Contribution
Conceptualization, Zhang X; methodology, Zhang H and Yin Y; writing-original draft preparation, Ren Y, Kang X, Jin L, Bai J, Wang Z; writing-review and editing, Zhang H, Zhang X, Yin Y; supervision, Zhang H, Yin Y. All authors have read and agreed to the published version of the manuscript.

Abbreviation List
CI, Confidence intervals
HER-2, Human epidermal growth factor receptor 2
HR, Hazard ratios
OS, Overall survival
PFS, Progression-free survival
RCTs, Randomized controlled trials
RR, Relative risks
SAE, Serious adverse events

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