



Differences in Efficacy and Safety Between Dual-Targeted Trastuzumab Combined with Pertuzumab and Trastuzumab Mono-Targeted Therapy for HER2-Positive Breast Cancer: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective: To investigate the differences in the efficacy and safety of dual-targeted trastuzumab combined with pertuzumab and trastuzumab monotherapy for HER2-positive breast cancer.

Methods: PubMed, Embase, and the Cochrane Collaboration were searched to identify clinically controlled trials on trastuzumab in combination with pertuzumab for HER2-positive breast cancer. The primary clinical outcome was the 3-year overall survival rate. The secondary clinical outcome was the progression-free survival rate. Safety evaluation outcomes included leukopenia, neutropenia, febrile neutropenia, diarrhea, alopecia, anemia, adverse cardiac events, and fatal adverse events. A meta-analysis was conducted using RevMan version 5.4 statistical software. For data with less heterogeneity, a fixed-effects model was used to compute the effect size. For data with substantial heterogeneity, a random-effects model was used to compute the effect size.

Results: A total of 7 randomized controlled studies involving 7,398 patients with breast cancer were included. The differences in the 3-year overall survival rate (OR: 1.31, 95% CI: 1.08-1.59, $P=0.005$), progression-free survival rate (OR: 1.27, 95% CI: 1.09-1.49, $P=0.003$), incidence of febrile neutropenia (OR: 1.23, 95% CI: 1.05-1.44, $P=0.01$), incidence of diarrhea (OR: 2.44, 95% CI: 2.11-2.83, $P<0.00001$), and incidence of anemia (OR: 1.30, 95% CI: 1.08-1.57, $P=0.006$) were statistically significant in the trastuzumab + pertuzumab group compared with the trastuzumab monotherapy group. The incidence of leukopenia (OR: 0.96, 95% CI: 0.76-1.22, $P=0.75$), neutropenia (OR: 1.08, 95% CI: 0.96-1.22, $P=0.19$), alopecia (OR: 1.03, 95% CI: 0.84-1.27, $P=0.75$), adverse cardiac events (OR: 1.04, 95% CI: 0.77-1.04, $P=0.81$), and fatal adverse events (OR: 0.86, 95% CI: 0.52-1.42, $P=0.55$) were not statistically significant between the two groups. Subgroup analysis showed that in patients with non-metastatic, adequately surgically resected HER2-positive breast cancer, the progression-free survival rate was improved in the trastuzumab + pertuzumab group (OR: 1.27, 95% CI: 1.04-1.55, $P=0.02$), while the overall survival rate was not significantly improved (OR: 1.15, 95% CI: 0.86-1.54, $P=0.35$). In patients with locoregionally recurrent, unresectable, or metastatic HER2-positive breast cancer, the overall survival rate (OR: 1.45, 95% CI: 1.13-1.87,

P=0.004) and incidence of febrile neutropenia (OR: 1.72, 95% CI: 1.14-2.60, P=0.01) were increased in the trastuzumab + pertuzumab group.

Conclusion: Trastuzumab in combination with pertuzumab improves the overall survival rate and progression-free survival rate in patients with HER2-positive breast cancer compared with trastuzumab monotherapy. It may reduce the risk of local recurrence and metastasis in patients with non-metastatic, adequately surgically resected tumors and may prolong survival in patients with locally recurrent, unresectable, or metastatic tumors. In terms of safety, dual-targeted therapy increases the risk of adverse reactions such as febrile neutropenia, diarrhea, and anemia. Febrile neutropenia is more common in patients with advanced or recurrent breast cancer.

Keywords

Receptor ErbB-2, Breast Neoplasms, Trastuzumab, Pertuzumab, Targeted Therapy

Introduction

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer accounts for 20-25% of breast carcinomas and up to 30% of breast cancer cases in China and is characterized by aggressiveness, high malignancy, and poor prognosis [1]. Targeted therapies are mainly used for the treatment of patients with HER2-positive breast cancer, of which trastuzumab and pertuzumab are the most prominent targeted drugs. Trastuzumab is a humanized monoclonal anti-HER2 antibody. Currently, the results of many studies have confirmed that trastuzumab can tightly bind to the transmembrane domain IV of HER2, which in turn induces antibody-dependent cell-mediated cytotoxicity (ADCC). Moreover, trastuzumab also inhibits HER2-mediated mitogenic signaling pathways [2,3].

Pertuzumab, a humanized monoclonal anti-HER2 antibody, has a complementary mechanism of action to trastuzumab [4]. By binding to the dimerization domain II of HER2, pertuzumab can induce ADCC while also inhibiting heterodimerization of HER2 with other HER family members, thereby inhibiting the production of downstream signals activated by HER2 heterodimerization [5-9]. In addition, pertuzumab does not compete with trastuzumab during HER2 binding, and the two agents inhibit the HER2 signaling process through different mechanisms. Therefore, dual inhibition with trastuzumab combined with pertuzumab is more comprehensive and effective than trastuzumab or pertuzumab alone in inhibiting the HER2 signaling pathway [6,10].

Materials and Methods

Literature Search:

All published randomized and non-randomized controlled clinical trials on the use of trastuzumab in combination with pertuzumab in patients with HER2-positive breast cancer were searched in PubMed, Embase, the Cochrane Collaboration, and other literature databases from database inception to November 2023. The following search terms were used: "Receptor, ErbB-2" [MeSH], "Breast Neoplasms" [MeSH], "Trastuzumab" [MeSH], "pertuzumab" [Supplementary Concept], "Antineoplastic Agents, Immunological" [MeSH], randomized controlled trial [Publication Type], controlled clinical trial [Publication Type], and clinical trials as topic [MeSH:noexp].

Inclusion Criteria:

1. **Subjects:** Patients with HER2-positive breast cancer, confirmed by a central laboratory as immunohistochemistry (IHC) 3+ or in situ hybridization positive.
2. **Interventions:** Dual-targeted therapy with pertuzumab combined with trastuzumab in the experimental group and trastuzumab monotherapy in the control group.
3. **Outcome Data:** Studies providing specific efficacy and safety data for the different treatment regimens. The primary clinical outcome was overall survival rate. The secondary clinical outcome was progression-free survival rate. Safety evaluation outcomes included leukopenia, diarrhea, adverse cardiac events, and other treatment-related adverse events.
4. **Follow-Up:** A follow-up period of not less than 12 months.
5. **Study Type:** Clinical randomized and non-

randomized controlled trials.

Exclusion Criteria:

1. Studies with inadequate information on patient treatment regimens.
2. Studies with a follow-up period of less than 12 months.
3. Studies involving pediatric patients.

Data Extraction:

Data extraction was performed independently by two investigators. Data from each study were extracted using a uniform standardized statistical table, including authors, year of publication, experimental design, study population, sample size, patient characteristics such as age distribution, estrogen receptor (ER) status, progesterone receptor (PR) status, lymph node status,

tumor size and grade, concomitant chemotherapy status, and interventions (**Table-1**).

Outcome Measures:

The primary clinical outcome was overall survival rate. The secondary clinical outcome was progression-free survival rate. Safety evaluation outcomes included the incidence of leukopenia, neutropenia, febrile neutropenia, diarrhea, alopecia, anemia, adverse cardiac events, and fatal adverse events.

Literature Quality Assessment:

All seven included studies were randomized controlled trials (RCTs). The included studies were assessed for risk of bias according to the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions.

Table-1: Basic Characteristics of the Included Studies

Studies	Study Year	Number of patients	Crowd	Inclusion criteria for enrolled patients
Baselga	2012	808	Global	1. Locally recurrent, unresectable or metastatic HER2-positive breast cancer. 2. By immunohistochemistry (3+ indicates positive) or fluorescence in situ hybridization (amplification ratio ≥ 2.0 indicates positive status). 3. Age 18 years or older. 4. Left ventricular ejection fraction of 50% or greater at baseline (as determined by echocardiography or multi-gated acquisition scan).
Minckwitz	2017	4804	Global	1. Patients with non-metastatic, adequately resected, histologically confirmed invasive HER2-positive breast cancer. 2. HER2 positivity must be centrally confirmed and defined as an immunohistochemical score of 3+ in more than 10% of immunoreactive cells or amplification of ERBB2 (the gene encoding HER2) by in situ hybridization. 3. The left ventricular ejection fraction must be at least 55%.
Pang	2020	329	Asia	1. Patients with advanced, locally invasive or metastatic breast cancer who are ERBB2-positive. 2. Primary tumors larger than 2 cm.
Rimawi	2018	258	Global	1. HER2-positive, hormone receptor-positive MBC/LABC. 2. The performance status of the Eastern Tumor Collaborative Group was 0 to 1. 3. Left ventricular ejection fraction (LVEF) $\geq 50\%$. 4. Life expectancy ≥ 12 weeks.
Shao	2021	558	China	1. Non-metastatic, adequately resected, invasive, centrally confirmed HER2-positive breast cancer. 2. Lymph node positive or lymph node negative disease with tumor diameter >1.0 cm (0.5-1.0 cm if age <35 years). 3. All patients required a left ventricular ejection fraction (LVEF) $\geq 55\%$.
Urruticoechea	2017	452	Global (Europe-based)	1. Pathologically confirmed metastatic breast cancer. 2. Center-confirmed HER2-positive disease (immunohistochemistry 3+ or chromogenic in situ hybridization positive). 3. Left ventricular ejection fraction (LVEF) $\geq 50\%$.
Xu	2020	243	China	1. HER2 positive (center-confirmed immunohistochemistry [IHC] 3+ or positive in situ hybridization). 2. Locally recurrent or metastatic breast cancer. 3. Twelve months or longer disease-free interval. 4. Left ventricular ejection fraction (LVEF) of 55% or greater (by echocardiography or multiple gated acquisition scans).

Statistical Analysis:

Statistical analysis was performed using RevMan version 5.4 software provided by the Cochrane Collaboration. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the outcomes of each study. Heterogeneity among the included studies was evaluated using the chi-square test and quantified using the I^2 statistic. We defined $I^2 < 50\%$ as indicating low heterogeneity and $I^2 \geq 50\%$ as indicating substantial heterogeneity among studies. For data with $I^2 < 50\%$, a fixed-effects model was used, whereas for data with $I^2 \geq 50\%$, a random-effects model was used.

Sensitivity analysis was then performed based on the results of the literature quality assessment and the characteristics of each study, including the enrolled population, intervention drugs, and tumor stage, to evaluate the stability and reliability of the meta-analysis results. Funnel plots were used to assess publication bias in the included studies. Greater funnel plot asymmetry indicated a greater degree of publication bias. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Literature Search Results:

A total of 118 publications were identified from the PubMed, Embase, and Cochrane Collaboration databases. After removing duplicates, 105 potentially relevant studies remained. Following screening of titles and abstracts, 84 studies were considered irrelevant and excluded, leaving 21 studies that met the initial search criteria.

After full-text review, 7 studies were excluded because the outcome measures were incomplete, 2 studies were excluded because their outcome measures were related to pathology or molecular biology rather than efficacy and safety, 1 study was excluded because it included three experimental groups, 1 study was excluded because it had no control group, 1 study was excluded because it evaluated the efficacy of trastuzumab with or without combination therapy rather than the efficacy of pertuzumab, and 2 studies were excluded because their study populations overlapped with those of the included literature.

Ultimately, 7 studies were included in the meta-analysis. The literature screening process and results are shown in (Fig-1).

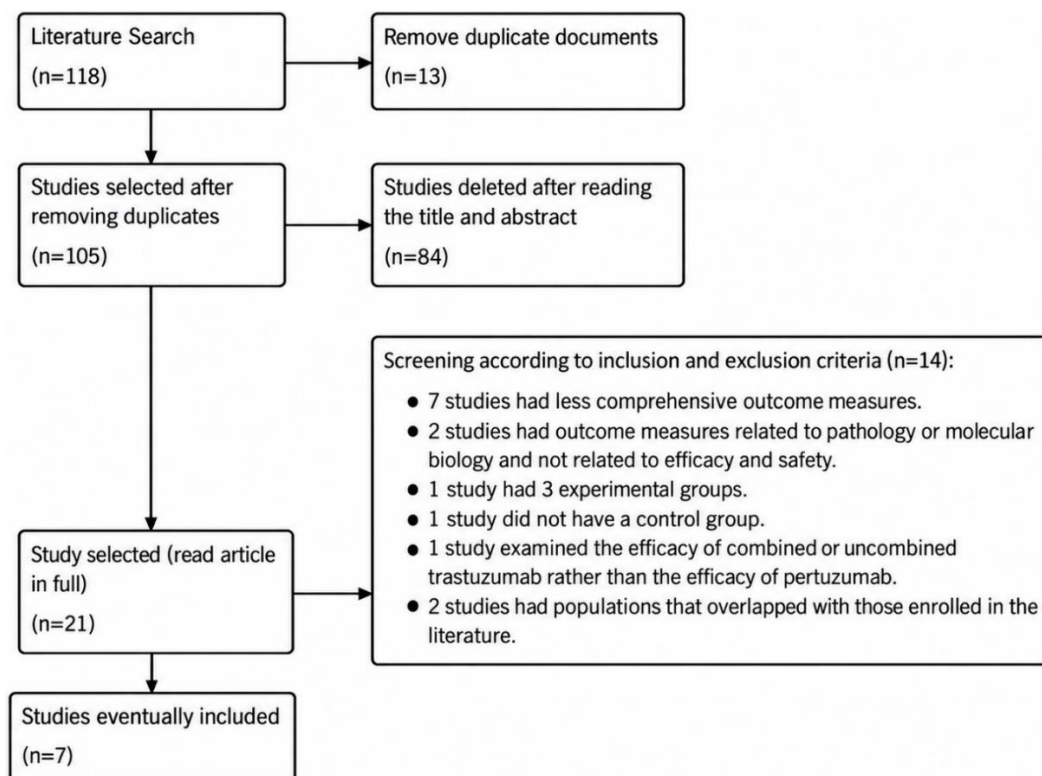


Fig-1: Flow Chart of Literature Screening

Table-2: Baseline Information of Patients in Each Included Study

Studies	Age Distribution	ER/PR Status	Lymph Node Status	Tumor Size	Interventions
Baselga	84.3% <65 years; 15.7% ≥65 years	48.0% ER+ or PR+; 50.5% ER- and PR-	NA	NA	Patients received a loading dose of trastuzumab 8 mg/kg, followed by a maintenance dose of 6 mg/kg every 3 weeks. Docetaxel was administered at a starting dose of 75 mg/m ² every 3 weeks for at least six cycles. Pertuzumab or placebo was administered at a fixed loading dose of 840 mg, followed by 420 mg every 3 weeks until disease progression or the occurrence of toxic effects that could not be adequately controlled. All drugs were administered intravenously.
von Minckwitz	84.3% <65 years; 15.7% ≥65 years	64.2% ER+ or PR+; 35.8% ER- and PR-	62.6% N+; 37.4% No	93.3% T1/T2; 6.7% T3/T4	Patients received either pertuzumab or placebo, with an 840 mg intravenous loading dose followed by 420 mg intravenously every 3 weeks, and trastuzumab, with an 8 mg/kg loading dose followed by 6 mg/kg every 3 weeks. Chemotherapy consisted of 3 or 4 cycles of 5-fluorouracil plus epirubicin or doxorubicin plus cyclophosphamide, followed by 3 or 4 cycles of docetaxel or 12 weeks of paclitaxel; 4 cycles of cyclophosphamide plus doxorubicin or epirubicin followed by 4 cycles of docetaxel or 12 weeks of paclitaxel; or 6 cycles of docetaxel plus carboplatin.
Pang	NA	16.1% ER+ or PR+; 17.3% ER- and PR-	21.6% N+; 11.9% No; 66.5% NA	0% T1; 100% T2/T3/T4	Patients received 4 cycles of intravenous pertuzumab, trastuzumab, and docetaxel or intravenous placebo, trastuzumab, and docetaxel every 3 weeks preoperatively. After surgery, patients received 3 cycles of intravenous fluorouracil, epirubicin, and cyclophosphamide.
Rimawi	66.7% <65 years; 33.3% ≥65 years	100% ER+ or PR+; 0% ER- and PR-	NA	NA	Patients received intravenous pertuzumab in combination with trastuzumab or trastuzumab alone every 3 weeks, together with daily oral anastrozole or letrozole. After randomization, docetaxel or paclitaxel was administered intravenously every 3 weeks or weekly, respectively, according to the product label.
Shao	94.5% <65 years; 5.5% ≥65 years	54.1% ER+ or PR+; 45.9% ER- and PR-	74.9% N+; 25.1% No	92.5% T1/T2; 7.5% T3/T4	Patients were randomized to receive standard adjuvant chemotherapy, consisting of 3-4 cycles of anthracycline-based chemotherapy followed by 3-4 cycles of paclitaxel, or 6 cycles of docetaxel plus carboplatin, together with 1 year of trastuzumab in combination with pertuzumab or placebo as adjuvant therapy.
Urruticoechea	83.7% <65 years; 16.3% ≥65 years	55.1% ER+ or PR+; 43.6% ER- and PR-	NA	NA	In the control group, trastuzumab was administered intravenously for 4 cycles, and capecitabine was administered orally twice daily. In the experimental group, 4 cycles of intravenous pertuzumab were added to the control regimen.
Xu	NA	58.4% ER+ or PR+; 41.6% ER- and PR-	NA	NA	Experimental group: pertuzumab 840 mg loading dose followed by 420 mg every 3 weeks, trastuzumab 8 mg/kg loading dose followed by 6 mg/kg every 3 weeks, and docetaxel 75 mg/m ² every 3 weeks. Control group: placebo, trastuzumab, and docetaxel.

A total of 7,398 patients were included in this study, of whom 3,740 received dual-targeted therapy with trastuzumab combined with pertuzumab and 3,658 received trastuzumab monotherapy. The basic

characteristics of the included studies and the baseline characteristics of the patients in each study are shown in **Table-1** and **Table-2**.

Original Research

Literature Quality Evaluation Results:

We evaluated the risk of bias based on several domains, including random sequence generation, allocation concealment, blinding of investigators and participants, blinded assessment of study outcomes, completeness of outcome data, selective reporting of study results, and other potential sources of bias. Detailed results are shown in Fig-2a and Fig-2b.

Overall Survival Rate:

We compared the overall survival rates of the P+T and T groups in four studies, with 3,050 patients (92.28%) surviving in the P+T group and 3,005 patients (90.59%) surviving in the T group. There was no statistically significant heterogeneity ($P=0.61$, $I^2=0\%$). A combined analysis using a fixed-effects model revealed a statistically significant difference in overall survival between the two groups (OR: 1.31, 95% CI: 1.08-1.59, $P=0.005$) (Fig-3).

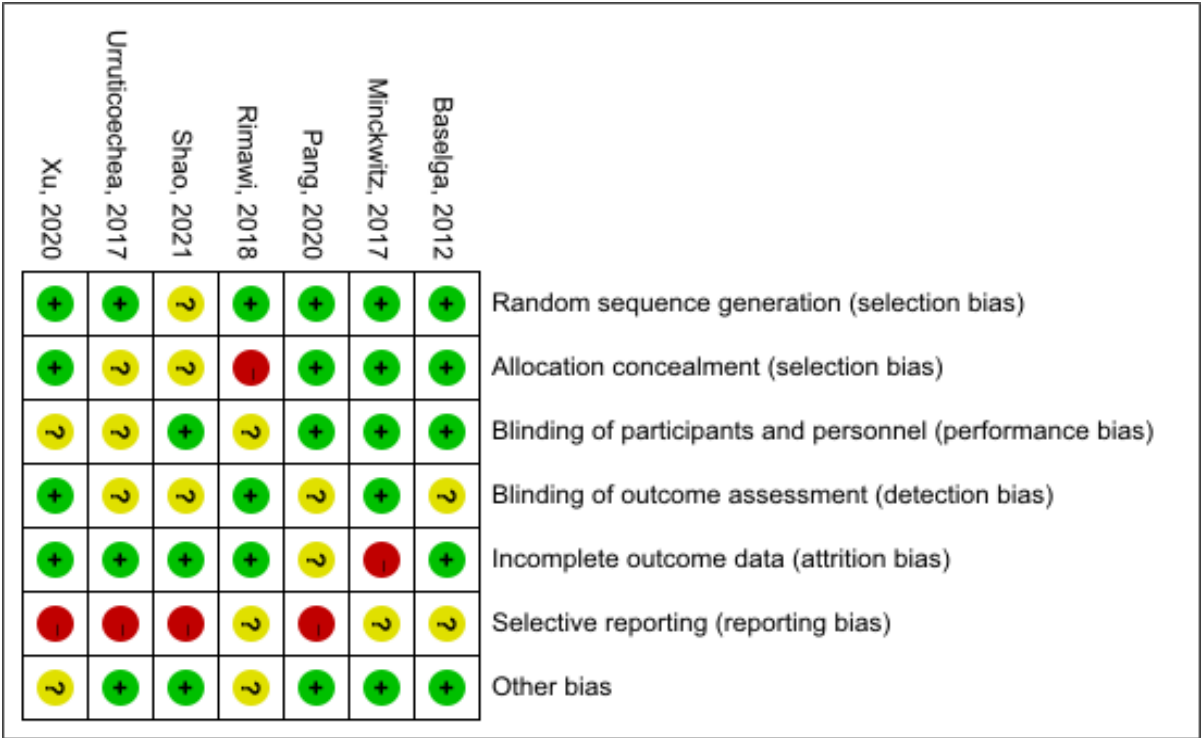


Fig-2a: Risk of bias evaluation results

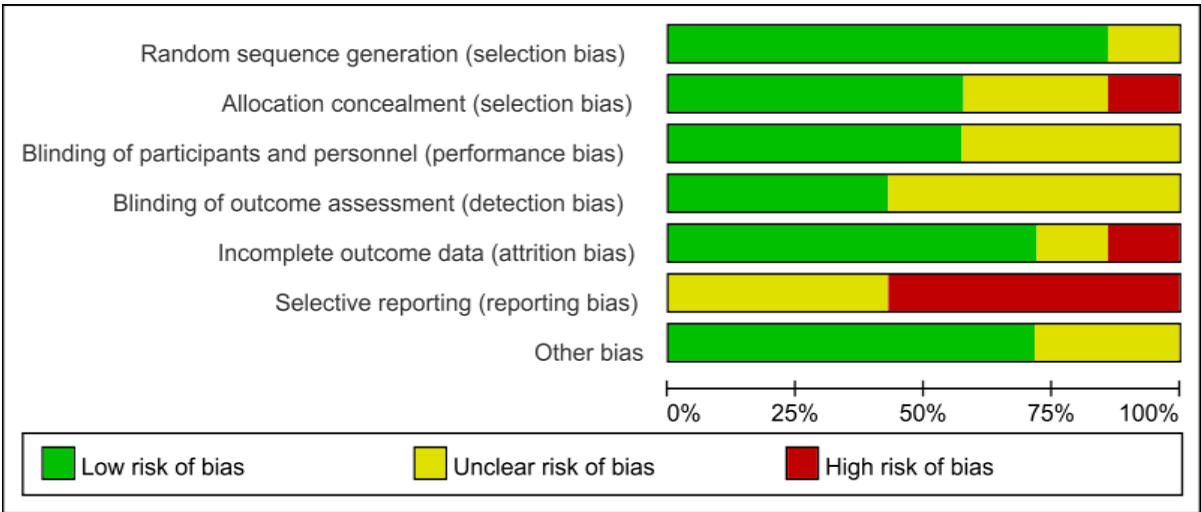


Fig-2b: Risk of bias evaluation results

Original Research

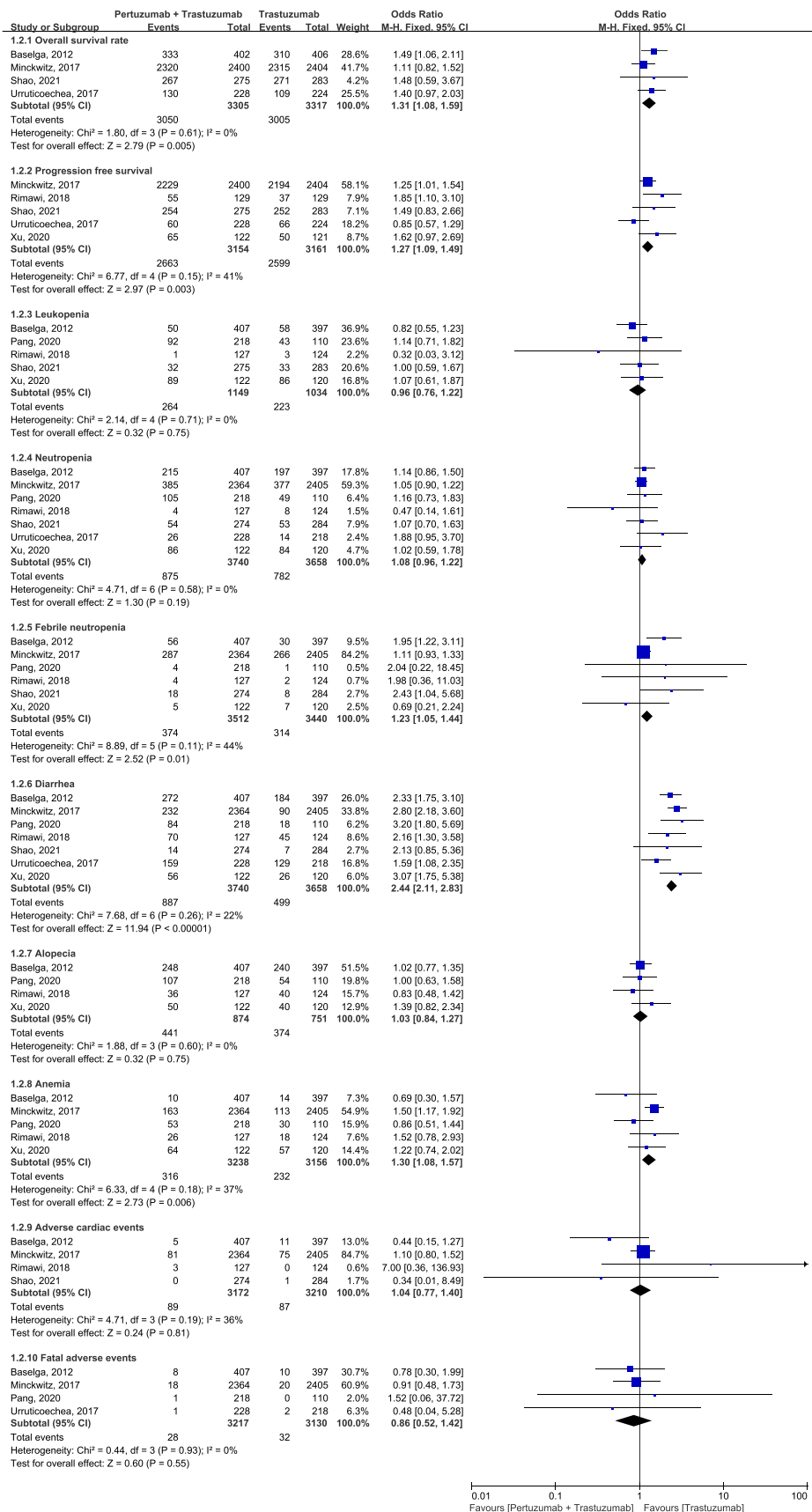


Fig-3: Comparison of overall survival rate, progression-free survival rate, incidence of leukopenia, neutropenia, febrile neutropenia, diarrhea, alopecia, anemia, adverse cardiac events, and fatal adverse events in the P+T group versus the T group.

Original Research

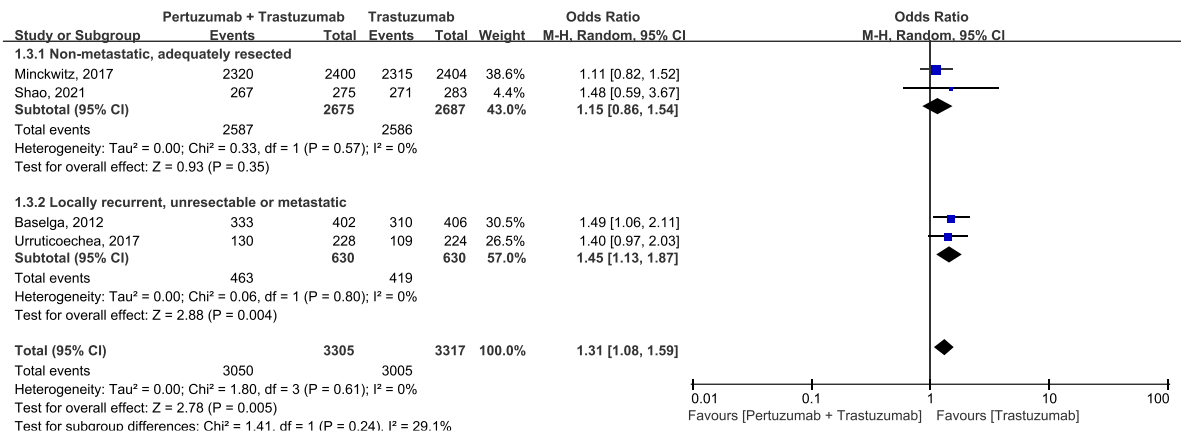


Fig-4: Subgroup analysis: comparison of overall survival rate between P+T and T groups in the non-metastatic, adequately surgically resected subgroup and the locally recurrent, unresectable or metastatic subgroup.

In addition, we divided the population into non-metastatic, adequately surgically resected subgroups and locoregionally recurrent, unresectable, or metastatic subgroups according to tumor stage, and further subgroup analysis was performed (Fig-4). We found that in the non-metastatic, adequately surgically resected subgroup, 2,587 patients (96.71%) survived in the P+T group and 2,586 patients (96.24%) survived in the T group, with no statistically significant difference in overall survival rate between the two groups (OR: 1.15, 95% CI: 0.86-1.54, P=0.35). In contrast, in the subgroup with locoregionally recurrent, unresectable, or metastatic disease, 463 patients (73.49%) survived in the P+T group and 419 patients (66.51%) survived in the T group, with a statistically significant difference in overall survival rate between the two groups (OR: 1.45, 95% CI: 1.13-1.87, P=0.004). Therefore, we conclude that the combination of pertuzumab is significantly more likely to improve overall survival in patients with locoregionally recurrent, unresectable, or metastatic HER2-positive breast cancer, but the improvement in overall survival in patients with non-metastatic, adequately surgically resected disease is not significant.

Progression-Free Survival Rate:

We compared progression-free survival rates between the P+T and T groups in five studies, with 2,663 patients (84.43%) in the P+T group and 2,599 patients (82.22%) in the T group not experiencing disease progression or death. There was moderate heterogeneity among the studies (P=0.15, I²=41%). Using a fixed-effects model for the combined analysis,

we found a statistically significant difference in progression-free survival rate between the two groups (OR: 1.27, 95% CI: 1.09-1.49, P=0.003).

Although there was only moderate heterogeneity among the studies, we still performed sensitivity analyses. Removing any of the studies revealed no substantial change in the combined effect sizes and no change in the direction of the forest plot, indicating that the results of this study were stable and reliable. In addition, sensitivity analysis (Table-3) showed that I² was 0% after excluding the Urruticoechea 2017 trial, while I² did not change significantly after removing the remaining trials. This may be because patients in the Urruticoechea 2017 trial received oral capecitabine as their chemotherapy regimen, whereas the remaining studies used paclitaxel-based or anthracycline-based regimens, suggesting that the heterogeneity among studies may be due to differences in the combined chemotherapy regimens.

Table-3: Sensitivity Analysis for the Comparison of Progression-Free Survival Rate Between the P+T and T Groups

Rejection studies	95% CI after excluding studies	Heterogeneity test	
		P value	I ² (%)
Minckwitz	1.31 [1.02, 1.67]	0.08	55
Rimawi	1.22 [1.03, 1.45]	0.21	34
Shao	1.26 [1.06, 1.48]	0.09	54
Urruticoechea	1.37 [1.15, 1.62]	0.47	0
Xu	1.24 [1.05, 1.47]	0.12	48

Original Research

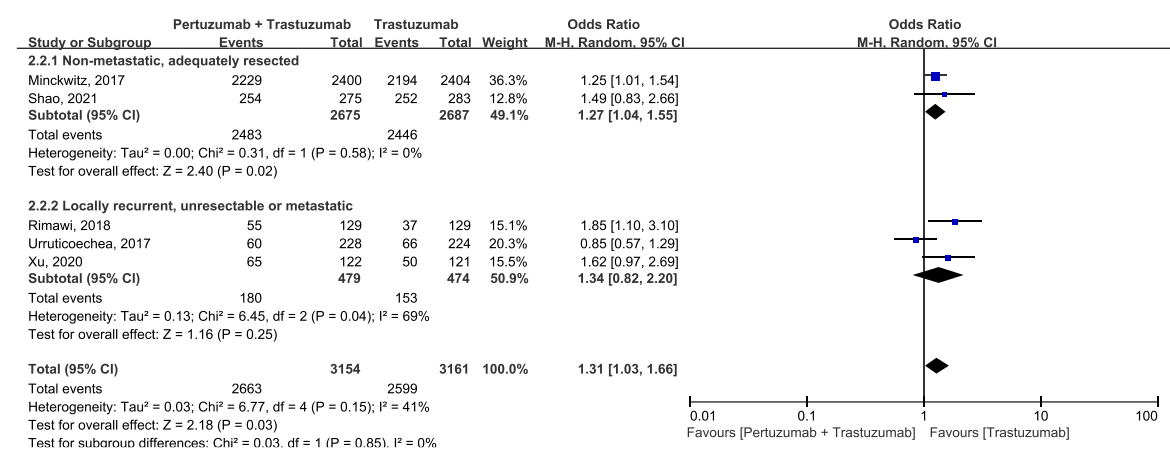


Fig-5: Subgroup analysis: progression-free survival rate in the P+T group compared with the T group in the non-metastatic, adequately surgically resected subgroup and the locally recurrent, unresectable or metastatic subgroup.

Furthermore, although the progression-free survival rate in the P+T group was not statistically different from that in the T group in the Urruticoechea 2017 trial ($P=0.46$, 95% CI: 0.57-1.29), the combined effect sizes remained statistically significant after excluding any of the studies ($P<0.05$). Therefore, we can conclude that trastuzumab in combination with pertuzumab is significantly superior to trastuzumab monotherapy in improving progression-free survival in patients with HER2-positive breast cancer.

In addition, we further performed a subgroup analysis to identify other factors contributing to heterogeneity and found that heterogeneity among studies was not associated with locoregional recurrence, advanced metastasis, or adequate surgical resection (Fig-5). However, subgroup analysis showed that in patients with non-metastatic, adequately surgically resected HER2-positive breast cancer ($P=0.58$, $I^2=0\%$), 2,483 patients (92.82%) in the P+T group and 2,446 patients (91.03%) in the T group did not experience disease progression or death, with a statistically significant difference between the two groups (OR: 1.27, 95% CI: 1.04-1.55, $P=0.02$). Therefore, we concluded that the combination of pertuzumab reduces the risk of tumor recurrence, metastasis, and death in patients with non-metastatic, adequately surgically resected HER2-positive breast cancer compared with trastuzumab alone.

Leukopenia:

Five studies compared the incidence of leukopenia

between the P+T and T groups. A total of 264 patients (22.98%) in the P+T group and 223 patients (21.57%) in the T group developed leukopenia. There was no statistically significant heterogeneity among the studies ($P=0.71$, $I^2=0\%$). A combined analysis using a fixed-effects model found no statistically significant difference in the incidence of leukopenia between the two groups (OR: 0.96, 95% CI: 0.76-1.22, $P=0.75$).

Neutropenia:

Seven studies compared the incidence of neutropenia between the P+T and T groups. A total of 875 patients (23.40%) in the P+T group and 782 patients (21.38%) in the T group developed neutropenia. There was no statistically significant heterogeneity among the studies ($P=0.58$, $I^2=0\%$). A combined analysis using a fixed-effects model found no statistically significant difference in the incidence of neutropenia between the two groups (OR: 1.08, 95% CI: 0.96-1.22, $P=0.19$).

Febrile Neutropenia:

Six studies compared the incidence of febrile neutropenia between the P+T and T groups. A total of 374 patients (10.65%) in the P+T group and 314 patients (9.13%) in the T group developed febrile neutropenia. Moderate heterogeneity was observed among the studies ($P=0.11$, $I^2=44\%$). Using a fixed-effects model for the combined analysis, we found a statistically significant difference in the incidence of febrile neutropenia between the two groups (OR: 1.23, 95% CI: 1.05-1.44, $P=0.01$).

Original Research

Table-4: Sensitivity Analysis Comparing the Incidence of Febrile Neutropenia Between the P+T and T Groups

Rejection studies	95% CI after excluding studies	Heterogeneity test	
		P value	I ² (%)
Baselga	1.15 [0.97, 1.36]	0.35	11
Minckwitz	1.84 [1.27, 2.66]	0.53	0
Pang	1.22 [1.04, 1.43]	0.07	54
Rimawi	1.22 [1.04, 1.43]	0.07	53
Shao	1.19 [1.01, 1.40]	0.18	36
Xu	1.24 [1.06, 1.46]	0.09	50

Meanwhile, sensitivity analysis performed by removing individual studies showed that I² decreased from 44% to 11% and 0% after excluding the Baselga 2012 trial and the von Minckwitz 2017 trial, respectively, while there was no significant change in I² after

excluding any of the other trials (Table-4). We considered the Baselga 2012 trial and the von Minckwitz 2017 trial to be important contributors to heterogeneity. However, subgroup analysis did not reduce the heterogeneity among studies. Therefore, we considered the heterogeneity to be independent of the study population, locoregional recurrence, advanced metastasis, and adequate surgical resection (Fig-6 and Fig-7).

Subgroup analysis further showed that in patients with locoregionally recurrent or advanced metastatic HER2-positive breast cancer (P=0.45, I²=0%), patients receiving pertuzumab in combination with trastuzumab were more likely to develop febrile neutropenia than those receiving trastuzumab monotherapy (OR: 1.72, 95% CI: 1.14-2.60, P=0.01) (Fig-7).

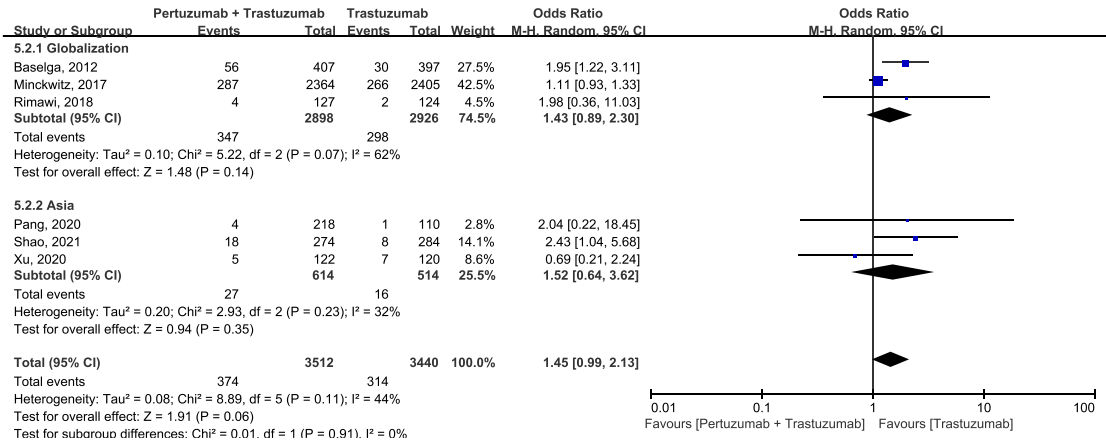


Fig-6: Subgroup analysis: comparison of the incidence of febrile neutropenia in the P+T group versus the T group in the global population subgroup and the Asian population subgroup.

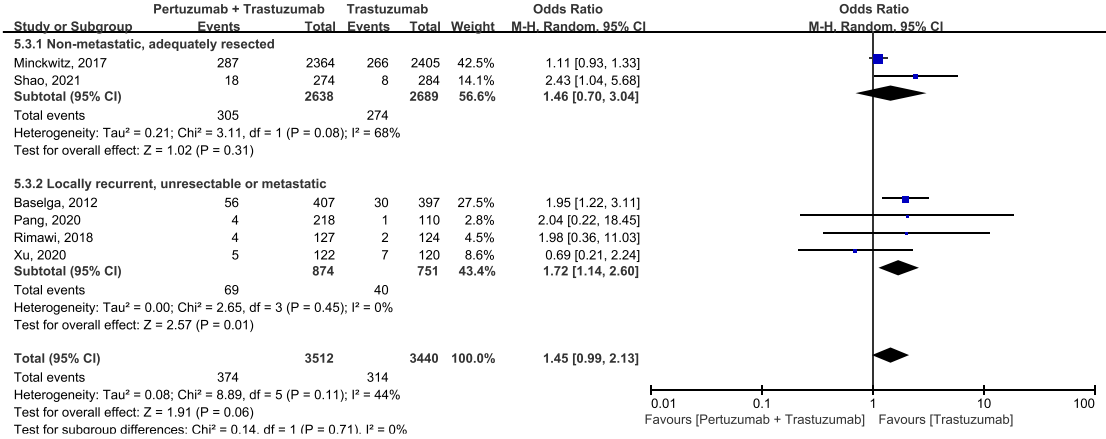


Fig-7: Subgroup analysis: incidence of febrile neutropenia in the P+T group compared with the T group in the non-metastatic, adequately surgically resected subgroup and the locally recurrent, unresectable or metastatic subgroup.

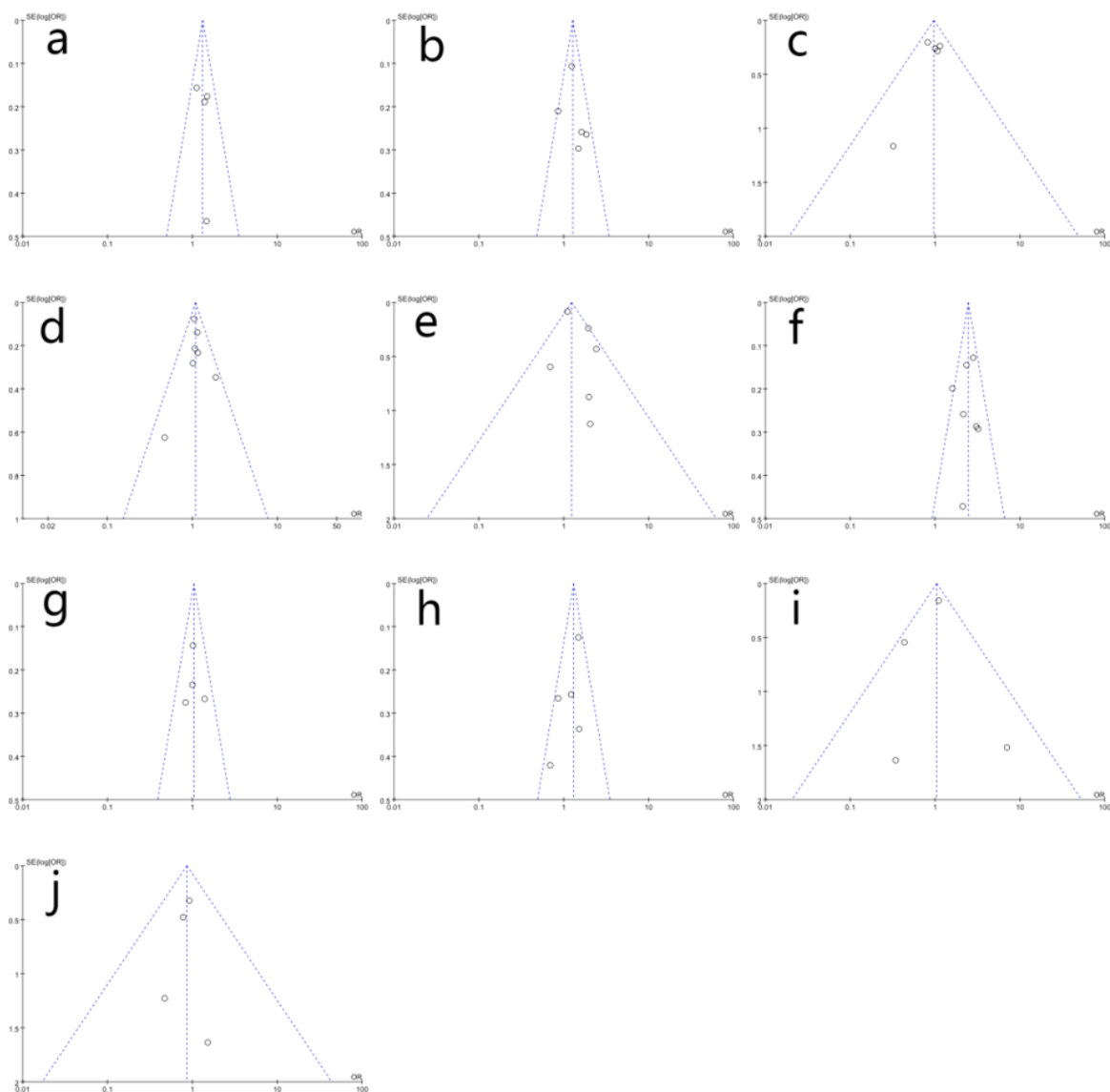


Fig-8:

Funnel plot analysis of publication bias (a: Overall survival, b: Progression-free survival, c: Leukopenia, d: Neutropenia, e: Febrile neutropenia, f: Diarrhea, g: Alopecia, h: Anemia, i: Adverse cardiac events, j: Fatal adverse events).

Diarrhea:

Seven studies compared the incidence of diarrhea between the P+T and T groups. A total of 887 patients (23.72%) in the P+T group and 499 patients (13.64%) in the T group developed diarrhea. There was no statistically significant heterogeneity among the studies ($P=0.26$, $I^2=22\%$). A combined analysis using a fixed-effects model revealed a statistically significant difference in the incidence of diarrhea between the two groups (OR: 2.44, 95% CI: 2.11-2.83, $P<0.00001$). Therefore, it can be concluded that the addition of pertuzumab is more likely to cause diarrhea in patients.

Alopecia:

Four studies compared the incidence of alopecia between the P+T and T groups. A total of 441 patients (50.46%) in the P+T group and 374 patients (49.80%) in the T group developed alopecia. There was no statistically significant heterogeneity among the studies ($P=0.60$, $I^2=0\%$). A combined analysis using a fixed-effects model found no statistically significant difference in the incidence of alopecia between the two groups (OR: 1.03, 95% CI: 0.84-1.27, $P=0.75$).

Anemia:

Four studies compared the incidence of anemia

between the P+T and T groups. A total of 316 patients (9.76%) in the P+T group and 232 patients (7.35%) in the T group developed anemia. Moderate heterogeneity was observed among the studies ($P=0.18$, $I^2=37\%$). A combined analysis using a fixed-effects model revealed a statistically significant difference in the incidence of anemia between the two groups (OR: 1.30, 95% CI: 1.08-1.57, $P=0.006$).

Adverse Cardiac Events:

Four studies compared the incidence of adverse cardiac events between the P+T and T groups, with 89 patients (2.81%) in the P+T group and 782 patients (2.71%) in the T group experiencing adverse cardiac events. Moderate heterogeneity was observed among the studies ($P=0.19$, $I^2=36\%$). A combined analysis using a fixed-effects model found no statistically significant difference in the incidence of adverse cardiac events between the two groups (OR: 1.04, 95% CI: 0.77-1.04, $P=0.81$).

Fatal Adverse Events:

Four studies compared the incidence of fatal adverse events between the P+T and T groups. A total of 28 patients (0.87%) in the P+T group and 32 patients (1.02%) in the T group experienced fatal adverse events. There was no statistically significant heterogeneity among the studies ($P=0.93$, $I^2=0\%$). A combined analysis using a fixed-effects model found no statistically significant difference in the incidence of fatal adverse events between the two groups (OR: 0.86, 95% CI: 0.52-1.42, $P=0.55$).

Evaluation of Publication Bias:

Publication bias was evaluated using funnel plots. Analysis of the seven included studies showed that the funnel plots for the P+T and T groups were approximately symmetrical, as shown in (Fig-8).

Discussion

This meta-analysis confirms that in patients with HER2-positive breast adenocarcinoma, the combination of trastuzumab with pertuzumab further reduces the risk of breast cancer recurrence, metastasis, and death. In particular, for patients with locally recurrent, unresectable, or metastatic HER2-positive breast cancer, the combination of trastuzumab with

pertuzumab can further improve overall survival and reduce the risk of death. For patients with non-metastatic, adequately surgically resected early-stage HER2-positive breast cancer, the addition of pertuzumab can further reduce the risk of recurrence and metastasis. In terms of safety, the results of this meta-analysis showed that patients receiving dual-targeted therapy were more likely to experience adverse events such as febrile neutropenia, diarrhea, and anemia, but there were no statistically significant differences in adverse cardiac events or fatal adverse events.

In the patient population of this study, the overall survival and progression-free survival rates were 92.28% and 84.43%, respectively. In contrast, the overall survival and progression-free survival rates in the trastuzumab monotherapy group were 90.59% and 82.22%, respectively, with statistically significant differences. Subgroup analysis indicated that in patients with locally recurrent, unresectable, or metastatic HER2-positive breast cancer, dual-targeted therapy with trastuzumab combined with pertuzumab improved overall survival [11-14]. However, the effect in patients with non-metastatic, adequately surgically resected disease was relatively insignificant [15]. In addition, dual-targeted therapy with trastuzumab in combination with pertuzumab reduced the risk of tumor recurrence, local invasion, distant metastasis, and death in patients with non-metastatic, adequately surgically resected HER2-positive breast cancer (OR: 1.27, 95% CI: 1.04-1.55, $P=0.02$) [16]. However, in the subgroup of patients with locally recurrent, unresectable, or metastatic HER2-positive breast cancer, we were unable to draw relevant conclusions because of substantial heterogeneity among the studies. A 4-year follow-up study corroborates our findings. This study revealed that a trastuzumab + pertuzumab regimen improved disease-free survival in patients with HER2-positive early-stage breast cancer more than trastuzumab monotherapy (DFS: 94.1% vs. 93.2%, $P=0.045$), and this improvement was more significant in patients with lymph node metastases [17]. Many studies have confirmed that dual-targeted therapy with trastuzumab in conjunction with pertuzumab provides a greater improvement in pathological complete response rate (pCR), clinical benefit rate (CBR), and

progression-free survival compared with single-targeted therapy [18,19], and is more effective regardless of the combined chemotherapy regimen [20].

In terms of safety, the incidence of diarrhea was 23.72% and 13.64% in the experimental and control groups, respectively (OR: 2.44, 95% CI: 2.11-2.83, $P < 0.00001$). Diarrhea is one of the most common adverse reactions associated with targeted therapy. When targeted drugs act on HER2 receptors in intestinal epithelial cells and neurons of the enteric nervous system, they may affect normal cellular function, which in turn can lead to gastrointestinal dysfunction and corresponding digestive symptoms such as diarrhea [21,22]. For hematologic effects, we found that dual-targeted therapy did not increase the incidence of leukopenia or neutropenia but was more likely to cause anemia and febrile neutropenia than single-targeted therapy. More notably, subgroup analysis showed that patients with HER2-positive breast cancer with locoregional recurrence or advanced metastasis were more likely to develop febrile neutropenia after dual-targeted therapy (OR: 1.72, 95% CI: 1.14-2.60, $P = 0.01$).

Febrile neutropenia is a serious and potentially life-threatening complication. In addition to the established association between febrile neutropenia and chemotherapy-induced myelosuppression, advanced age, locoregional recurrence, unresectable or metastatic advanced tumors, infection, and concomitant hepatic or renal dysfunction are independent risk factors [23-26]. One study reported that the incidence of febrile neutropenia in patients treated with targeted therapy in combination with chemotherapy was more than 20% in clinical practice. Meanwhile, a meta-analysis including 17 studies found a 27.6% incidence of febrile neutropenia in patients with HER2-positive breast cancer receiving targeted therapy without prophylactic granulocyte colony-stimulating factor therapy [27]. Therefore, febrile neutropenia remains a complication that cannot be ignored in patients receiving targeted therapy, especially in elderly patients and those with recurrent or metastatic advanced HER2-positive breast cancer. The risks should be carefully evaluated, and preventive measures should be considered when

chemotherapy is combined with dual-targeted therapy [28,29].

Conclusion

In conclusion, this meta-analysis confirms that in patients with early-stage HER2-positive breast cancer, the addition of pertuzumab to trastuzumab decreases the risk of breast cancer recurrence and metastasis. For patients with advanced or surgically unresectable HER2-positive breast cancer, the addition of pertuzumab may prolong survival and reduce the risk of death, although whether it can reduce recurrence and metastasis rates remains uncertain. In terms of safety, the combination of pertuzumab increases the risk of diarrhea, anemia, and febrile neutropenia. Febrile neutropenia tends to be more prevalent in patients with advanced breast cancer.

Conflict of Interest

The authors have read and approved the final version of the manuscript and declare no conflicts of interest.

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