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ORIGINAL RESEARCH

Efficacy and safety of targeted therapy for metastatic HER2-positive breast cancer in the first-line treatment: a Bayesian network meta-analysis

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Purpose: Numerous HER2-targeted therapy clinical trials have demonstrated efficacy and safety in the first-line treatment of metastatic breast cancer (MBC). However, the direct or indirect comparison of these drugs is unclear. This network meta-analysis can solve this issue to some extent.

Materials and methods: PubMed, Embase, and the Cochrane Library were searched for Phase II/III randomized controlled trials (RCTs) on metastatic HER2-positive breast cancer for first-line treatment up to December 16, 2017. Paired meta-analyses were performed to compare the regimens directly with the TP (trastuzumab plus taxane) regimen. Bayesian network meta-analysis was used to synthesize available evidence of direct or indirect comparison.

Results: The database search identified 1,935 articles, among which 13 articles (10 RCTs) were eligible for the analysis involving 5,177 patients treated with 11 different regimens. The progression-free survival (PFS) in the Bayesian network meta-analysis suggested that the PTP (pertuzumab and trastuzumab plus taxane) regimen had the highest probability to be the preferred treatment (surface under the cumulative ranking [SUCRA]: 0.967) followed by the TPC (carboplatin and trastuzumab plus taxane) regimen (SUCRA: 0.923). The PTP regimen (SUCRA: 0.926) was similarly preferred for overall survival (OS). For objective response rate (ORR), the PTC regimen might be the optimal treatment (SUCRA: 0.935), followed by the PTP regimen.

Conclusion: Overall, PTP might be the optimal first-line treatment for HER-2-positive MBC to improve the PFS and OS. Meanwhile, TPC might be most effective treatment in terms of the ORR. Regarding safety, the two regimens showed acceptable grade 3 or greater hematologic toxicity and heart failure.

Keywords: breast cancer, metastasis, HER2-positive, HER2-targeted agents, network meta-analysis, randomized controlled trial

Introduction

Amplification or overexpression of the human epidermal growth factor receptor-2 (HER2) gene, as a proto-oncogene, accounts for ~20% of breast cancers[1] and is associated with more aggressive behavior and a poorer prognosis than breast cancers that do not overexpress this gene.[2,3] The percentage of HER2-positive breast cancers may be different depending on the population being tested by individual laboratories.[4] Presently, HER2 status is based on protein overexpression by immunohistochemistry (IHC3+) or HER2 gene amplification in situ hybridization (fluorescence in situ hybridization [FISH]); when the results are equivocal, reflex testing should be performed using an alternative assay (IHC or ISH).[4] Trastuzumab, as the first HER2-targeted drug, was approved for HER2-positive patients by the US Food and Drug Administration in

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1998. In past decades, trastuzumab in addition to taxane significantly improved the clinical efficacy of patients and has been the standard treatment for both early and metastatic HER2-positive breast cancer.[5,6] The M77001 Study Group found that trastuzumab combined with docetaxel prolonged the overall survival (OS) than docetaxel alone and was similar to vinorelbine plus trastuzumab in the first-line therapy of metastatic or locally advanced HER2-positive breast cancer.[7,8]

Some trials have compared the efficiency and safety of mono anti-HER2 therapy with the dual blockade of HER2 therapy. CLEOPATRA[9,10] indicated that trastuzumab plus docetaxel in addition to pertuzumab compared with trastuzumab plus docetaxel improved the median progression-free survival (PFS) by 6.1 months and the median OS. In another dual target therapy trial BOLERO, the addition of everolimus was based on trastuzumab and docetaxel not prolonging the PFS or OS.[11,12] Unsatisfied with the present outcome of the mono and dual target HER2 regimens, other anti-HER2 agents trials were designed, including trastuzumab emtansine (T-DM1), an antibody–drug conjugate of trastuzumab that significantly improved PFS with a similar OS and favorable safety among the patients with HER-2 positive metastatic breast cancer (MBC), compared with trastuzumab plus docetaxel.[13] A semblable meta-analysis showed that trastuzumab and docetaxel plus pertuzumab (TDP) may be the preferred regimen for HER-2-positive MBC[14] but was not included in the NEfERT-T[15] and the BOLERO-1 trials.[11,12] Neratinib, an oral small-molecule tyrosine kinase inhibitor of ERBB1, ERBB2, and ERBB4,[16] plus paclitaxel compared with trastuzumab–paclitaxel showed the similar outcomes in the PFS (12.9 vs 12.9 months) and OS.

The efficacy of HER2-targeted therapy has been confirmed with the growing number of anti-HER2 agents; however, the most efficient remains inadequate. Network meta-analysis could address these issues[17] by evaluating and comparing the efficacy and safety of various anti-HER2 regimens in HER2-positive MBC. Network meta-analysis is widely used to summarize the direct and indirect comparisons from the publication clinical trials, providing guidance for the clinicians.[18]

Materials and methods

Literature and search strategy

PRISMA was used to report our systematic review and meta-analysis. We searched PubMed, EMBASE, and the Cochrane Library for randomized controlled trials (RCTs) of metastatic HER2-positive breast cancer up to December 16, 2017, with English language restriction. The latest publications were utilized for analysis if the result was reported for the same patient cohort in a different publication. We manually searched the reference lists of the included bibliographies and related reviews to supplement the primary sources.

We used the search terms as the Medical Subject Headings/Emtree combined with free text words of "breast cancer", "breast neoplasms", "metastatic", "advanced", "randomized controlled trial", and known HER2-targeted agents (ie, "trastuzumab", "lapatinib", "pertuzumab", "T-DM1"). The search strategy was made by two authors, one with an advanced statistical background (Jinhui Tian) and the other with a carcinoma clinician background (Fubin Feng). The gray literature was excluded. Detailed information of search strategies is given in the "Supplementary materials" section.

Selection criteria

Two of the (Fubin Feng and Tingting Zhang) independently evaluated the titles and abstracts of articles. If disagreements existed, a third researcher (Lingyu Qi) joined to reach a consensus via discussion to ensure that the studies of relevant systematic reviews would not be inadvertently omitted. The selected publications met the following criteria: 1) Phase II or III RCT with a blinded design; 2) patients with HER2-positive breast neoplasms; 3) stage of the patients was proven to be metastatic or advanced; 4) first-line treatment regimens; 5) the regimens were compared in at least two arms; and 6) the primary outcome was PFS, and the secondary outcomes were OS and objective response rate (ORR). The exclusion criteria were as follows: 1) recurrent or metastatic HER2-positive breast cancer as the second- or other-line treatment; 2) HER2-positive breast cancer with endocrine therapy; and 3) review and meta-analysis.

Data extraction and quality assessments

The two investigators (Fubin Feng and Tingting Zhang) independently extracted the data with the predefined extraction Excel. The data were based on the article's intention-to-treat analysis if provided. Excel included the following information: trial design, first author's name, publication year, journal, sample size, source of foundation support, information of intervention (dose, treatment duration, frequency), characteristics of participants (such as median age, HR status, HER2 status, prior treatment, disease sites, percentage of measurable disease, and Eastern Cooperative Oncology Group performance status), duration of follow-up, primary outcomes (PFS and OS), secondary outcome (ORR), and common adverse events (AEs) (hematologic toxicity and

cardiac safety). In the crossover trials, we extracted only the first-period data. As the program of publications was selected, the third researcher (Lingyu Qi) joined to reach a consensus via discussion if disagreements existed.

The quality of the included studies was assessed using the Cochrane Collaboration's risk of bias assessment tool, which evaluated grades of "high risk of bias", "unclear risk of bias", or "low risk of bias" across seven specified domains.[19] When any disagreements existed between two authors, they were resolved by a third author (Jinhui Tian).

Statistical methods

The network plot were drew using command in STATA13.0 to show the included publications' interaction of the different regimens.[20] To account for the PFS and OS of the studies, the HRs were the ideal effect size for providing time-to-event outcomes.[21] The data of HRs with 95% CI were extracted from the included studies. The ORR and severe AEs (hematologic toxicity and cardiac safety) were calculated for dichotomous outcomes. The statistics heterogeneity across the regimen was calculated by means of the I^2 statistic. I^2 indicates heterogeneity caused by total variation across studies rather than chance. Values $<25\%$ are indicative of a small inconsistency and those $>50\%$ indicate a large amount of inconsistency.[22]

The Bayesian statistical model was used to analyze the direct and indirect treatments and rank the results in the network meta-analysis. Because there was only one closed loop in the network plot, the Bayesian consistency analysis was ignored.[23,24] The regimes were estimated using the Markov Chains Monte Carlo method with WinBUGS, version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). The sampler run with three chains in different initial values, and each chain run 50,000 iterations to get the posterior distribution. We calculated HRs with TP (trastuzumab plus taxane) as the baseline regimen to serve as the effect measure as the treatment proved to be the standard regiments for HER2-positive breast cancer and mostly studies were compared with the TP regimen. For the outcomes, we used 5,000 burn-ins and thinning interval of 10. We selected the fixed model or random model based on the value of deviance information criteria (DIC). The pooled estimate, a 95% credible interval, was presented, which derived from the 2.5 and 97.5 percentiles.

The surface under the cumulative ranking (SUCRA) is an important indicator to rank the safety and effectiveness of regiments in network analysis. The SUCRA value would be 100%, indicating that the regimen is always the best, and 0%, indicating that the regimen is always the worst.[25] As there is a loop in three arms, the node-splitting method was used to evaluate the inconsistency between direct and indirect comparisons.[26] The publication bias was investigated by funnel plots and tested using Begger's and Egger's tests. The results of Begg's and Egger's test demonstrated no significant publication bias ($P>0.05$). The statistical analyses were performed using Stata.

The risk of bias was evaluated by Review Manager (version 5.3), the network plot and analysis of SUCRA were done by STATA 13.0 (StataCorp LP, College Station, TX, USA), and WinBUGS1.4.3 (multiple-treatments of meta-analysis models). A P-value <0.05 was considered as statistically significant.

Results

Overview of the literature search

In total, 2,625 articles were identified by database searching, among which 690 articles were removed because of duplication. Next, 1,882 articles were excluded that obviously did not meet the inclusion criteria after screening the titles and abstracts. Additionally, 50 potentially eligible articles were reviewed in full text, among which 37 articles were excluded because they were non-RCTs (n=11), contained inappropriate participants (n=3), had no relevant outcome (n=13), or comprised only one study (n=10). Ultimately, 13 eligible studies (10 RCTs) were included.[8–13,15,27–32] The details of the search and the results are shown in Figure 1.

Characteristics of the included studies

Ten RCTs were reported in the 13 eligible publications included for the network analysis.[8–13,15,27–32] Overall, 5,177 patients were included in the publications, and 11 different treatment regimens were assessed: the TPC (carboplatin and trastuzumab plus taxane) regimen, the TP regimen, the TV (trastuzumab plus vinorelbine) regimen, the LP (lapatinib plus taxane) regimen, the MTP (NPLD and trastuzumab plus taxane) regimen, T-DM1, the ETP (everolimus and trastuzumab plus taxane) regimen, the PTP (pertuzumab and trastuzumab plus taxane) regimen, the NP (neratinib plus taxane) regimen, the T-DM1+Pzmb (T-DM1 plus pertuzumab) regimen, and taxane. The direct or indirect relationship of these regimens is shown in Figure 2.

In the present network analysis, we merged docetaxel and paclitaxel into the group of taxanes. The patients were enrolled in ten RCTs published between 2006 and 2017, and the median age of the study subjects ranged from 52 years to 56 years. Among most of the RCTs, the status of HER2

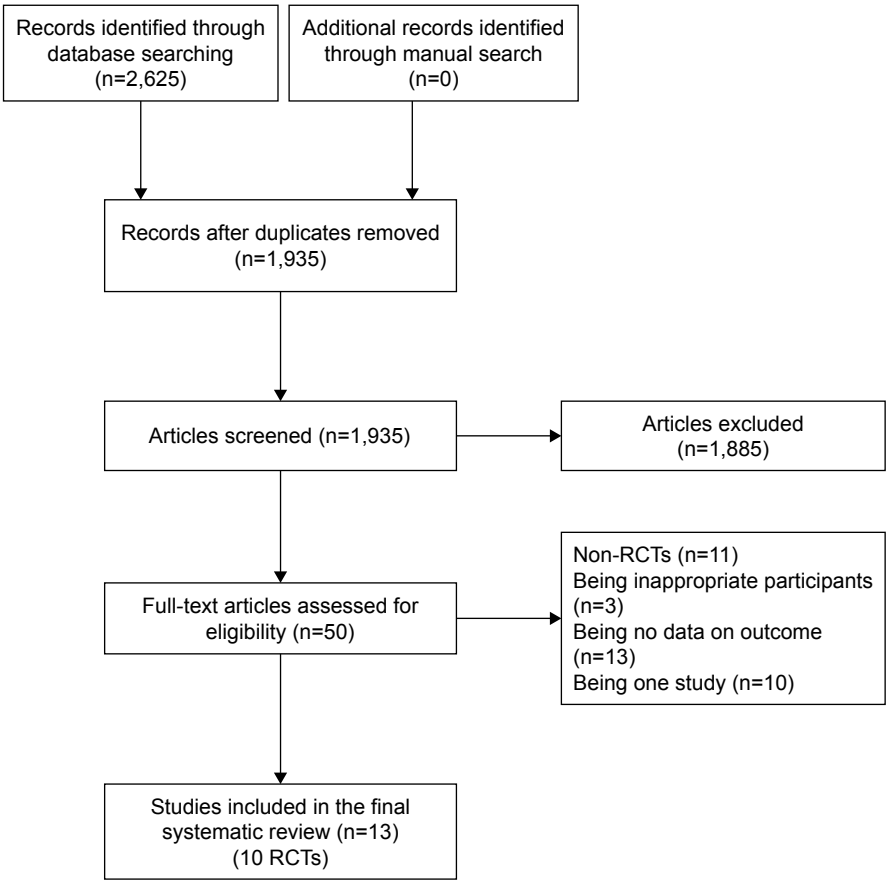


Figure 1 PRISMA flow diagram of study selection.
Abbreviation: RCT, randomized controlled trial.

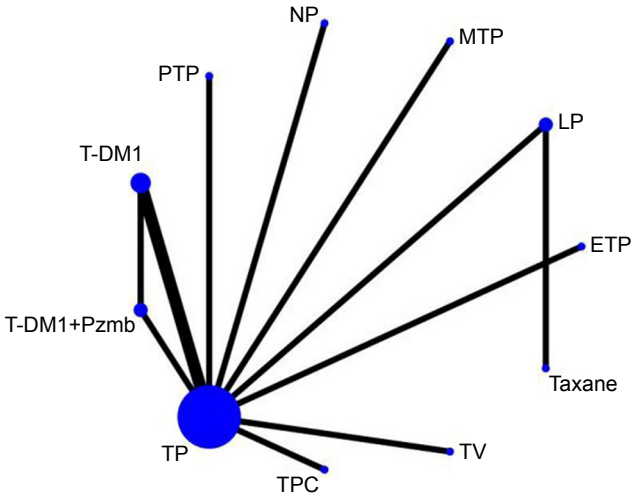


Figure 2 Network diagram of comparison of studies for Bayesian network meta-analysis.
Notes: The size of each node is proportional to number of patients who received the treatment. The widths of the lines are proportional to the number of studies comparing the particular arms.
Abbreviations: ETP, everolimus and trastuzumab plus taxane; LP, lapatinib plus taxane; MTP, NPLD and trastuzumab plus taxane; NP, neratinib plus taxane; NPLD, nonpegylated liposomal doxorubicin; PTP, pertuzumab and trastuzumab plus taxane; T-DM1, trastuzumab emtansine; T-DM1+Pzmb, T-DM1 plus pertuzumab; TP, trastuzumab plus taxane; TPC, carboplatin and trastuzumab plus taxane; TV, trastuzumab plus vinorelbine.

was tested by IHC or FISH. The MARIANNE trial, a three-arm study, reported the PFS or OS,[27,28] while the other trials were two-arm studies. Seven publications have explicitly reported the data both PFS and OS in one study,[8,13,15,29–32] and the other six publications only mention one of the two indicators.[9–12,27,28] The ORR and common AEs (hematologic toxicity and cardiac safety) were abstracted from the publications included. All the included publications were RCTs, the study qualities were reliable, and they were supported by related companies. The characteristics of the eligible studies are summarized in Table 1.

Assessment of the risk of bias

The inclusion studies of the risk of bias involving ten RCTs are presented in Figure 3. Five RCTs did not record details about randomization, which we deemed to have a high risk of bias. Among all the RCTs, four employed double blinding[9,11,30,31] and three clearly proposed open-label designs.[13,15,32] The remaining two RCTs did not specify the method applied.[8,29] All the trials were funded by pharmaceutical companies.

Table 1 Characteristics of ten included RCTs in network meta-analysis

Study	Year	Sample size	Type of phase trial	Ratio of allocation	Age, years	PS		HR-positive pts, n (%)	Intervention	Control	Primary end point
						0	1				
Robert et al[29]	2006	196	III	98:98	55 (35–81) 56 (33–83)	59 (60%) 35 (36%) 60 (61%) 35 (36%)		51 (52%) 63 (64%)	Trastuzumab+taxane+ carboplatin	Trastuzumab+taxane	ORR
Andersson et al[8]	2011	284	III	143:141	56 (33–72) 57 (29–72)	94 (65.7%) 38 (26.6%) 96 (68.1%) 36 (25.5%)		76 (53.1%) 85 (60.3%)	Trastuzumab+taxane	Trastuzumab+vinorelbine	TTP
Guan et al[31]	2013	444	III	222:222	50 (25–74) 50.5 (26–73)	103 (46%) 119 (54%) 113 (51%) 109 (49%)		111 (50%) 113 (51%)	Lapatinib+taxane	Taxane	OS
Hurvitz et al[13]	2013	137	II	70:67	52 (33–75) 55 (27–82)	63.8%–36.2% 65.7%–34.3%		54.3% 49.3%	Trastuzumab+taxane	T-DM1	PFS
Baselga et al[30]	2014	363	III	181:182	52 (22–79) 53 (30–76)	113 (62%) 68 (38%) 112 (62%) 70 (38%)		75 (41%) 81 (45%)	NPLD+trastuzumab+ taxane	Trastuzumab+taxane	PFS
Gelmon et al[32]	2015	652	III	326:326	55.4 54.4	196 (60%) 118 (36%) 204 (63%) 112 (34%)		213 (65%) 208 (64%)	Lapatinib+taxane	Trastuzumab+taxane	PFS
Awada et al[15]	2016	479	III	242:237	54.5 (46–61) 55.0 (47–62)	150 (62.0%) 86 (35.5%) 152 (64.1%) 79 (33.3%)		128 (52.9%) 123 (51.9%)	Neratinib+taxane	Trastuzumab+taxane	PFS
Hurvitz et al[11]	2015	719	III	480:239	54.0 (23–86) 52 (19–82)	278 (58%) 202 (42%) 148 (62%) 91 (38%)		271 (57%) 135 (57%)	Everolimus+trastuzumab+ taxane	Trastuzumab+taxane	PFS
Baselga et al[9]	2012	808	III	402:404	54 (22–82) 54 (27–89)	274 (68.2%) 125 (31.1%) 248 (61.1%) 157 (38.7%)		189 (47.0%) 199 (49.0%)	Pertuzumab+trastuzumab+ taxane	Trastuzumab+ taxane	PFS

(*Continued*)

Table 1 (*Continued*)

Study	Year	Sample size	Type of phase trial	Ratio of allocation	Age, years	PS		HR-positive pts, n (%)	Intervention	Control	Primary end point
						0	1				
Perez et al[27]	2017	1,095	III	363:367:365	52 (27–86) 52 (27–82) 55 (22–88)	245 (64.7%) 127 (35.0%) 239 (65.1%) 128 (34.9%) 245 (67.1%) 119 (32.6%)		198 (54.5%); 195 (53.1%); 207 (56.7%)	T-DM1+trastuzumab T-DM1	Trastuzumab+taxane	PFS

Note: Taxane included docetaxel and pacitaxel.

Abbreviations: HR-positive pts, hormone receptor-positive patients; NPLD, nonpegylated liposomal doxorubicin; ORR, objective response rate; O, overall survival; PFS, progression-free survival; PS, performance status; RCT, randomized controlled trial; T-DM1, trastuzumab emtansine; TTP, time to progression.

Results of direct comparisons

Traditional meta-analysis was used to compare the studies directly with the trials, including the TP regimen. Nine RCTs for the PFS, OS, and OR included in the traditional meta-analysis suggested that no difference was found between the combined regimens and the TP regimen. The pooled HRs of PFS and OS were 0.93 (95% CI: 0.77–1.12; I^2=87.3%) and 0.93 (95% CI: 0.83–1.03; I^2=56.7%), respectively, with a random-effects model. Moreover, for the OR of the objective response, the pooled OR was 1.01 (95% CI: 0.94–1.08; I^2=58.8%) with large inconsistency (Figure 4).

Bayesian network meta-analysis

As shown in Figure 2, there was only a closed triangular loop (closed paths involving three different treatments) in T-DM1 plus pertuzumab–T-DM1-trastuzumab plus taxane, among all comparisons. Meanwhile, the three regimens were from a multi-arm trial[27] and a two-arm trial.[13] The inconsistency was mainly caused by the two-arm trial. The inconsistency factors were 0.573 (95% CI: 0.00–1.16) for TTP/PFS (P=0.056) and 0.093 (95% CI: 0.00–0.96) for OS (P=0.834).

A comprehensive analysis of the efficacy and tolerability was made to illuminate the comparisons. The PFS and OS were reported in the 10 RCTs of the 13 publications. The PFS values of the random-effects model (DIC =–5.493) and fixed-effects model (DIC =–5.566) were similar to the OS values of the random-effects model (–4.334) and fixed-effects model (DIC =–4.359). The DIC values of the PFS and OS were similar, and we chose the fixed-effects model in the present network.

In the directed comparison of the trials included, the TPC and PTP regimens were both superior to the TP regimen (trastuzumab plus paclitaxel) in PFS and OS (HR =0.66, 95% CI: 0.59–0.73; HR =0.90, 95% CI: 0.88–0.92; HR =0.62, 95% CI: 0.51–0.75; HR =0.68, 95% CI: 0.56–0.83); the LP regimen (paclitaxel and lapatinib) was better than paclitaxel alone in PFS and OS (HR =0.52, 95% CI: 0.42–0.64; HR =0.74, 95% CI: 0.58–0.94); the LP regimen (paclitaxel and lapatinib) was better than paclitaxel alone in PFS and OS (HR =0.52; 95% CI: 0.42–0.64; HR =0.74, 95% CI: 0.58–0.94) but inferior to the TP regimen (trastuzumab plus paclitaxel) regardless of the PFS or OS (HR =1.48, 95% CI: 1.20–1.83; HR =1.47, 95% CI: 1.03–2.09). The results of all possible comparisons are presented in Table 2.

According to the SUCRA values, regarding PFS, the PTP regimen showed the highest value (0.967), followed

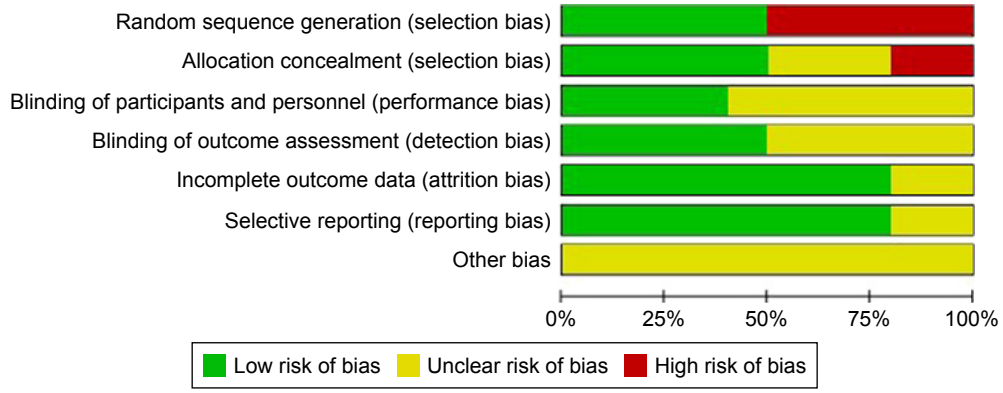


Figure 3 Cochrane risk of bias tool assessment.

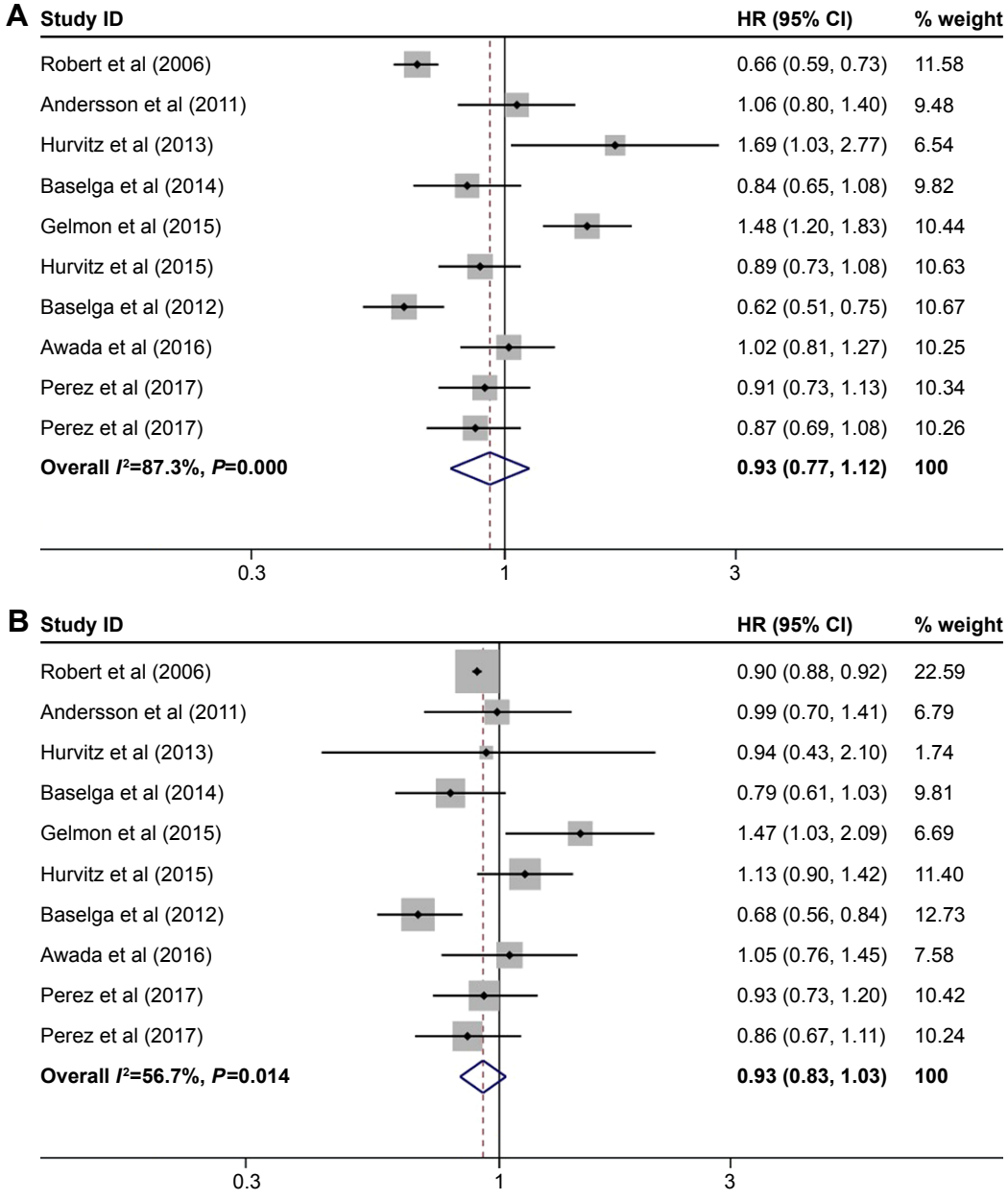


Figure 4 (*Continued*)

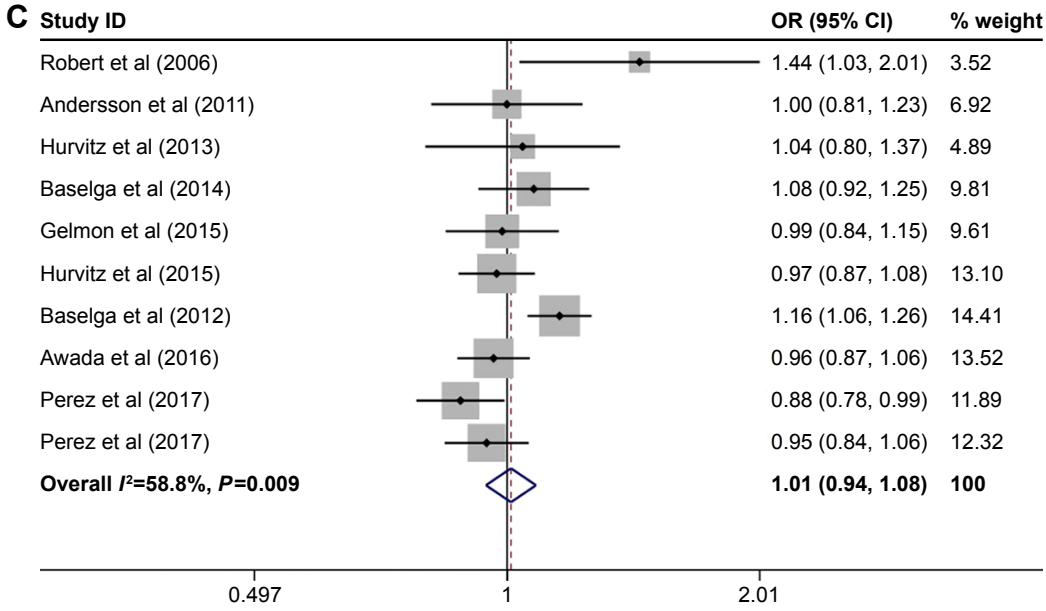


Figure 4 Forest plot of the direct comparison results.
Notes: Random-effects meta-analyses of the results, (**A**) PFS, (**B**) OS, and (**C**) ORR, among the treatment regimens' direct comparison with the TP regimen. The size of the gray shaded area indicates the weight of each study. Horizontal lines show 95% CIs. Weights are from random-effects analysis.
Abbreviations: PFS, progression-free survival; OS, overall survival; ORR, objective response rate.

by the TPC regimen (0.923) and MTP regimen (0.737). The probability rank to be number 1 were 70.3% for the PTP regimen, 27.9% for the TPC regimen, and 1.6% for the MTP regimen. For OS, the PTP regimen showed the highest SUCRA value (0.926), followed by the MTP regimen (0.794) and TPC regimen (0.670). Detailed information is presented in Figure 5. For ORR, the PTP regimen again showed ideal efficacy compared with the other regimens except for the TPC regimen (OR =0.92; 95% CI: 0.46–1.83), with no statistical difference. TPC may be the preferred regimen, with a probability of 57.3% (SUCRA: 0.935), followed by the PTP regimen (SUCRA: 0.927). Similar to PFS and OS, taxane alone showed the worst efficacy of all eleven regimens. The ORRs of the comparisons are summarized in Table 3 and Figure 5.

The safety of the regimens concerning hematologic toxicity and heart failure revealed that the MTP regimen (SUCRA: 0.99) likely had the largest influence and ETP (SUCRA: 0.901) may account for the heart failure, as presented in Table 4 and Figure 5.

Table 2 Network meta-analysis comparison of eleven therapies for PFS (bottom left) and OS (upper right)

TP	0.95 (0.43–2.08)	**1.98 (1.30–3.05)**	0.99 (0.70–1.40)	**0.90 (0.88–0.92)**	**1.47 (1.03–2.09)**
1.70 (1.04–2.78)	T-DM1	2.10 (0.86–5.16)	1.05 (0.44–2.48)	0.95 (0.43–2.10)	1.55 (0.66–3.69)
2.84 (2.11–3.83)	1.68 (0.94–2.98)	Taxane	**0.50 (0.29–0.86)**	**0.45 (0.30–0.70)**	**0.74 (0.58–0.94)**
1.06 (0.80–1.41)	0.63 (0.35–1.11)	**0.37 (0.25–0.56)**	TV	0.91 (0.64–1.29)	1.49 (0.90–2.44)
0.66 (0.59–0.73)	**0.39 (0.23–0.65)**	**0.23 (0.17–0.32)**	**0.62 (0.46–0.84)**	TPC	**1.63 (1.15–2.32)**
1.48 (1.20–1.83)	0.87 (0.51–1.49)	**0.52 (0.42–0.64)**	1.39 (0.98–1.98)	**2.24 (1.77–2.84)**	LP
0.84 (0.65–1.08)	**0.49 (0.28–0.86)**	**0.29 (0.20–0.44)**	0.79 (0.54–1.16)	1.27 (0.96–1.67)	**0.57 (0.41–0.79)**
0.89 (0.73–1.08)	**0.52 (0.31–0.89)**	**0.31 (0.22–0.45)**	0.84 (0.59–1.18)	**1.35 (1.08–1.69)**	**0.60 (0.45–0.80)**
0.62 (0.51–0.75)	**0.37 (0.22–0.62)**	**0.22 (0.15–0.31)**	**0.58 (0.41–0.82)**	0.94 (0.75–1.17)	**0.42 (0.31–0.56)**
1.02 (0.81–1.28)	0.60 (0.35–1.04)	**0.36 (0.25–0.52)**	0.96 (0.67–1.38)	**1.55 (1.20–1.98)**	**0.69 (0.51–0.94)**
1.624 (0.90–2.91)	0.96 (0.70–1.31)	0.57 (0.30–1.10)	1.53 (0.80–2.92)	**2.46 (1.36–4.46)**	1.10 (0.59–2.04)

Note: Bold values indicate the comparison is statistically significant.
Abbreviations: ETP, everolimus and trastuzumab plus taxane; LP, lapatinib plus taxane; MTP, NPLD and trastuzumab plus taxane; NP, neratinib plus taxane; NPLD, nonpegylated liposomal doxorubicin; OS, overall survival; PFS, progression-free survival; PTP, pertuzumab and trastuzumab plus taxane; T-DM1, trastuzumab emtansine; T-DM1+Pzmb, T-DM1 plus pertuzumab; TP, trastuzumab plus taxane; TPC, carboplatin and trastuzumab plus taxane; TV, trastuzumab plus vinorelbine.

Publication bias

The funnel plots did not demonstrate the obvious asymmetry for PFS, OS, and ORR (Figure 6). The *P*-values of Egger's test for the PFS, OS, and ORR were 0.062, 0.826, 0.475, respectively, and no significant publication bias was observed for the included articles.

Discussion

The emergence of trastuzumab has made a major breakthrough in the treatment of HER2-positive breast cancer. Since then, several trials relevant to anti-HER2 therapy were conducted, but confusion ensued regarding which was the preferred regimen because of the lack of direct comparisons among the different anti-HER2 regimens. Network analysis could help solve the confusion in some ways.

Our network analysis showed that, regarding treatment with dual anti-HER2 therapy, the PTP regimen was superior to the other treatments in both PFS and OS from the synthetic evidence. Followed by the TPC regimen, the trastuzumab-based triplets showed a statistically significant improvement in PFS/OS. In the terms of ORR, the TPC regimen was likely the optimal treatment, with no significant difference compared with the PTP regimen. A similar result for pathological complete response (pCR) was reported in another network analysis for neoadjuvant therapy for HER2-positive breast cancer.[33] Regarding dual anti-HER2 therapy using adjuvant chemotherapy in early breast cancer, the 3-year rate of invasive disease-free survival in the pertuzumab plus trastuzumab group was 92.0% compared with 90.2% in the trastuzumab group, in the subgroup of node-positive disease.[34] The cardiac events were infrequent in both groups, and only diarrhea of grade 3 or higher was more frequent in the combined group (9.8% vs 3.7%, respectively). Presently, the follow-up time is short, and future data are expected. The results agreed with those regarding the treatment of MBC in the CLEOPATRA trial.[9,10] No additional benefit regarding PFS or OS was noted for the subgroup of patients with non-visceral metastases, comparing the pertuzumab plus trastuzumab regimen with the trastuzumab plus docetaxel regimen.[10,35] The 5-year follow-up analysis of the patients in the neratinib group revealed fewer invasive disease-free survival events than that in the trastuzumab group (116 vs 163 events, respectively; HR =0.73; 95% CI: 0.57–0.92; *P*=0.0083) without increased AEs.[36]

Compared with mono anti-HER2 therapy, in the NEfERT-T trial, combined therapy with trastuzumab–paclitaxel and neratinib–paclitaxel had no superior efficacy in PFS or overall efficacy.[15] In the present network analysis, the SUCRA of neratinib–paclitaxel was less than that of trastuzumab–paclitaxel. Other dual anti-HER2 regimens, ETP and T-DM1+Pzmb, were also used to treat MBC but with no satisfactory result. There were no statistical differences in the PFS, OS, and ORR regarding the standard TP regimen (trastuzumab and taxane) for MBC, although the hormone receptor status of patients had an effect.[12] T-DM1 is recommended as a second-line or further-line treatment.[37]

For the regimen of T-DM1+Pzmb in the Phase III MARIANNE trial, no superiority was shown in survival compared with trastuzumab and taxane.[27,28] The TP regimen was shown to be superior to the T-DM1 regimen in the Phase II trial conducted by Hurvitz.[13] The difference in the findings need further analysis in future clinical trials. There was no direct comparison of the dual anti-HER2 therapy of

0.79 (0.61–1.03)	1.13 (0.90–1.42)	**0.68 (0.56–0.83)**	1.05 (0.76–1.45)	0.88 (0.37–2.08)
0.84 (0.36–1.94)	1.19 (0.53–2.72)	0.72 (0.32–1.63)	1.11 (0.47–2.61)	0.93 (0.65–1.32)
0.40 (0.24–0.66)	**0.57 (0.35–0.92)**	**0.34 (0.21–0.55)**	**0.53 (0.31–0.90)**	0.44 (0.17–1.16)
0.80 (0.52–1.24)	1.14 (0.75–1.73)	0.69 (0.46–1.03)	1.06 (0.66–1.71)	0.88 (0.35–2.25)
0.88 (0.66–1.15)	1.26 (0.99–1.58)	**0.76 (0.62–0.92)**	1.17 (0.84–1.61)	0.97 (0.41–2.31)
0.54 (0.35–0.84)	0.77 (0.50–1.17)	**0.46 (0.31–0.69)**	0.71 (0.44–1.15)	0.60 (0.23–1.52)
MTP	**1.42 (1.01–2.02)**	0.86 (0.62–1.20)	1.32 (0.87–2.01)	1.11 (0.45–2.74)
1.06 (0.77–1.47)	ETP	**0.60 (0.44–0.82)**	0.93 (0.62–1.38)	0.77 (0.32–1.89)
0.74 (0.54–1.02)	**0.70 (0.53–0.92)**	PTP	**1.54 (1.06–2.27)**	1.29 (0.53–3.12)
1.22 (0.87–1.72)	1.15 (0.85–1.54)	**1.64 (1.22–2.22)**	NP	0.84 (0.33–2.10)
1.94 (1.02–3.68)	1.83 (0.98–3.38)	**2.62 (1.42–4.83)**	1.59 (0.85–2.97)	T-DM1+Pzmb

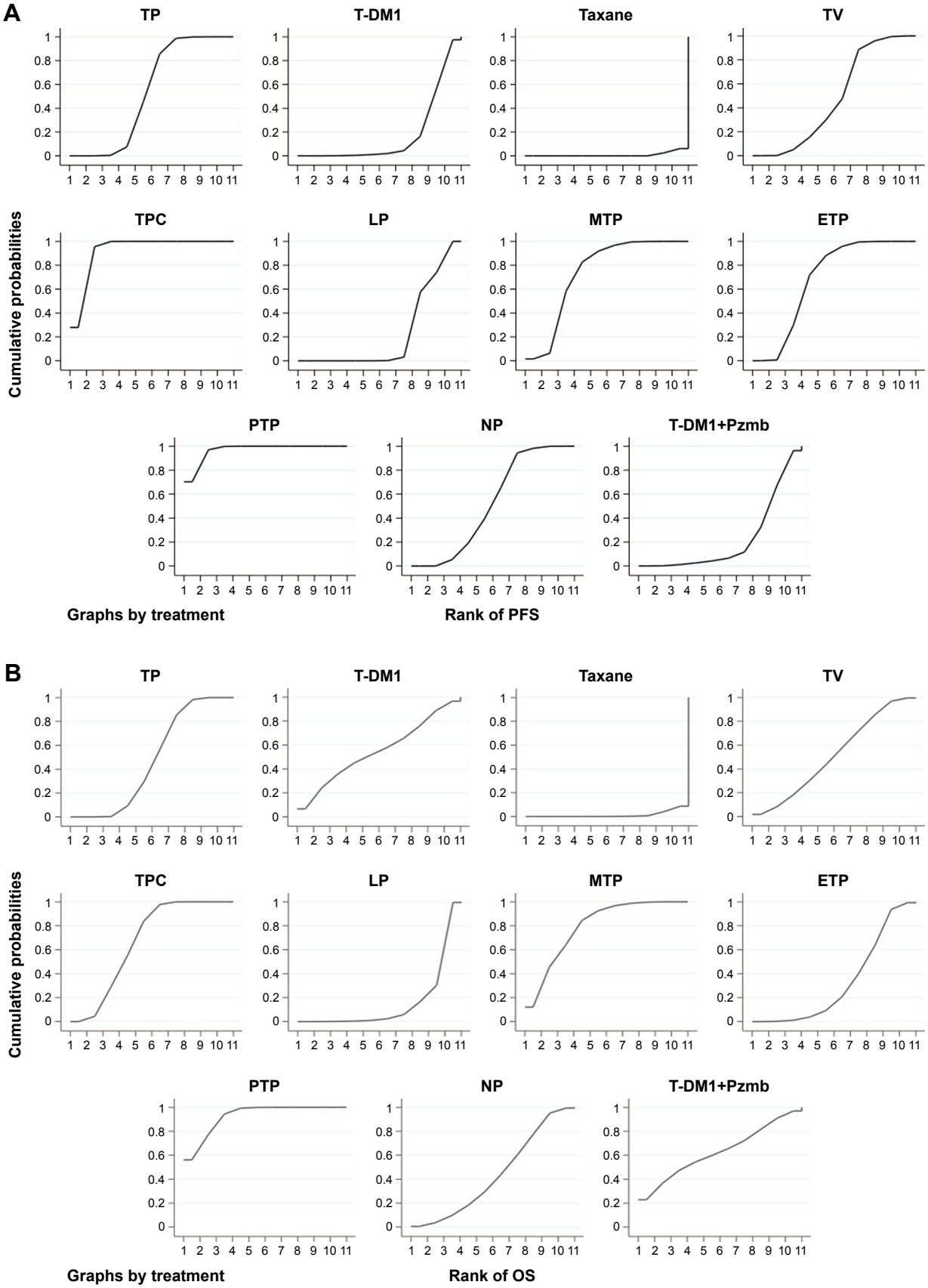
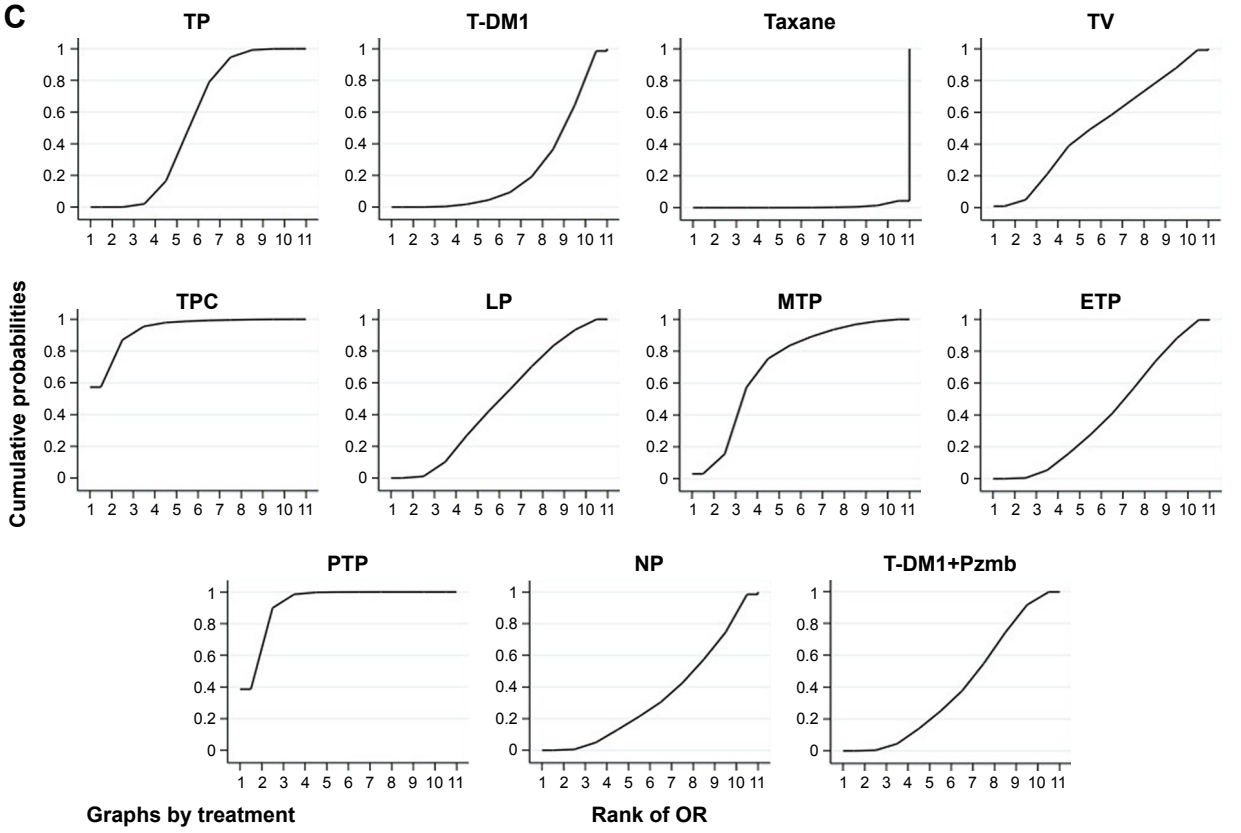
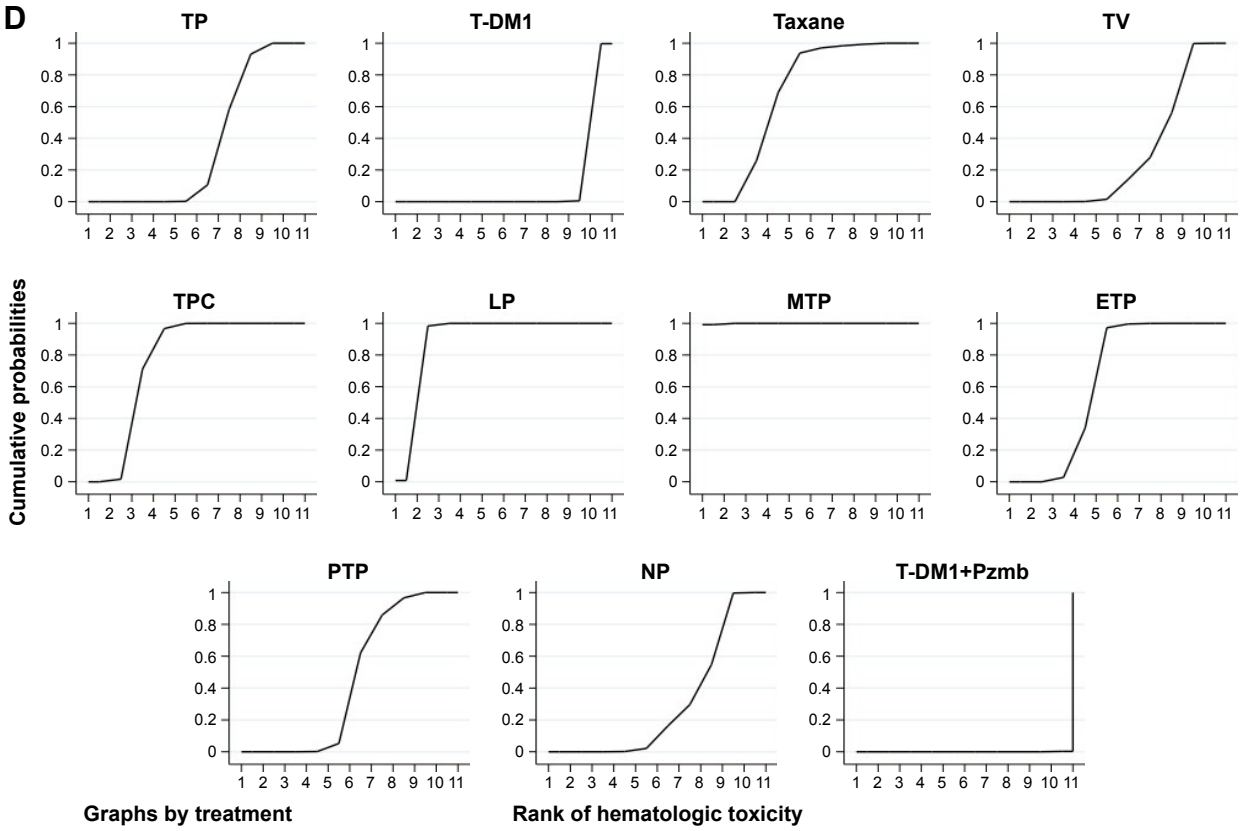


Figure 5 (*Continued*)





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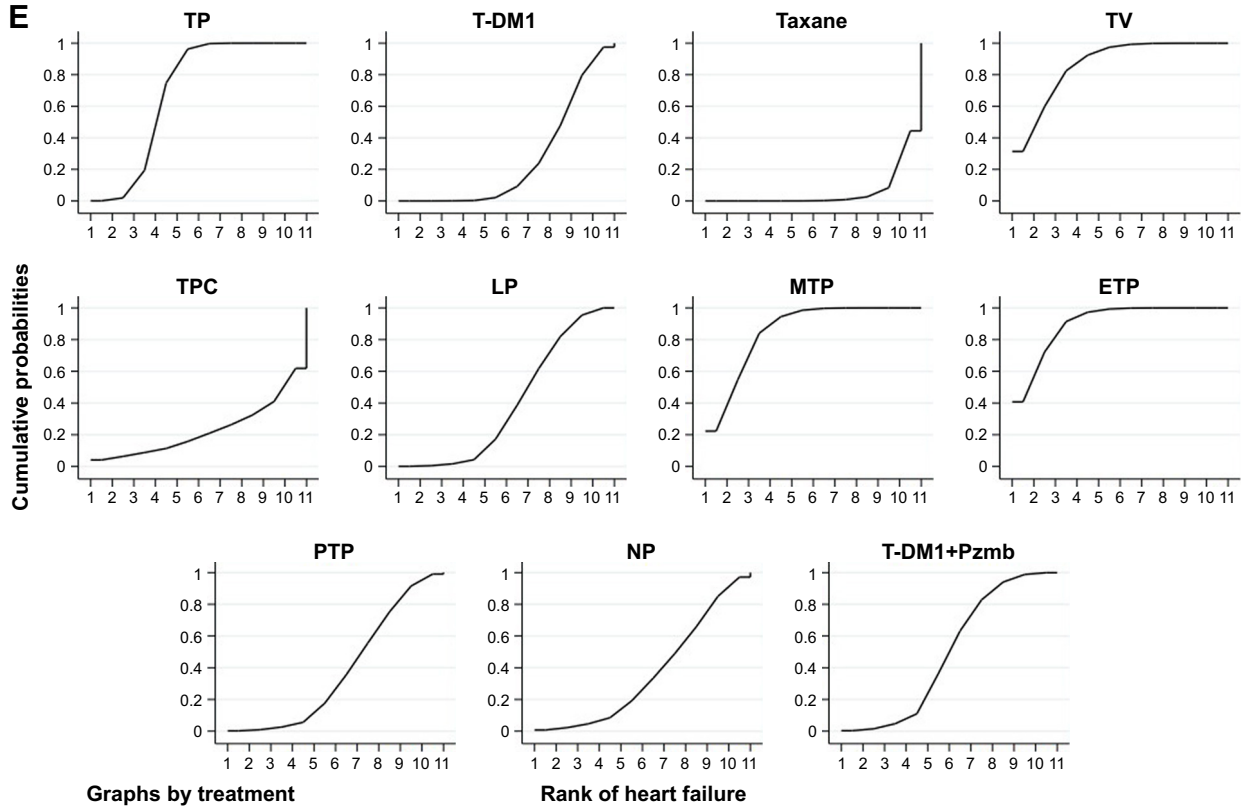

Figure 5 The SUCRA probability curve of the comparisons.

Notes: The SUCRA of (**A**) PFS, (**B**) OS, (**C**) ORR, (**D**) hematologic toxicity, and (**E**) heart failure among the treatment regimens. The larger the SUCRA, the higher the ranking.

Abbreviations: ETP, everolimus and trastuzumab plus taxane; LP, lapatinib plus taxane; MTP, NPLD and trastuzumab plus taxane; NP, neratinib plus taxane; NPLD, nonpegylated liposomal doxorubicin; PFS, progression-free survival; PTP, pertuzumab and trastuzumab plus taxane; ORR, objective response rate; OS, overall survival; SUCRA, surface under the cumulative ranking; T-DM1, trastuzumab emtansine; T-DM1+Pzmb, T-DM1 plus pertuzumab; TP, trastuzumab plus taxane; TPC, carboplatin and trastuzumab plus taxane; TV, trastuzumab plus vinorelbine.

lapatinib plus trastuzumab in the treatment of HER-2-positive MBC. MA.31 showed that the LP showed a shorter PFS and OS than TP for HER2-positive MBC.[32] The results were similar to those in the ALLTO trial, which showed that lapatinib and trastuzumab were not statistically superior to trastuzumab in neoadjuvant treatment.[38] Additionally, in vivo athymic mice[39] and the Phase I trial study[40] showed that the combination of lapatinib and trastuzumab produced

Table 3 Network meta-analysis comparison of eleven therapies for OR (bottom left)

TP				
0.79 (0.58–1.07)	T-DM1			
0.42 (0.25–0.70)	**0.53 (0.29–0.97)**	Taxane		
1.00 (0.60–1.67)	1.27 (0.70–2.31)	**2.38 (1.15–4.97)**	TV	
1.94 (1.08–3.51)	**2.46 (1.27–4.80)**	**4.63 (2.12–10.15)**	1.94 (0.89–4.27)	TPC
0.97 (0.69–1.37)	1.23 (0.78–1.95)	**2.32 (1.57–3.43)**	0.97 (0.52–1.80)	**0.50 (0.25–0.99)**
1.23 (0.80–1.90)	1.57 (0.92–2.66)	**2.94 (1.50–5.77)**	1.23 (0.63–2.42)	0.64 (0.31–1.31)
0.91 (0.65–1.27)	1.16 (0.74–1.82)	**2.17 (1.18–4.04)**	0.91 (0.49–1.70)	**0.47 (0.24–0.92)**
1.79 (1.27–2.55)	**2.27 (1.43–3.63)**	**4.28 (2.29–7.98)**	1.80 (0.96–3.36)	**0.92 (0.46–1.83)**
0.85 (0.56–1.30)	1.08 (0.64–1.82)	**2.04 (1.04–3.98)**	0.85 (0.44–1.67)	**0.44 (0.21–0.90)**
0.90 (0.65–1.25)	1.15 (0.83–1.58)	**2.15 (1.16–3.98)**	0.90 (0.49–1.67)	**0.47 (0.23–0.91)**

Note: Bold values indicate the comparison is statistically significant.

Abbreviations: ETP, everolimus and trastuzumab plus taxane; LP, lapatinib plus taxane; MTP, NPLD and trastuzumab plus taxane; NP, neratinib plus taxane; NPLD, nonpegylated liposomal doxorubicin; PTP, pertuzumab and trastuzumab plus taxane; T-DM1, trastuzumab emtansine; T-DM1+Pzmb, T-DM1 plus pertuzumab; TP, trastuzumab plus taxane; TPC, carboplatin and trastuzumab plus taxane; TV, trastuzumab plus vinorelbine.

good results in HER2-positive cell lines or advanced HER2-positive breast cancer.[35] For HER2-positive breast cancer with the failure of TP, the chemotherapy regimen can be replaced by vinorelbine plus trastuzumab as reported in the HERNATA trial.[8]

As multi-targeted therapy indicates higher toxic side effects and heavier economic burden, the clinical application should weigh the efficacy, toxicity, and economic factors. Meanwhile, the efficacy of multi-targeted therapy is uncertain. Thus, the traditional pairwise meta-analysis program was conducted to show the efficacy of combined multi-targeted regimens compared with the standard TP regimen. No difference was found in the random-effects model, with the I^2 value >50% indicating great inconsistency. The results suggested that trastuzumab and taxane remain the standard regimen of HER2-positive breast cancer, although with various combined anti-HER2 therapies.

Regarding the side effects of all the regimens, hematologic toxicity and abnormal left ventricular ejection fraction (LVEF) or heart failure were abstracted and analyzed in the present meta-analysis, which were the most common in the patients of HER2-positive breast cancer engaging in the antitumor treatment. Trastuzumab combined with chemotherapy drugs, especially anthracycline chemotherapy drugs, can increase myocardial damage and severe heart failure. Therefore, patients with recurrent MBC are not recommended for trastuzumab combined with anthracycline chemotherapy, and adjuvant trastuzumab therapy should be used after anthracycline chemotherapy. The risk of abnormal LVEF or heart failure was greatest in the ETP group, followed by the TV group and MTP group in the present analysis. The ORR of the top 3 in the hematologic toxicity comparison was cross 1, with no significant difference. The application of anthracycline drugs and trastuzumab can significantly increase cardiotoxicity, and the National Comprehensive Cancer Network (NCCN) and other guidelines do not recommend their simultaneous use. To reduce the side effects, sequential administration is advised. Nonpegylated liposomal doxorubicin (NPLD) produced by nanotechnology action on the tumor microvasculature can reduce the risk of the cardiac events.[41] The frequency of AEs was high with the MTP regimen. Additionally, for cardiac toxicity, there was no significant difference,[30] similar to the BOLERO-1 and HERNATA trials.[8,11]

The study provides insight into the treatment of metastatic HER2-positive breast cancer using a Bayesian statistical model. However, some limitations exist in the study. First, three of the studies were reported as open label, which would lead to measurement bias and performance bias, reducing the reliability of our review. Second, the number of included studies was small because only high-quality RCTs were included in our study, and some of the treatments lacked direct comparisons, which could generate inconsistency. Third, the estrogen receptor status in some studies was indistinct, and the biological differences may affect the prognosis, although endocrine therapy was excluded. Further studies could analyze the difference in the prognosis in subgroup analysis. Finally, regarding the safety analysis, we only focused on the most common side effects of hematologic toxicity and heart failure, which would omit some side effects of other regimens inevitably.

Conclusion

This network analysis showed that the PTP regimen might be the optimal first-line treatment for HER-2-positive MBC to improve the PFS and OS. The TPC regimen might be more

LP					
1.27 (0.73–2.21)	MTP				
0.94 (0.58–1.52)	0.74 (0.43–1.28)	ETP			
1.85 (1.13–3.01)	1.45 (0.83–2.54)	**1.96 (1.21–3.19)**	PTP		
0.88 (0.51–1.52)	0.69 (0.38–1.27)	0.94 (0.55–1.61)	**0.48 (0.27–0.82)**	NP	
0.93 (0.58–1.49)	0.73 (0.43–1.26)	0.99 (0.62–1.59)	**0.50 (0.31–0.82)**	1.06 (0.62–1.81)	T-DM1+Pzmb

Table 4 Network meta-analysis comparison of eleven therapies for hematologic toxicity (3/4) and cardiac events

TP	**0.28 (0.10–0.68)**	**0.07 (0.01–0.32)**	1.59 (0.69–3.84)	0.13 (0.00–3.00)
0.35 (0.23–0.52)	T-DM1	0.248 (0.03–1.52)	**5.66 (1.65–21.69)**	0.47 (0.00–12.56)
2.45 (1.03–6.61)	**7.16 (2.73–20.85)**	Taxane	**22.95 (4.06–163.3)**	1.84 (0.00–70.86)
0.873 (0.54–1.41)	**2.54 (1.35–4.77)**	**0.35 (0.12–0.96)**	TV	0.08 (0.00–2.11)
3.49 (1.93–6.44)	**10.16 (4.94–21.22)**	1.42 (0.45–4.13)	**4.00 (1.87–8.70)**	TPC
9.99 (4.71–24.76)	**29.14 (12.32–78.32)**	**4.08 (2.70–6.26)**	**11.49 (4.66–32.01)**	**2.88 (1.09–8.46)**
38.44 (20.97–75.32)	**112.00 (53.90–245.50)**	**15.69 (4.90–47.02)**	**44.16 (20.41–100.50)**	**11.04 (4.67–26.88)**
1.92 (1.28–2.95)	**5.59 (3.14–10.13)**	0.78 (0.27–2.07)	**2.21 (1.18–4.18)**	0.55 (0.27–1.14)
1.13 (0.86–1.49)	**3.28 (2.01–5.43)**	0.46 (0.17–1.15)	1.30 (0.75–2.26)	**0.32 (0.17–0.62)**
0.87 (0.51–1.48)	**2.53 (1.30–4.95)**	**0.35 (0.12–0.99)**	1.00 (0.49–2.03)	**0.25 (0.11–0.55)**
0.13 (0.06–0.25)	**0.38 (0.17–0.75)**	**0.05 (0.02–0.16)**	**0.15 (0.06–0.33)**	**0.04 (0.01–0.09)**

Notes: Data are the ORs and 95% credibility intervals (95% CI) in the column-defining treatment compared with those in the row-defining treatment. OR <1 favors the column-defining treatment. The bold indicates the comparison is statistically significant.

Abbreviations: ETP, everolimus and trastuzumab plus taxane; LP, lapatinib plus taxane; MTP, NPLD and trastuzumab plus taxane; NP, neratinib plus taxane; NPLD, nonpegylated liposomal doxorubicin; PFS, progression-free survival; PTP, pertuzumab and trastuzumab plus taxane; OS, overall survival; T-DM1, trastuzumab emtansine; T-DM1+Pzmb, T-DM1 plus pertuzumab; TP, trastuzumab plus taxane; TPC, carboplatin and trastuzumab plus taxane; TV, trastuzumab plus vinorelbine.

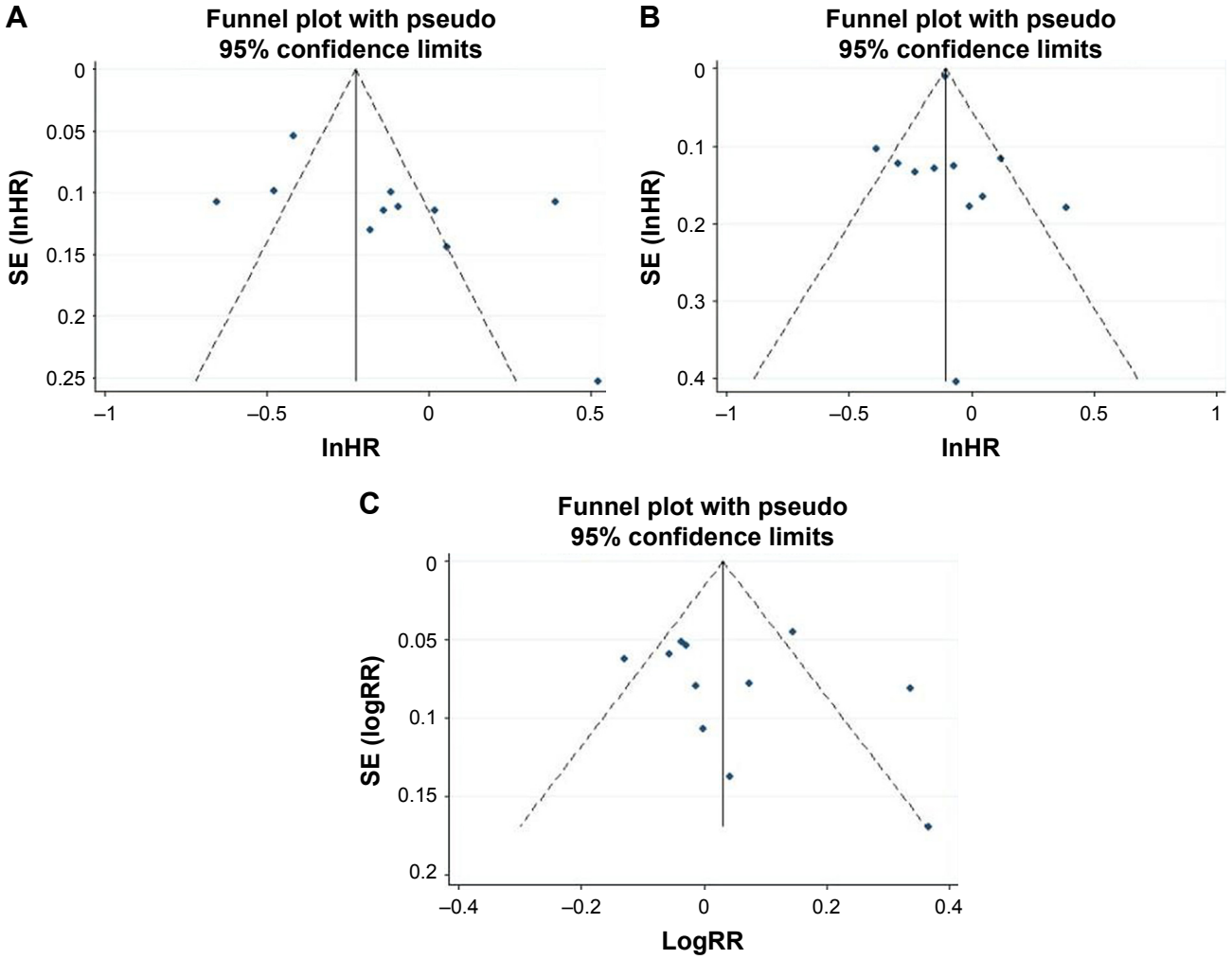

Figure 6 Funnel plot for publication bias.

Notes: (**A**) PFS, (**B**) OS, and (**C**) ORR.

Abbreviations: PFS, progression-free survival; ORR, objective response rate; OS, overall survival; SE, standard error.

0.45 (0.17–1.09)	1.50 (0.77–2.96)	1.76 (0.88–3.84)	**0.42 (0.13–1.19)**	0.38 (0.08–1.45)	0.58 (0.24–1.32)
1.57 (0.42–6.14)	**5.34 (1.74–18.21)**	**6.26 (1.99–22.57)**	1.48 (0.33–6.34)	1.35 (0.22–7.27)	2.04 (0.69–6.44)
6.18 (1.96–28.8)	**21.56 (4.15–143.20)**	**25.34 (4.74–173.70)**	5.96 (0.89–46.49)	5.45 (0.61–50.25)	**8.27 (1.44–58.78)**
0.28 (0.07–0.95)	0.94 (0.32–2.77)	1.11 (0.36–3.46)	0.26 (0.06–1.01)	0.24 (0.04–1.16)	0.36 (0.10–1.18)
3.376 (0.13–1,547)	11.45 (0.47–5,263)	13.50 (0.54–6,225)	3.20 (0.11–1,522)	2.91 (0.09–1,427)	4.41 (0.17–2,023)
LP	**3.40 (1.12–11.13)**	**3.98 (1.26–13.79)**	0.94 (0.21–3.95)	0.86 (0.14–4.52)	1.30 (0.37–4.71)
3.84 (1.30–10.52)	MTP	1.17 (0.44–3.25)	**0.28 (0.07–0.96)**	0.25 (0.05–1.13)	0.38 (0.13–1.11)
0.19 (0.07–0.46)	**0.05 (0.02–0.10)**	ETP	**0.24 (0.06–0.84)**	**0.21 (0.04–0.98)**	**0.33 (0.10–0.98)**
0.11 (0.04–0.25)	**0.03 (0.01–0.06)**	**0.59 (0.35–0.97)**	PTP	0.91 (0.14–5.43)	1.39 (0.35–5.81)
0.09 (0.03–0.22)	**0.02 (0.01–0.005)**	**0.45 (0.23–0.88)**	0.77 (0.42–1.40)	NP	1.52 (0.30–9.07)
0.01 (0.00–0.04)	**0.00 (0.00–0.01)**	**0.07 (0.03–0.14)**	**0.11 (0.05–0.23)**	**0.15 (0.06–0.34)**	T-DM1+Pzmb

efficient in the ORR. The two regimens showed no additional hematologic toxicity and heart failure.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist*. 2009;14(4):320–368.
2. Moasser MM. The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. *Oncogene*. 2007; 26(45):6469–6487.
3. Vogel UF. Confirmation of a low HER2 positivity rate of breast carcinomas – limitations of immunohistochemistry and in situ hybridization. *Diagn Pathol*. 2010;5:50.
4. Wolff AC, Hammond MEH, Schwartz JN, et al. American Society of clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol*. 2006;25(1):118–145.
5. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol*. 2014;32(33):3744–3752.
6. von Minckwitz G, Schwedler K, Schmidt M, et al; GBG 26/BIG 03-05 study group and participating investigators. Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. *Eur J Cancer*. 2011; 47(15):2273–2281.
7. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2–Positive metastatic breast cancer administered as first-line treatment: the M77001 Study Group. *J Clin Oncol*. 2005;23(19):4265–4274.
8. Andersson M, Lidbrink E, Bjerre K, et al. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. *J Clin Oncol*. 2011;29(3):264–271.
9. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366(2):109–119.
10. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015; 372(8):724–734.
11. Hurvitz SA, Andre F, Jiang Z, et al. Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial. *Lancet Oncol*. 2015;16(7): 816–829.
12. Yardley D, Hurvitz S, Jiang Z-F, et al. Abstract P4-22-13: everolimus plus trastuzumab and paclitaxel as first-line therapy in women with HER2+ advanced breast cancer: overall survival results from BOLERO-1. *Cancer Res*. 2017;77(4):P4-22-13.
13. Hurvitz SA, Dirix L, Kocsis J, et al. Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol*. 2013;31(9):1157–1163.
14. Leung HWC, Leung JH, Chan ALF. Efficacy and safety of a combination of HER2-targeted agents as first-line treatment for metastatic HER2-positive breast cancer: a network meta-analysis. *Expert Opin Drug Saf*. 2018;17(1):1–7.
15. Awada A, Colomer R, Inoue K, et al. Neratinib plus paclitaxel vs trastuzumab plus paclitaxel in previously untreated metastatic ErbB2-positive breast cancer: the NEfERT-T randomized clinical trial. *JAMA Oncol*. 2016;2(12):1557–1564.
16. Davis MI, Hunt JP, Herrgard S, et al. Comprehensive analysis of kinase inhibitor selectivity. *Nat Biotechnol*. 2011;29(11):1046–1051.
17. Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res*. 2008;17(3):279–301.
18. Barbui C, Cipriani A. What are evidence-based treatment recommendations? *Epidemiol Psychiatr Sci*. 2011;20(1):29–31.
19. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011; 343:d5928.
20. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One*. 2013;8(10):e76654.
21. Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. *BMC Med Res Methodol*. 2010;10(1):54.

22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.
23. Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ*. 2005;331(7521):897–900.
24. White IR, Barrett JK, Jackson D. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Syn Meth*. 2012;3(2):111–125.
25. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol*. 2015;15(1):58.
26. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23(20):3105–3124.
27. Perez EA, Barrios C, Eiermann W, et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: primary results from the phase III MARIANNE study. *J Clin Oncol*. 2017;35(2):141–148.
28. Perez EA, Barrios CH, Eiermann W, et al. Phase III, randomized study of first-line trastuzumab emtansine (T-DM1) ± pertuzumab (P) vs. trastuzumab + taxane (HT) treatment of HER2-positive MBC: final overall survival (OS) and safety from MARIANNE. *J Clin Oncol*. 2017;35(15):1003.
29. Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2006;24(18):2786–2792.
30. Baselga J, Manikhas A, Cortés J, et al. Phase III trial of nonpegylated liposomal doxorubicin in combination with trastuzumab and paclitaxel in HER2-positive metastatic breast cancer. *Ann Oncol*. 2014;25(3):592–598.
31. Guan Z, Xu B, Desilvio ML, et al. Randomized trial of lapatinib versus placebo added to paclitaxel in the treatment of human epidermal growth factor receptor 2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2013;31(16):1947–1953.
32. Gelmon KA, Boyle FM, Kaufman B, et al. Lapatinib or trastuzumab plus taxane therapy for human epidermal growth factor receptor 2-positive advanced breast cancer: final results of NCIC CTG MA.31. *J Clin Oncol*. 2015;33(14):1574–1583.
33. Nagayama A, Hayashida T, Jinno H, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. *J Natl Cancer Inst*. 2014;106(9):dju203.
34. von Minckwitz G, Procter M, de Azambuja E, et al; APHINITY Steering Committee and Investigators. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377(2):122–131.
35. Loibl S, Gianni L. HER2-positive breast cancer. *Lancet*. 2017;389(10087):2415–2429.
36. Martin M, Holmes FA, Ejlertsen B, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(12):1688–1700.
37. Krop IE, Kim SB, González-Martín A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15(7):689–699.
38. Piccart-Gebhart M, Holmes E, Baselga J, et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. *J Clin Oncol*. 2016;34(10):1034–1042.
39. Konecny GE, Pegram MD, Venkatesan N, et al. Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells. *Cancer Res*. 2006;66(3):1630–1639.
40. Storniolo AM, Pegram MD, Overmoyer B, et al. Phase I dose escalation and pharmacokinetic study of lapatinib in combination with trastuzumab in patients with advanced ErbB2-positive breast cancer. *J Clin Oncol*. 2008;26(20):3317–3323.
41. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783–792.