Received: 11 January 2024 | Accepted: 2 March 2024

DOI: 10.1002/cai2.126

CANCER INNOVATION

META-ANALYSIS

Efficacy and safety of first-line regimens for advanced HER2-positive breast cancer: A Bayesian network meta-analysis

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Funding information
National Key Research and Development Program of China, Grant/Award Number: 2021YFF1201300; National Natural Science Foundation of China, Grant/Award Number: 82230058

Abstract

Background: The current standard of care for advanced human epidermal growth factor receptor 2 (HER2)-positive breast cancer is pertuzumab plus trastuzumab and docetaxel as first-line therapy. However, with the development of newer treatment regimens, there is a lack of evidence regarding which is the optimal treatment strategy. The aim of this network meta-analysis was to evaluate the efficacy and safety of first-line regimens for advanced HER2-positive breast cancer by indirect comparisons.

Methods: A systematic review and Bayesian network meta-analysis were conducted. The PubMed, EMBASE, and Cochrane Library databases were searched for relevant articles published through to December 2023. The hazard ratio (HR) and 95% credible interval (CrI) were used to compare progression-free survival (PFS) between treatments, and the odds ratio and 95% CrI were used to compare the objective response rate (ORR) and safety.

Results: Twenty randomized clinical trials that included 15 regimens and 7094 patients were analyzed. Compared with the traditional trastuzumab and docetaxel regimen, PFS was longer on the pyrotinib and trastuzumab plus docetaxel regimen (HR: 0.41, 95% CrI: 0.22–0.75) and the pertuzumab and trastuzumab plus docetaxel regimen (HR: 0.65, 95% CrI: 0.43–0.98). Consistent with the results for PFS, the ORR was better on the pyrotinib and trastuzumab plus docetaxel regimen and the pertuzumab and trastuzumab plus docetaxel regimen than on the traditional trastuzumab and docetaxel regimen. The surface under the cumulative ranking curve indicated that the pyrotinib and trastuzumab plus docetaxel regimen was most likely to rank first in achieving

Abbreviations: AEs, adverse events; Bev, bevacizumab; CI, confidence interval; CrI, credible interval; Eve, everolimus; H, trastuzumab; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; Lapa, lapatinib; Nera, neratinib; NPLD, nonpegylated liposomal doxorubicin; ORR, objective response rate; ORs, odds ratios; OS, overall survival; P, pertuzumab; PBO, placebo; PFS, progression-free survival; PRISMA, preferred reporting items for systematic reviews and meta-analyses; Pyro, pyrotinib; RCTs, randomized controlled trials; SUCRA, surface under the cumulative ranking curve; T, taxane; TCbH, trastuzumab + paclitaxel/docetaxel + carboplatin; T-DM1, trastuzumab emtansine; TH, trastuzumab + docetaxel/paclitaxel; TKI, tyrosine kinase inhibitor; TTP, time to progression; VRN, vinorelbine; X, capecitabine.

the best PFS and ORR. Comparable results were found for grade ≥3 AE rates of ≥10%.

Conclusions: Our results suggest that the pyrotinib and trastuzumab plus docetaxel regimen is most likely to be the optimal first-line therapy for patients with HER2-positive breast cancer.

KEYWORDS

Bayesian network meta-analysis, first-line treatment, HER2-positive breast cancer

1 | INTRODUCTION

Breast cancer is the most commonly diagnosed malignancy in female patients worldwide. Approximately, 15%–20% of breast cancers are human epidermal growth factor receptor 2 (HER2) positive with an aggressive nature and a poor prognosis [1, 2]. During the past few decades, with the emergence of HER2-targeted agents, the survival outcomes for patients with HER2-positive breast cancer have improved significantly [3]. Based on the results of the CLEOPATRA study [4, 5], the current standard of care for patients with HER2-positive breast cancer in the first-line setting is dual HER2 blockade plus chemotherapy (pertuzumab + trastuzumab + docetaxel).

Several randomized controlled trials (RCTs) have investigated new treatment regimens and agents, such as pyrotinib, lapatinib, bevacizumab, and neratinib and reported favorable clinical outcomes [6–9]. Consequently, there is increasing interest in which regimen might be optimal for patients with HER2-positive breast cancer.

Although many head-to-head studies and pairwise meta-analyses have been conducted, they have all used direct comparisons, and thus, they have not been able to answer the question of which is the optimal treatment [10, 11]. Furthermore, the clinical trials and corresponding treatment strategies included in these studies need to be updated.

Therefore, we conducted this Bayesian network meta-analysis to compare all first-line treatment regimens that have been investigated in RCTs for patients with HER2-positive breast cancer. Our aims were to (1) identify potential treatment options other than the current standard of care by synthesizing direct and indirect evidence of clinical benefits and safety profiles and (2) determine the overall ranking probabilities of progression-free survival (PFS) and objective response rate (ORR) to provide a reference for choosing the optimal regimen in clinical practice.

2 | METHODS

This Bayesian network meta-analysis was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension statement [12] (Table S1). The protocol was registered in PROSPERO (CRD42024496986). The Bayesian approach was used to compare different treatments by combining direct and indirect information and to estimate the effectiveness and safety rankings of the interventions [13].

2.1 | Data sources and search strategy

We searched the PubMed, EMBASE, and Cochrane Library databases for relevant phase II/phase III RCTs published through to December 2023 using the search terms “HER2,” “breast cancer,” “first-line,” “advanced,” and “randomized controlled trial.” Further details of the search strategies are provided in Table S2.

2.2 | Study selection

Phase II/III RCTs that met the following criteria were included: patients with advanced HER2-positive breast cancer who received first-line treatments; PFS, time to progression (TTP), or ORR reported; PFS and TTP defined as time from randomization to disease progression or death, whichever occurred first; ORR defined as the proportion of patients who obtained a complete or partial response after first-line treatment; and adverse events (AEs) evaluated and graded by the NCI Common Terminology Criteria for Adverse Events. Study protocols, abstracts without full text available, retrospective studies, and post hoc studies of RCTs were excluded.

Titles and abstracts were screened before obtaining the full-text versions. When long-term follow-up and updated data were reported for the same clinical trial, only the most recent and mature data were included.

2.3 | Data extraction and quality assessment

Detailed data were extracted from RCTs by two authors working independently. Differences in opinions were discussed until consensus was reached. Trial information, including study ID, first author, publication year, number of patients enrolled, and patient characteristics, was recorded. The hazard ratios (HRs) and odds ratios (ORs) for study outcomes of PFS, TTP, ORR, and grade ≥3 AE rates of ≥10% with a corresponding effect size were collected and compared.

The Cochrane risk-of-bias tool (2.0) was used to assess the quality of each study. The assessment was conducted based on five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, and selection of the reported results. The results for these five domains were then synthesized and categorized as low risk, high risk, or some concerns.

2.4 | Statistical analysis

The primary study outcome was PFS, and the secondary outcomes were the ORR and grade ≥3 AE rates of ≥10%. Effect sizes of the PFS were compared using the HR with the 95% credible intervals (CrIs), and effect sizes of the ORR and grade ≥3 AE rates of ≥10% were compared using ORs with the 95% CrIs.

This Bayesian network meta-analysis was performed with a Markov Chain Monte Carlo simulation to compare and rank the treatment effects obtained from indirect comparisons of different treatments. The heterogeneity between trials was calculated using the Q test and I^2 statistic, with low heterogeneity defined as an I^2 value below 25%, moderate heterogeneity as an I^2 value between 25% and 50%, and high heterogeneity as an I^2 value over 50%. For each outcome measure, Markov chains were established by running 10,000 burn-ins and 50,000 sample iterations with one step size iteration using a fixed-effect consistency model if I^2 was not over 50% and a random-effects consistency model for high heterogeneity (I^2 greater than 50%). Publication bias was assessed using a funnel plot. Subgroup analyses of PFS and ORR were performed for patients who received dual-targeted regimens. The Bayesian approach also provided overall ranking probabilities for each combination of dual-targeted drugs, and each outcome measurement was ranked from best to worst by calculating the surface under the cumulative ranking curve (SUCRA). Consistency between direct and indirect results was not analyzed because there was only one closed loop in the network plot from the MARIANNE study. All statistical analyses were performed using R software (version 4.1.3) with package gemtc (version 1.0-2) and JAGS software (version 4.3.0). A two-sided p-value of 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Systematic review and study characteristics

A total of 3431 potentially relevant articles were identified in the PubMed, EMBASE, and Cochrane Library databases. After initial review, 3336 irrelevant records and duplicates were removed. After screening of the titles and abstracts of the remaining articles, 26 articles were subjected to full-text review. Finally, 20 RCTs with 7094 participants were included [5–7, 9, 14–29] (Figure 1). Of note, no link to the network could be made for the VEG20007 study (lapatinib plus pazopanib vs. lapatinib monotherapy); so, this study was not included in the comparison. Detailed baseline data are shown for each study in Table 1.

3.2 | Progression-free survival

All the PFS data for the 18 studies and 15 regimens were compared (Figure S1a). PFS was better for combination therapies that included both targeted and chemotherapy agents than for trastuzumab monotherapy, with the exception of the lapatinib plus paclitaxel regimen (HR: 2.13, 95% CrI: 0.99–4.67). Compared with the traditional trastuzumab plus docetaxel/paclitaxel regimen, PFS was improved in patients who received the pyrotinib and trastuzumab plus docetaxel regimen (HR: 0.41, 95% CrI: 0.22–0.75) or the pertuzumab and trastuzumab plus docetaxel regimen (HR: 0.65, 95% CrI: 0.43–0.98) (Figure S1b,c).

Indirect comparisons of the five treatment regimens that included dual-targeted agents were also conducted (Figure 2a). These regimens included pertuzumab plus trastuzumab plus docetaxel, trastuzumab plus paclitaxel plus everolimus, T-DM1 plus pertuzumab, bevacizumab plus trastuzumab plus docetaxel, and pyrotinib plus trastuzumab plus docetaxel, which encompass all currently available dual-targeted combinations with results available from RCTs. The lapatinib plus pazopanib regimen in the VEG20007 study was not included because of inability to connect to the network. The trastuzumab and docetaxel regimen was included as a transitivity node. The only significant difference found was between the pyrotinib and trastuzumab plus docetaxel regimen and the trastuzumab plus docetaxel regimen (HR: 0.41, 95% CrI: 0.17–0.99). No statistically significant differences were found among any of the other regimens that used dual-targeted agents (Figure 2b,c).

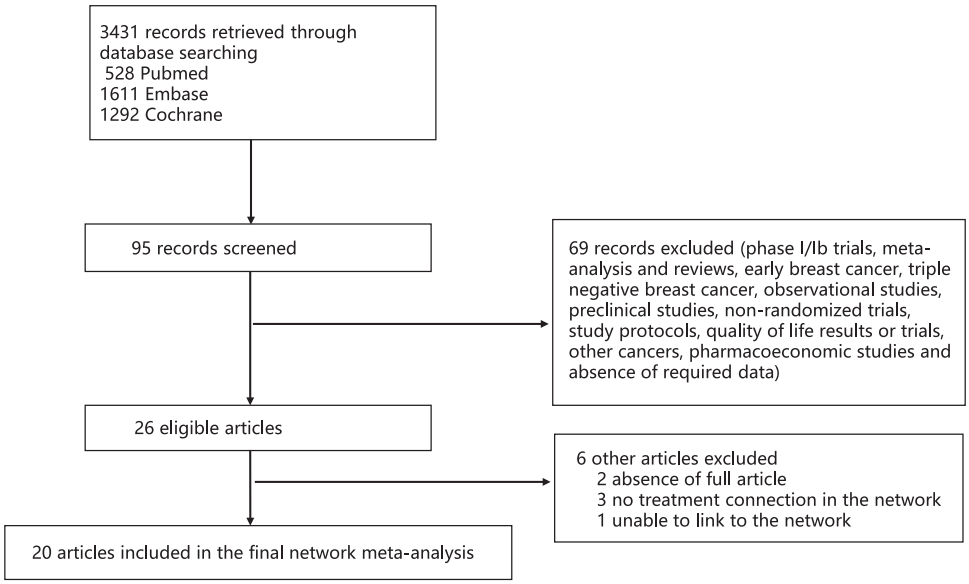

FIGURE 1 Flowchart showing the study selection process.

The SUCRA values indicated that the pyrotinib and trastuzumab plus docetaxel regimen was most likely to rank first for PFS (92.53%), followed by the pertuzumab and trastuzumab plus docetaxel regimen (69.19%), the trastuzumab plus docetaxel plus bevacizumab regimen (45.28%), and the T-DM1 plus pertuzumab regimen (38.39%) (Figure 2d).

3.3 | Objective response rate

In terms of the ORR, data available for 13 studies with 12 regimens were compared. The ORR was significantly better for the pyrotinib and trastuzumab plus docetaxel regimen (OR: 0.02, 95% CrI: 0–0.56) and the trastuzumab plus docetaxel/paclitaxel regimen (OR: 0.08, 95%: CrI 0.01–0.84) than for trastuzumab monotherapy, which is consistent with the PFS results (Figure S2a–c).

We also compared the ORR results for dual-targeted therapies from four studies (Figure 3a). These treatment regimens included pertuzumab plus trastuzumab plus docetaxel, trastuzumab plus paclitaxel plus everolimus, T-DM1 plus pertuzumab, and pyrotinib plus trastuzumab plus docetaxel. The bevacizumab plus trastuzumab plus docetaxel regimen was not included because of lack of available ORR data, and the lapatinib plus pazopanib regimen was not included because of inability to link to the network. The trastuzumab and docetaxel regimen was regarded as a transitivity node. There were no significant differences between the treatment regimens (Figure 3b,c). The pyrotinib and trastuzumab plus docetaxel regimen was most likely to rank first for ORR (89.78%), followed by the pertuzumab and trastuzumab plus docetaxel regimen (64.57%) and the trastuzumab and docetaxel regimen (36.33%) (Figure 3d).

3.4 | Adverse events

Our analysis of grade ≥3 AE rates of ≥10% included all 7 studies that assessed AEs by the NCI Common Terminology Criteria from Adverse Events (Figure 4a), and the results were comparable (Figure 4b). The trastuzumab and vinorelbine regimen ranked last for causing grade ≥3 AE rates of ≥10% (9.85%), while the nonpegylated liposomal doxorubicin and trastuzumab plus paclitaxel regimen had the highest possibility of ranking first for toxicities (89.44%) (Figure S3).

3.5 | Quality assessment and publication bias

Publication bias was assessed for the dual-targeted regimens. The funnel plots were symmetrical, indicating absence of publication bias (Figure S4a–c). The quality of the included studies was assessed using the Cochrane risk-of-bias tool (2.0). The majority of studies were found to have a low risk of bias (Figure S5).

4 | DISCUSSION

This network meta-analysis compared the efficacy and safety of the first-line treatments used in patients with advanced HER2-positive breast cancer. All treatment

TABLE 1 Baseline characteristics of studies.

Study (phase, design)	Source (year)	Registered ID	Sample size	Intervention arm	Control arm	Reported outcomes
M77001 (II, open-label)	J Clin Oncol (2005)	NA	188 (1:1)	trastuzumab + docetaxel	docetaxel	ORR, OS, TTP, TTF, and safety
TPCb (III, open-label)	J Clin Oncol (2006)	NCT00542191	196 (1:1)	trastuzumab + paclitaxel + carboplatin	trastuzumab + paclitaxel	ORR, PFS, and safety
TRAVIOTA (III, open-label)	Cancer (2007)	NA	81 (1:1)	trastuzumab + vinorelbine	trastuzumab + taxane therapy	ORR, TTP, TTF, and safety
LapaT2008 (III, double-blind)	J Clin Oncol (2008)	NA	579 (1:1)	lapatinib + paclitaxel	paclitaxel	TTP, OS, EFS, and safety
JO17360 (III, open-label)	Breast Cancer Res Treat (2010)	NA	112 (1:1)	trastuzumab	trastuzumab + docetaxel	PFS, OS, ORR, TTF, and safety
CHAT (II, open-label)	J Clin Oncol (2010)	NA	225 (1:1)	trastuzumab + docetaxel + capecitabine	trastuzumab + docetaxel	ORR, PFS, TTP, OS, and safety
HERNATA (III, open-label)	J Clin Oncol (2011)	NCT03811418	284 (1:1)	trastuzumab + vinorelbine	trastuzumab + docetaxel	TTP, OS, ORR, TTF, and safety
BCIRG 007 (III, open-label)	J Clin Oncol (2011)	NA	263 (1:1)	trastuzumab + carboplatin + docetaxel	trastuzumab + docetaxel	TTP, OS, and safety
HERTAX (II, open-label)	Clin Breast Cancer (2011)	NA	101 (1:1)	trastuzumab	trastuzumab + docetaxel	PFS, OS, and safety
AVEREL (III, open-label)	J Clin Oncol (2013)	NCT00391092	424 (1:1)	bevacizumab + trastuzumab + docetaxel	trastuzumab + docetaxel	PFS, OS, ORR, and safety
LapaT2013 (III, double-blind)	J Clin Oncol (2013)	NCT00281658	444 (1:1)	lapatinib + paclitaxel	paclitaxel	OS, PFS, ORR, and safety
TDM4450g (II, open-label)	J Clin Oncol (2013)	NCT00679341	137 (1:1)	T-DM1	trastuzumab + docetaxel	PFS, OS, ORR, and safety
NPLD (III, open-label)	Ann Oncol (2014)	NCT00294996	363 (1:1)	nonpegylated liposomal doxorubicin + trastuzumab + paclitaxel	trastuzumab + paclitaxe	PFS, OS, and safety
BOLERO-1 (III, double-blind)	Lancet Oncol (2015)	NCT00876395	719 (2:1)	trastuzumab + paclitaxel + everolimus	trastuzumab + paclitaxel	PFS and safety
MA.31 (III, open-label)	J Clin Oncol (2015)	NCT00667251	652 (1:1)	lapatinib + taxane	trastuzumab + taxane	ITT, PFS, and safety

(Continues)

TABLE 1 (Continued)

Study (phase, design)	Source (year)	Registered ID	Sample size	Intervention arm	Control arm	Reported outcomes
NEfERT-T (III, open-label)	JAMA Oncol (2016)	NCT00915018	479 (1:1)	neratinib + paclitaxel	trastuzumab + paclitaxel	PFS, ORR, and safety
MARIANNE (III, open-label)	J Clin Oncol (2017)	NCT01120184	1095 (1:1:1)	T-DM1 + placebo and T-DM1 + pertuzumab	trastuzumab + taxane	PFS, OS, ORR, and safety
CLEOPATRA (III, double-blind)	Lancet Oncol (2020)	NCT00567190	1196 (1:1)	pertuzumab + trastuzumab + docetaxel	trastuzumab + docetaxel	PFS, OS, ORR, and safety
PUFFIN (III, double-blind)	Breast Cancer Res Treat (2020)	NCT02896855	243 (1:1)	pertuzumab + trastuzumab + docetaxel	trastuzumab + docetaxel	PFS, OS, ORR, and safety
PHILA (III, double-blind)	BMJ (2023)	NCT03863223	590 (1:1)	pyrotinib + trastuzumab + docetaxel	trastuzumab + docetaxel	PFS, OS, ORR, and safety

Abbreviations: EFS, event-free survival; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure; TTP, time to progression.

strategies with available PFS, ORR, and safety data were compared. The PFS and ORR results in studies with dual-targeted agents were analyzed further. After comprehensive analysis, the main results were as follows: PFS was longer for all dual-target therapies than for chemotherapy alone with the exception of T-DM1 plus pertuzumab, indicating that, overall, dual-targeted regimens have better efficacy; there was no significant difference in PFS or ORR between the dual-targeted therapies; combination therapy with pyrotinib and trastuzumab plus docetaxel had the highest probability of ranking first for PFS and ORR, which was consistent with the clinical results; and toxicities were comparable for all treatment regimens with available data, indicating that the pyrotinib and trastuzumab plus docetaxel regimen has the best balance of efficacy and safety.

The primary outcome in this study was PFS. Compared with the traditional trastuzumab plus docetaxel regimen, PFS was inferior on chemotherapy alone (HR: 2.84, 95% CrI: 1.34–6.02) and on trastuzumab monotherapy (HR: 3.15, 95% CrI: 1.91–5.29), which is in line with the findings of the JO17360 and M77001 trials [14, 17]. There was no statistically significant difference in PFS between the combination of T-DM1 plus pertuzumab and the other regimens, which is consistent with the results of the phase III MARIANNE study, in which no significant differences were found between the T-DM1 plus pertuzumab group and the T-DM1 monotherapy group (HR: 0.91, 97.5% confidence interval (CI): 0.73–1.13) [8]. The latest survival outcomes were updated for that study in 2019, and similar trends were observed for OS outcomes [28]. Preclinical studies have demonstrated a synergistic effect when chemotherapy is combined with HER2 inhibitors in terms of damaging DNA in tumor cells [30, 31]. These findings suggest that HER2-targeted therapy combined with chemotherapy plays an indispensable role in the first-line treatment of patients with advanced HER2-positive breast cancer.

Given that the current standard of care for patients with advanced HER2-positive breast cancer in the first-line setting is dual-HER2 blockade plus chemotherapy, we also compared the PFS and ORR for dual-targeted blockade regimens and found them to be comparable for both PFS and ORR.

In this study, the combination of pyrotinib plus trastuzumab and docetaxel has the highest probability of ranking first for PFS. Although no significant differences were observed, a trend of prolonged PFS was found in patients who received the pyrotinib plus trastuzumab and docetaxel regimen than in those who received the standard pertuzumab plus trastuzumab and docetaxel regimen (HR: 0.62, 95% CrI: 0.21–1.95), which is consistent with the findings of the PHILA and CLEOPATRA

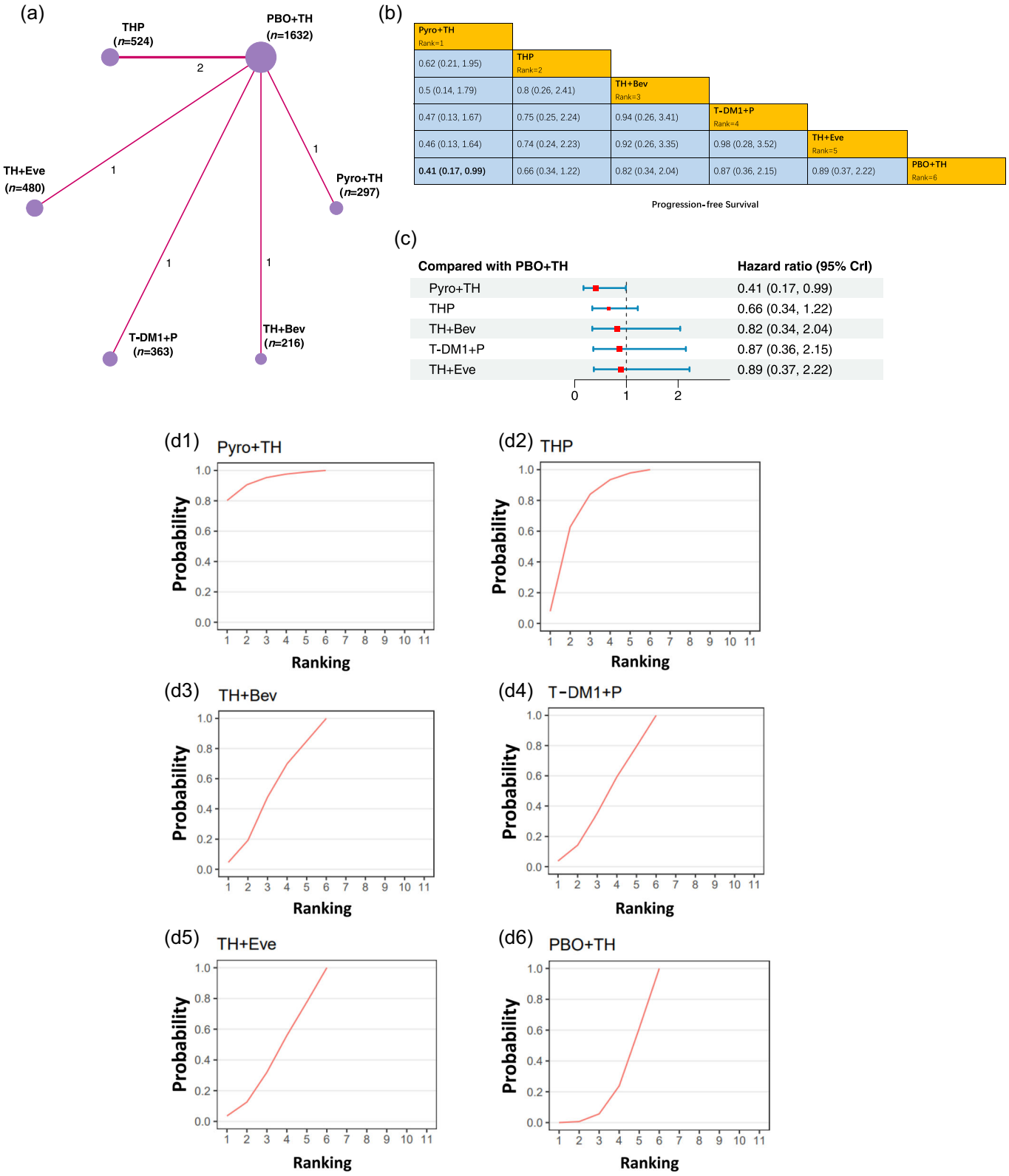

FIGURE 2 Network meta-analysis for progression-free survival (PFS). (a) Network comparisons of PFS in patients who received dual-targeted regimens. (b) Hazard ratios and 95% credible intervals for network meta-analysis of PFS based on dual-targeted regimens. (c) Forest plots showing PFS for the dual-targeted regimens. (d) Ranking profile of each regimen. Bev, bevacizumab; Eve, everolimus; P, pertuzumab; PBO, placebo; Pyro, pyrotinib; T-DM1, trastuzumab emtansine; TH, trastuzumab + docetaxel/paclitaxel.

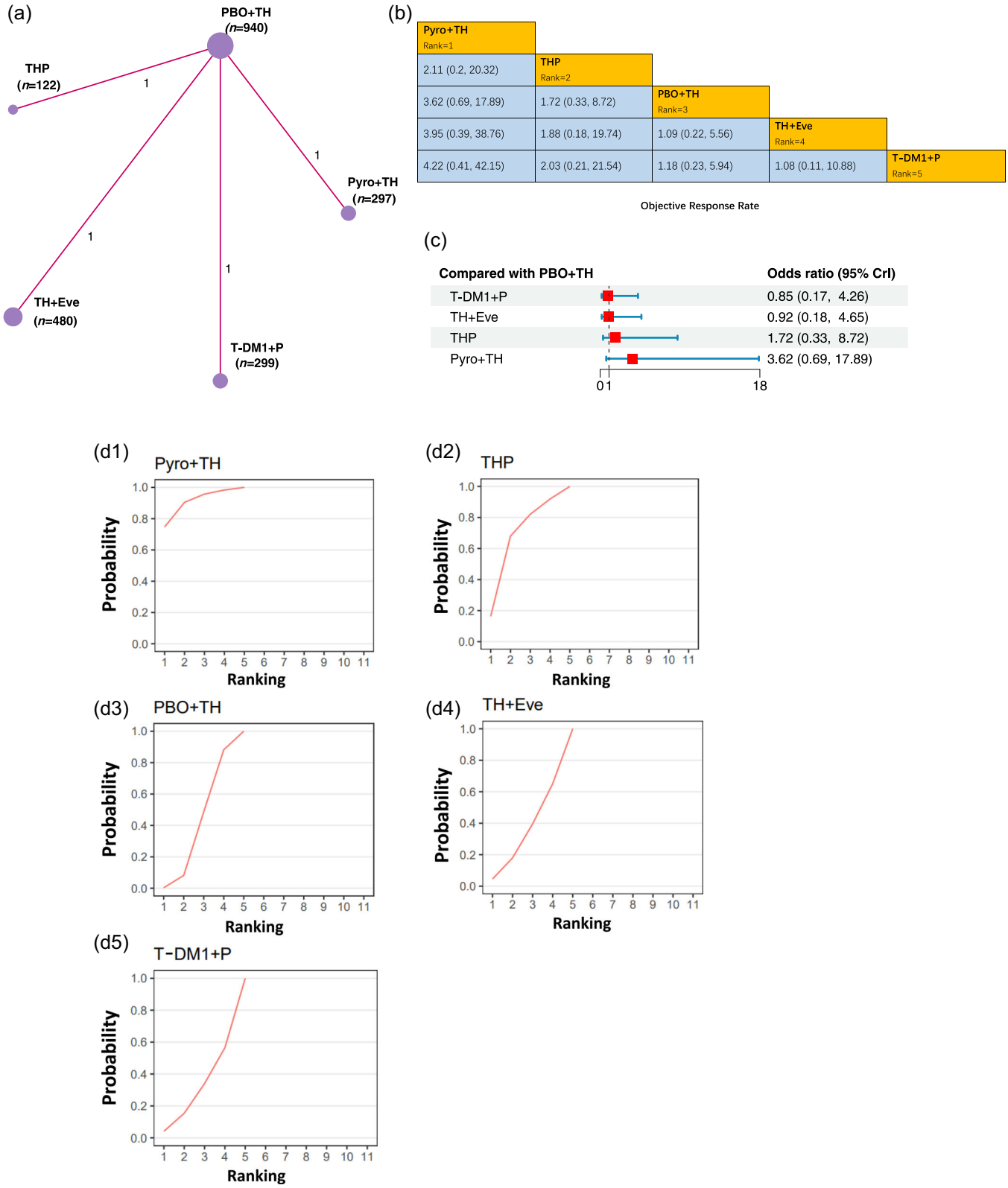

FIGURE 3 Network meta-analysis of the objective response rate (ORR). (a) Network of the ORR based on dual-targeted regimens. (b) Odds ratios and 95% credible intervals for network meta-analysis of the ORR based on dual-targeted regimens. (c) Forest plots showing the ORR for all dual-targeted regimens. (d) Ranking profile of each regimen. Bev, bevacizumab; Eve, everolimus; P, pertuzumab; PBO, placebo; Pyro, pyrotinib; T-DM1, trastuzumab emtansine; TH, trastuzumab + docetaxel/paclitaxel.

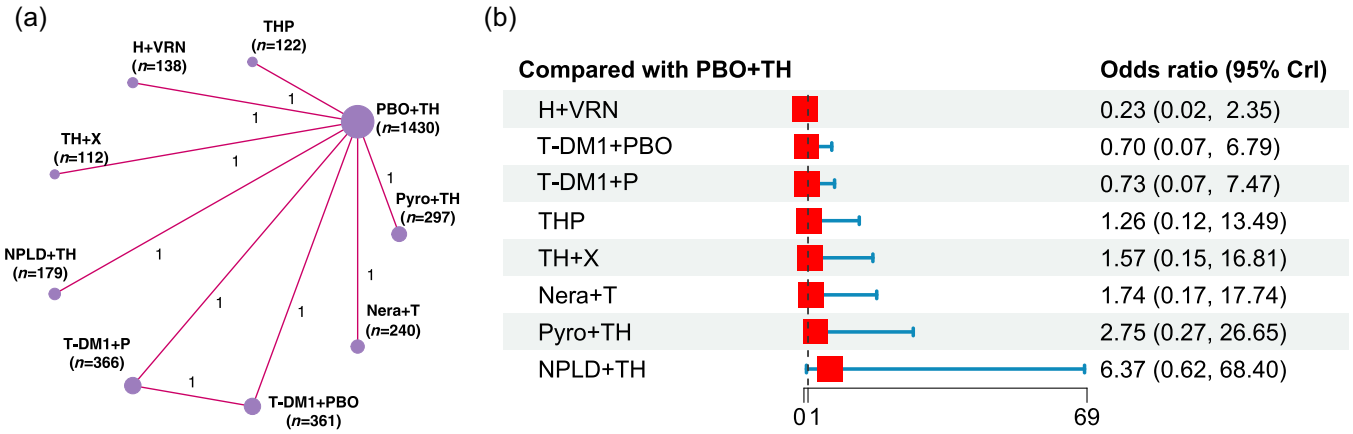

FIGURE 4 Network meta-analysis of grade ≥3 adverse event rates of ≥10%. (a) Comparative network plots. (b) Forest plots showing grade ≥3 adverse event rates of ≥10% for all dual-targeted regimens. Bev, bevacizumab; Eve, everolimus; H, trastuzumab; Nera, neratinib; P, pertuzumab; PBO, placebo; Pyro, pyrotinib; T, taxane; VRN, vinorelbine; X, capecitabine.

studies. In the randomized phase III PHILA study, patients who received the pyrotinib, trastuzumab, and docetaxel regimen had a PFS of 24.3 months (95% CI: 19.1–33.0) [9]. Meanwhile, patients who received the trastuzumab plus pertuzumab and docetaxel regimen in the CLEOPATRA study had a PFS of 18.7 months (95% CI: 16.6–21.6) [32]. Pyrotinib is an irreversible small-molecule pan-HER receptor tyrosine kinase inhibitor (TKI) that inhibits HER2 downstream signaling by binding to the intracellular kinase domain [33]. Trastuzumab and pertuzumab are both monoclonal antibodies that bind to the HER2 extracellular domain; therefore, trastuzumab combined with pyrotinib and a taxane might have a better complementary action [34]. Moreover, in a study of patients with HER2-positive breast cancer previously treated with trastuzumab, survival outcomes were better in the TKI group than in the monoclonal antibody group [35]. Like pyrotinib, lapatinib and neratinib are also TKIs; however, lapatinib is reversible [36]. In the phase III PHOEBE trial, median PFS was longer in patients with HER2-positive metastatic breast cancer who received pyrotinib plus capecitabine than in their counterparts who received lapatinib plus capecitabine (12.5 vs. 6.8 months; HR: 0.39, 95% CI: 0.27–0.56) [37]. Furthermore, other research has demonstrated that bioavailability is higher and efficacy is better for pyrotinib than for neratinib [38].

Compared with trastuzumab monotherapy, the ORR was significantly higher for the pyrotinib and trastuzumab plus docetaxel regimen (OR: 46.58, 95% CrI: 1.78–1176.63) and the trastuzumab and docetaxel regimen (OR: 13.00, 95% CrI: 1.19–142.27). When evaluated using linear regression analysis, a strong correlation was found between PFS and OS in the first-line treatment of metastatic breast cancer [39, 40]. However, no correlation between ORR and OS could be confirmed, implying that ORR results may not translate into OS. Furthermore, the ORR is often used as a secondary endpoint in clinical trials, which may lead to measurements that are less accurate than those for PFS.

In terms of AEs, all grade ≥3 AE rates of ≥10% were included and showed similar results, indicating no increase in toxicity when targeted therapies were combined with other regimens.

The strengths of our study are that it analyzed the most up-to-date information, included a broad research field encompassing all possible treatment regimens [41], and performed a network comparison using the Bayesian method. Therefore, it provides the most current evidence regarding the first-line treatment options for patients with advanced HER2-positive breast cancer.

Our systematic review and statistical comparison of first-line treatment regimens for patients with HER2-positive breast cancer suggest that the pyrotinib plus trastuzumab plus docetaxel regimen may have potentially more clinical benefits than the pertuzumab plus trastuzumab plus docetaxel regimen, with no increase in toxicity. Given that both regimens are included in the class I recommendations for first-line therapy in patients with advanced HER2-positive breast cancer in the Chinese Society of Clinical Oncology Guidelines and the Chinese Anticancer Association Guidelines, the pyrotinib plus trastuzumab plus docetaxel regimen can be considered the optimal treatment option.

This research has several limitations. First, we only extracted data from published RCTs; therefore, we could not include data for individual study participants. Second, study participants with advanced HER2-positive breast cancer were not stratified and analyzed based on factors that may influence clinical efficacy, such as hormone receptor status and clinical stage. Third, our

primary endpoint was PFS, which may fail to translate into an OS benefit. Fourth, we did not include the combination treatment with lapatinib plus pazopanib and lapatinib monotherapy in the analysis because of inability to connect to the network and compare the results with those of other regimens.

In conclusion, our findings suggest that the pyrotinib and trastuzumab plus docetaxel regimen is the optimal first-line treatment for patients with advanced HER2-positive breast cancer. Further head-to-head clinical trials are needed to confirm our results.

AUTHOR CONTRIBUTIONS

Lixi Li: Data curation (equal); methodology (lead); writing—original draft (lead); writing—review and editing (equal). **Yun Wu**: Data curation (equal); methodology (Equal); writing—review and editing (equal). **Bo Lan**: Data curation (equal); methodology (equal); writing—review and editing (equal). **Fei Ma**: Conceptualization (equal); funding acquisition (lead); supervision (equal).

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets supporting the conclusions of this article are included within the article and its additional file.

ETHICS STATEMENT

Not applicable.

INFORMED CONSENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Li L, Wu Y, Lan B, Ma F. Efficacy and safety of first-line regimens for advanced HER2-positive breast cancer: a Bayesian network meta-analysis. Cancer Innov. 2024;3:e126. https://doi.org/10.1002/cai2.126