Review A meta-analysis of the efficacy and safety of additional anti-HER2-targeting drugs in HER2-positive advanced breast cancers

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Research

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Abstract

Background The purpose of this study was to analyze the efficacy and safety of additional anti-HER2 (human epidermal growth factor receptor 2)-targeting drugs in HER2-positive advanced breast cancers.

Methods For this study, the following databases were searched for articles published from its inception until December 2019: PubMed, Web of Science, EBSCO, and Cochrane library, of which the main outcomes were the progression-free survival (PFS) and overall survival (OS).

Results We conducted a meta-analysis and the results showed that additional anti-HER2-targeting drugs improved the HER2-positive advanced breast cancer patients' PFS (HR: 0.66, $p < 0.001$), OS (HR: 0.77, $p < 0.001$), respectively. In terms of drug types, the efficacy of lapatinib was the most (HR: 0.53, 95% CI: 0.39–0.67, $p < 0.001$), followed by pertuzumab (HR: 0.72, 95% CI: 0.55–0.89, $p = 0.001$). Trastuzumab benefited the least, with no difference statistical significance (HR: 0.87, 95% CI: 0.31–1.44, $p = 0.594$). In terms of treatment regimen, first-line treatment (HR: 0.67, 95% CI: 0.52–0.82, $p < 0.001$) had a greater benefit than non-first-line treatment (HR: 0.82, 95% CI: 0.71–0.94, $p = 0.004$). The main adverse events (AEs) observed were diarrhea and the main cardiotoxicity observed was decreased ejection fraction.

Conclusions Additional anti-HER2-targting drugs may improve long-term prognosis in HER2-positive advanced breast cancers. Moreover, the AEs were safe and tolerable. Besides, lapatinib had the best benefit, and pertuzumab followed by, trastuzumab had the least benefit in terms of drug selection. From the aspect of treatment, it recommended significantly to use anti-HER2-targeting drugs in first-line therapy based on our research in HER2-positive advanced breast cancers.

Background

Human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 25% of breast cancers and is associated with an aggressive phenotype and poor prognosis [1, 2]. Trastuzumab, a humanized monoclonal antibody that targets HER2, is the first targeted therapy that is clinically approved for the treatment of HER2-positive breast cancer and is currently routinely used as first-line therapy [3], which targets the extracellular domain of the HER2 protein, treats overexpressing HER2 metastatic breast cancer, thereby improve response rate, disease-free survival and overall survival (OS) in combination with chemotherapy [4]. Therefore, this drug has dramatically changed the treatment and prognosis of HER2-positive breast cancer [3, 5–8]. Although trastuzumab is useful, it is easy for patients to develop drug resistance. Studies have shown that when trastuzumab develops resistance, patients have a poorer prognosis [5, 9]. In response to these limitations, some studies have adopted some combination therapies in the hope of improving the long-term prognosis of patients, including anti-HER2-targeting drugs combined with chemotherapy for treatment and combined with multiple anti-HER2-targeting drugs using simultaneously. In the scheme of anti-HER2-targeting drugs combined with chemotherapeutic drugs, the widely adopted clinical practice is the combination of anti-HER2-targeting drugs and taxanes [10]. In recent studies, trastuzumab emtansine (T-DM1) is one of the more promising drugs [11–13]. T-DM1 is an

antibody-conjugated drug that consists of two core functional components: antibodies and strong chemotherapeutics. Both of these are combined through a special linker, which combines the targeting of antibody drugs and the dominant lethality of chemotherapeutic drugs and is applied to HER2-positive metastatic breast cancer [14].

In the combination therapy with multiple anti-HER2-targeting drugs, that is, in the NeoSphere trial [15], compared with trastuzumab plus docetaxel, the new adjuvant trastuzumab plus docetaxel added pertuzumab (a HER2-directed monoclonal antibody) significantly increased the proportion of patients who achieved complete pathological remission. For most HER2-positive early breast cancer patients, multidrug chemotherapy and dual HER2 blockade should be considered [16, 17]. Giordano et al. [18] also suggested the combination of trastuzumab, pertuzumab, and taxanes for first-line treatment. For anti-HER2-targeting drugs, cardiotoxicity is a problem that cannot be ignored [19]. It can cause patients to interrupt treatment or even severe adverse events (AEs) [20]. In response to this problem, some recent studies have shown [21, 22] that trastuzumab combined with angiotensin-converting enzyme inhibitors and beta-blockers can treat patients with HER2-positive early breast cancer to prevent a decrease in left ventricular ejection fraction associated with cancer treatment.

Regarding the benefits of additional anti-HER2-targeting drugs, we conducted a systematic meta-analysis to investigate whether additional anti-HER2-targeting drugs could benefit HER2-positive advanced breast cancers. In addition, we further explored the AEs associated with anti-HER2-targeting drugs, with the aim of effectively and safely guiding clinical medication.

Methods

Search strategy

The meta-analysis searched the PubMed, Web of Science, EBSCO, and Cochrane libraries from the beginning to December 2019 to identify relevant studies. A combination of free-text terms and medical subject heading terms for topic search. Search terms include “HER2” or “human epidermal growth factor receptor 2” or “breast cancer” or “breast neoplasms” or “trastuzumab” or “pertuzumab” or “lapatinib” or “neratinib” or “trastuzumab emtansine” or “T-DM1”. Also, manually search for references in the literature. This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement [23].

Inclusion and exclusion criteria

Inclusion criteria: (1) the included article is an English report of a clinical trial on the efficacy and safety of an additional anti-HER2-targeting drug. (2) The included articles are phases II and III of randomized clinical trials (RCTs) containing an additional anti-HER2-targeting drug. (3) Included articles mention long-term prognosis, including OS or/and progression-free survival (PFS).

Exclusion criteria: (1) research regimen includes neoadjuvant therapy. (2) The study contains inappropriate subgroup analysis or single-arm therapy. (3) Research data cannot be extracted. (4) If there are repeated publications or continuous updates, we will use the latest articles as the basis.

Outcome measures

The main results of this study are efficacy (OS, PFS) and safety (AEs and cardiotoxicity). The AEs were under the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 [24].

Assessment of the risks of bias and data extraction

We assessed the potential risks of bias in trials by using the Cochrane Collaboration Risk of Bias Assessment tool [25]. Two investigators completed the review independently. A third investigator resolved disagreements.

Two researchers independently extracted the basic information of each study. Basic information includes author, year of publication, treatment regimen, the number of participants, baseline, and survival benefit indicators, including OS, PFS, AEs, and cardiac toxicity.

Statistical analysis

We compared the PFS and OS of additional anti-HER2-targeting drugs group and the control group, expressed by hazard ratio (HR) and a confidence interval of 95% (95%CI). The AEs and cardiotoxicity involved were also used by risk ratio (RR) and a 95%CI to represent. We used the Begg's and Egger's test to evaluate publication bias and the Stata 12.0 Software to perform the sensitivity bias [26]. Because this study included a variety of treatments, we used a random-effects model in order to increase credibility. Statistically significant was measured at p values of 0.05.

Results

Eligible studies and inclusion characteristics

According to the search strategy, 24,992 clinical trial data from the database were initially retrieved, including 16 studies that were manually retrieved. After the final screening and qualification assessment, a total of 9 clinical studies were included. This study did not include single-arm studies, neoadjuvant therapy, not contain a comparison of the efficacy of anti-HER2-targeting drugs, phase I clinical trials and other combinations of unrelated results. The detailed search and filtering process were shown in Fig. 1. Among the nine studies [13, 20, 27–33] included in this study, a total of involving 3,374 cases, including 8 phase III trials and 1 phase II trial. Of the nine studies, there were four studies comparing lapatinib, three studies comparing pertuzumab, and two studies comparing trastuzumab. Among these regimens, there were five studies of anti-HER2-targeting versus non-anti-HER2-targeting and four studies of dual-anti-HER2-targeting versus single-anti-HER2-targeting drug. In terms of the treatment plan, three studies involved first-line treatment, while other treatments were non-first-line treatment. The research features included were detailed in Supplementary Table 1.

Efficacy

In this study cohort, there were nine studies involving PFS, covering 3,374 patients, including 1,689 in the experimental group and 1,685 in the control group. The total PFS was beneficial in HER2-positive advanced breast cancers, combined with the total effect rate (HR: 0.66, 95% CI: 0.54–0.78, $p < 0.001$; Fig. 2). Also, considering the heterogeneity of PFS, this study conducted a subgroup analysis on PFS and found that it was beneficial to add an anti-HER2-targeting to chemotherapy and add an anti-HER2-targeting to an anti-HER2-targeting drug (HR: 0.66, HR: 0.68, respectively) in HER2-positive advanced breast cancers. In terms of the types of anti-HER2-targeting drugs, we performed a subgroup analysis on them and found that lapatinib benefited the most (HR: 0.53, 95% CI: 0.39–0.67, $p < 0.001$), followed by pertuzumab (HR: 0.72, 95% CI: 0.55–0.89, $p = 0.001$). Trastuzumab benefited the least, with no difference statistical significance (HR: 0.87, 95% CI: 0.31–1.44, $p = 0.594$). Then, we conducted a subgroup analysis on the treatment regimen, and the results showed that first-line treatment (HR: 0.58, 95% CI: 0.44–0.73, $p < 0.001$) had a greater benefit than non-first-line treatment (HR: 0.73, 95% CI: 0.55–0.92, $p = 0.01$) in HER2-positive advanced breast cancers, as shown in Table 1.

Table 1
Subgroup analysis of the survival for the additional anti-HER2-targeting drugs.

	No. of studies	HR	95%CI	*p*	Heterogeneity (I^2) (%)
Progression-free survival (PFS)					
Single targeted vs. untargeted therapy	5	0.66	0.43–0.89	**0.005**	70.8
Dual-targeted vs. single targeted therapy	4	0.68	0.55–0.81	**< 0.001**	59.0
Lapatinib	4	0.53	0.39–0.67	**< 0.001**	41.3
Pertuzumab	3	0.72	0.55–0.89	**0.001**	65.2
Trastuzumab	2	0.87	0.31–1.44	0.594	80.8
First-line treatment	3	0.58	0.44–0.73	**< 0.001**	39.8
Non-first-line treatment	6	0.73	0.55–0.92	**0.01**	75.6
Overall survival (OS)					
Single targeted vs. untargeted therapy	4	0.79	0.65–0.93	**0.005**	0
Dual-targeted vs. single targeted therapy	3	0.78	0.59–0.97	**0.03**	47.7
Lapatinib	3	0.75	0.60–0.90	**0.002**	0
Pertuzumab	2	0.80	0.47–1.13	0.205	73.3
Trastuzumab	2	0.90	0.66–1.14	0.400	0
First-line treatment	2	0.67	0.52–0.82	**< 0.001**	0
Non-first-line treatment	5	0.82	0.71–0.94	**0.004**	0

HR, hazard ratio.

Among the included studies, seven studies involved OS, covering 2825 patients, including 1414 in the experimental group and 1411 in the control group. The data recorded in the study showed that overall analysis was allowed. Survival as a time variable of seven events would be compared in the addition of an anti-HER2-targeting drug to the control regimen. The study found that adding an anti-HER2-targeting drug was associated with long-term survival in HER2-positive advanced breast cancers, combined total effect rate (HR: 0.77, 95% CI: 0.67–0.86, $p < 0.001$; Fig. 3), without heterogeneity. Besides, this study conducted a subgroup analysis on OS, which showed that it was beneficial to add an anti-HER2-targeting to chemotherapy and add an anti-HER2-targeting to an anti-HER2-targeting drug (HR: 0.79, HR: 0.78, respectively) in HER2-positive advanced breast cancers. In terms of the types of anti-HER2-targeting drugs, we conducted a subgroup analysis, and found that lapatinib benefited the most (HR: 0.75, 95% CI: 0.60–0.90, $p = 0.002$), followed by pertuzumab (HR: 0.80, 95% CI: 0.47–1.13, $p = 0.205$), and trastuzumab

benefited the least (HR: 0.90, 95% CI: 0.66–1.14, $p = 0.400$). Then we conducted a subgroup analysis on the treatment regimen, and the results showed that first-line treatment (HR: 0.67, 95% CI: 0.52–0.82, $p < 0.001$) had a greater benefit than non-first-line treatment (HR: 0.82, 95% CI: 0.71–0.94, $p = 0.004$) in HER2-positive advanced breast cancers, as shown in Table 1.

Publication bias and sensitivity analysis of PFS

We conducted the publication bias test on the relationship between PFS and the addition of an anti-HER2-targeting drug. The results showed that there was no publication bias ($p > 0.05$). Then we used the Stata 12.0 Software to perform the sensitivity analysis. The result showed that it was stable to remove each group sequentially (Supplementary Fig. 1 and Fig. 2).

Safety

Among the included articles, a total of 6 articles mentioned AEs. AEs for all grades were shown in Table 2. Analysis of it found that there was no overall increase in any grade AEs in HER2-positive advanced breast cancers. In specific AEs, the incidence of anti-HER2-targeting drugs added the group was increased in the decreased appetite (RR: 1.43, $p = 0.05$), diarrhea (RR: 1.83, $p = 0.001$), rash (RR: 1.76, $p = 0.001$), vomiting (RR: 1.39, $p = 0.01$), which the difference was statistically significant. In the grade 3 or higher AEs, there was no increase in the overall side effects, specifically in diarrhea, the incidence of an anti-HER2-targeting drug group increased, with statistically significant differences (RR: 4.54, $p = 0.03$) in HER2-positive advanced breast cancers.

Table 2
Subgroup analysis of the adverse events (AEs) for the additional anti-HER2-targeting drugs..

Experimental vs. control	No. of studies	RR	95%CI	*p*	Heterogeneity (I^2)
Any grade adverse events	4	1.01	0.97–1.06	0.50	90
Any grade alopecia	4	0.98	0.90–1.08	0.72	0
Any grade arthralgia	3	1.06	0.76–1.48	0.72	42
Any grade decreased appetite	3	1.43	0.99–2.07	**0.05**	65
Any grade diarrhea	6	1.83	1.47–2.27	**< 0.001**	81
Any grade edema peripheral	3	0.94	0.67–1.30	0.70	55
Any grade fatigue	4	1.17	0.90–1.51	0.23	52
Any grade headache	3	1.33	0.83–2.13	0.24	56
Any grade nausea	6	1.17	0.99–1.38	0.07	59
Any grade neutropenia	3	1.15	0.79–1.67	0.48	91
Any grade rash	5	1.76	1.33–2.33	**< 0.001**	73
Any grade vomiting	6	1.39	1.07–1.80	**0.01**	64
Grade 3 or higher adverse events	4	1.10	0.95–1.27	0.20	54
Grade 3 or higher anemia	3	1.48	0.88–2.48	0.14	0
Grade 3 or higher diarrhea	5	4.54	1.20-17.15	**0.03**	78
Grade 3 or higher fatigue	4	1.36	0.51–3.59	0.54	8
Grade 3 or higher hypertension	3	0.99	0.63–1.55	0.96	0
Grade 3 or higher nausea	3	1.31	0.41–4.23	0.65	0
Grade 3 or higher neutropenia	3	0.99	0.30–3.22	0.98	88
Grade 3 or higher vomiting	3	1.45	0.59–3.57	0.42	0

In this study, we had a separate analysis of cardiac events, the results showed that adding an anti-HER2-targeting drug resistance had no effect on overall cardiac AEs, but the grade 3 or higher cardiac AEs increased the risk with statistical significance (RR: 3.61, $p = 0.01$) in HER2-positive advanced breast cancers. At the same time, serious cardiac AEs also increased, which the difference was statistically significant (RR: 4.35, $p = 0.008$). In terms of specific types of cardiac AEs, the risk of decreased ejection fraction did not increase. However, the risk of heart failure level increased, with a statistically significant

difference (RR: 8.76, $p = 0.04$) in HER2-positive advanced breast cancers. Detailed data were shown in Table 3.

Table 3
Subgroup analysis of the cardiac adverse events (AEs) for the additional anti-HER2-targeting drugs.

Experimental vs. control	No. of studies	RR	95%CI	*p*	Heterogeneity (I^2) (%)
Any grade cardiac adverse events	5	2.18	0.76–6.25	0.15	80
Grade 3 or higher cardiac adverse events	3	3.61	1.32–9.91	**0.01**	12
Ejection fraction decreased	5	1.95	0.60–6.29	0.27	72
NYHA class III New York Heart Association	2	8.76	1.11–68.95	**0.04**	0
Serious cardiac adverse events	2	4.35	1.47–12.87	**0.008**	0

Discussion

In HER2-positive advanced breast cancers, trastuzumab plus taxanes are one of the most widely used options in first-line treatment [34]. However, not all patients will initially respond, and for those who respond to treatment, resistance will inevitably develop over time [35]. Besides, trastuzumab has lower permeability across the blood-brain barrier, so its benefits are mainly due to better control of extracranial disease [36–38], which is sufficient for patients with HER2-positive brain metastases reduced [39] and more severe cardiotoxicity [40]. Based on its resistance and cardiotoxicity, pertuzumab makes up for this limitation. Studies have shown that compared with single-anti-HER2-targeting treatment, dual-anti-HER2-targeting drugs increase the number of patients who achieve complete pathological remission [15, 41] and could significantly reduce previously generated cardiotoxicity. However, a study by Urruticoechea et al. [42] showed that the addition of pertuzumab to trastuzumab and capecitabine did not significantly improve PFS as assessed by independent review agencies. It is that the use of this drug is also controversial. Therefore, there is currently no evident and effective treatment for HER2-positive metastatic breast cancer. This study attempts to start with the addition of an anti-HER2-targeting drug, to explore the current controversial issues in the clinic, for new clinical ideas.

Combining with subgroup analysis, we found that the efficiency of single-anti-HER2-targeting drug was excellent for therapies without anti-HER2-targeting drugs. Moreover, the efficacy of dual-anti-HER2-targeting drugs was superior to single-anti-HER2-targeting drug. The results of this study have caused us great interest. The conclusion was confirmed by Baselga [43] et al. in clinical trials. This may be related to the synergistic inhibition of the growth of breast cancer cells by trastuzumab and pertuzumab [44]. Studies have shown that the new monoclonal antibodies pertuzumab and trastuzumab have an extracellular structure on HER2 different epitopes of the domain bind HER2 and prevent HER2 from

dimerizing with other members of the HER family [45] to synergistically inhibit the growth of breast cancer cells, thereby improving the prognosis of HER2-positive metastatic breast cancer; it is also possible that anti-HER2 blockers can avoid the side effects of chemotherapy [46] and improve patients' quality of life after healing. In addition, we found a phenomenon is that the efficacy of dual-anti-HER2-targeting drugs is best. In this regard, Xie [47] et al. wrote a network meta by including 13 RCTs and reached the same conclusion as ours, which the efficacy of dual-anti-HER2-targeting drugs is best.

Then, we conducted a subgroup analysis of specific types of anti-HER2-targeting drugs and found that lapatinib had the best benefit, followed by pertuzumab, and trastuzumab had the least benefit. Yardley [48] et al. showed the research that lapatinib was an oral small molecule tyrosine kinase epidermal growth factor receptor-1/HER2 inhibitor with anti-tumor activity against HER2-positive breast cancer cells (including trastuzumab-resistant cells) [49]. However, HER2 belongs to the HER receptor tyrosine kinase family. Lapatinib can completely block all HER receptors and induce apoptosis in HER2-positive breast cancer cells [50]. Trastuzumab, which was a humanized monoclonal antibody, could reidentification the extracellular domain of HER2. When HER2 combined with trastuzumab, its functionality could disrupt in several ways, which could lead to growth inhibition and apoptosis of HER2-positive breast cancer cells [51], and partially act on the HER receptor [52]. Therefore, we speculate that this conclusion may have a great connection with the molecular mechanism of drugs.

Interestingly, trastuzumab did not show the absolute advantages of the drug itself in this analysis. It is speculated that the number of articles about trastuzumab we included this time is too small. In addition, the combination of trastuzumab and other different drugs shows different levels of cardiotoxicity and the cardiotoxicity produced by the function of trastuzumab itself [53], which will affect the results. All in all, the cardiotoxicity caused by trastuzumab [54] may also be a reason for its reduced benefit.

Finally, we performed a subgroup analysis of the treatment regimen. The study found that first-line treatment showed more enormous advantages than non-first-line therapy in terms of efficacy. As tracked by Inoue [55] et al., the effectiveness and safety of the microtubule kinetics inhibitor Brin were beneficial as a first-line or second-line treatment. Therefore, they suggested that Brin may be a first-line treatment for patients with advanced HER2-negative breast cancer. Slamon [56] et al. also pointed out that patients with first-line treatment of hormone receptor-positive (HR-positive) and HER2-negative advanced breast cancer had a more prolonged median PFS and more significant benefit in phase III clinical trial. Therefore, we recommend the use of anti-HER2-targeting drugs in the first-line treatment of HER2-positive patients, to achieve complete remission of lesions through first-line treatment, reduce the recurrence rate of HER2-positive breast cancer patients, and improve the OS of this population in clinical medicine.

In terms of AEs, we analyzed that the incidence of AEs did not increase significantly with the addition of an anti-HER2-targeting drug. Among all the AEs, the occurrence of AEs was not noticeable. Specific AEs such as decreased appetite, vomiting, rash, and diarrhea, which were consistent with the studies of Krop [57] et al. In grade 3 and higher AEs, there was no significant increase in the overall incidence of AEs, and diarrhea was the only significant increase in the specific AEs. This conclusion was consistent with the

study results of Schneeweiss [58] et al. We speculated that diarrhea might be related to gastric epidermal cells expressing HER2 [59]. Studies have shown that for elderly patients who are more prone to dehydration, continuous grade 1–2 diarrhea may be debilitating [60], which prompts us to pay more attention to the association between AEs. In addition, Wildiers et al. [46] pointed out in the study that the premature cessation of trastuzumab and pertuzumab combination therapy before the condition worsens may be related to the observation of diarrhea in a large proportion of patients. Prompts us that the number of participants in the trial, age, physical fitness, and other factors will affect the AEs. All in all, there were no serious AEs observed according to our analysis. Therefore, we recommend that the dual-anti-HER2-targeting drugs regimen preferred to the treatment of patients with metastatic HER2-positive breast cancer. However, this conclusion still needed to be verified in a large number of clinical trials.

For anti-HER2-targeting drugs, it is the AEs of the heart that one of the specific side effects of the drugs-related. This phenomenon was mentioned by Antonio [61] et al., in their experiments, so we also conducted a separate analysis of cardiac AEs. The results showed that the risk did not increase in total cardiac AEs. However, in grade 3 and higher cardiac AEs and the severe cardiac AEs, the risk was raised, and the difference was statistically significant. This result also confirmed by Clifton [62], et al. In specific cardiac AEs, there was no significant increase in the risk of AEs associated with decreased ejection fraction. In contrast, an increase in heart failure grade increased the risk of AEs, with statistically significant differences.

Studies have shown: trastuzumab, pertuzumab, and lapatinib can affect the ErbB2-ErbB4 signaling pathway by inhibiting MAPK (Erk1, Erk2) and Akt [63]. The complex of ErbB2/ErbB4 can control the survival of cardiomyocytes and the disturbance of myofibrils in cardiomyocytes [64, 65]. Furthermore, ErbB4 signaling can also induce myocardial cell proliferation, thereby promoting myocardial regeneration after myocardial injury [66]. Pooja et al. [54] indicated that cardiotoxicity is the most adverse effect of trastuzumab. Regarding cardiotoxicity, the most common is an asymptomatic decrease in left ventricular ejection fraction, while congestive heart failure is not common [67]. In addition, Chavez-MacGregor et al. [68] studies have shown that the incidence of cardiac toxicity is variable, depending on the definition used in various clinical trials. It is reported that trastuzumab monotherapy which the overall prevalence is 2–7%, the total incidence of trastuzumab and paclitaxel is 2–13%, and up to 27% when combined with anthracyclines (usually a cumulative dose greater than 300 mg/m2) [53]. This prompts us to consider many factors when evaluating drug side effects comprehensively. Studies have shown that pertuzumab inhibits HER2 signaling by binding to a different HER2 epitope than trastuzumab. Based on this, it is speculated that pertuzumab appears to be associated with minimal cardiac insufficiency [69], which has minimal toxicity and higher safety factor. Additionally, it was pointed out that pertuzumab may be more active in HER2-positive tumours than HER2-negative breast cancer, which may also be one aspect of pertuzumab's association with cardiac toxicity. For lapatinib, partly because it recognizes an ErbB2 epitope different from the other two antibodies [63], and partly because it is a dual tyrosine kinase inhibitor of the epidermal growth factor receptor and HER2 receptors. The early clinical experiment shows that it produces less cardiotoxicity compared to trastuzumab [70]. However, there is no clear explanation about the specific mechanism between anti-HER2-targeting drugs and cardiotoxicity so far [63].

In a word, our conclusions indicate that the addition of an anti-HER2-targeting drug is tolerable in terms of cardiotoxicity. However, in patients with impaired cardiac function or older patients, doctors need to perform a comprehensive heart examination on the patient before using dual-anti-HER2-targeting therapy; that is, care must be taken when using a dual-anti-HER2-targeting treatment in patients.

This study comprehensively and systematically analyzed the efficacy and AEs of anti-HER2-targeting drugs for the treatment of HER2-positive metastatic breast cancer. However, there are still many deficiencies in this research. First, the number of clinical trials included in the study was insufficient. Besides, the treatment regimens are diversified, and there is some heterogeneity. Therefore, the conclusions of this study need to be further confirmed at the clinical stage.

Conclusion

In general, the addition of an anti-HER2-targeting drug was beneficial in terms of efficacy. Moreover, the side effects are safe and tolerable. Besides, lapatinib had the best benefit, and pertuzumab followed by trastuzumab had the least benefit in terms of drug selection. From the aspect of treatment, it recommended significantly to use anti-HER2-targeting drugs in first-line therapy based on our research. However, the number of articles included in this study was too small, so the conclusions of the study needed to be further proved at the clinical stages.

Abbreviations

HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine; PFS, progression-free survival;

OS, overall survival; AEs, adverse events; HR, hazard ratio; RR, risk ratio; confidence interval of 95% (95%CI);

Declarations

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Data availability

The datasets used and analyzed in the current study are avaliable from the corresponding authors on reasonable request.

Compliance with ethical standards

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed consent

Not applicable.

Research involving animal and animal rights

This article does not contain any studies with animals performed by any of the authors.

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Description Of Supplementary Files

Supplementary Fig. 1. Publication bias of the progression-free survival (PFS) for additional anti-HER2-targeting drugs. (Egger's) $p = 0.712$; (Begg's) $p = 0.466$.

Supplementary Fig. 2. Sensitivity analysis of the progression-free survival (PFS) for additional anti-HER2-targeting drugs.

Supplementary Table 1. Characteristics of included clinical trials in the meta-analysis.

Figures

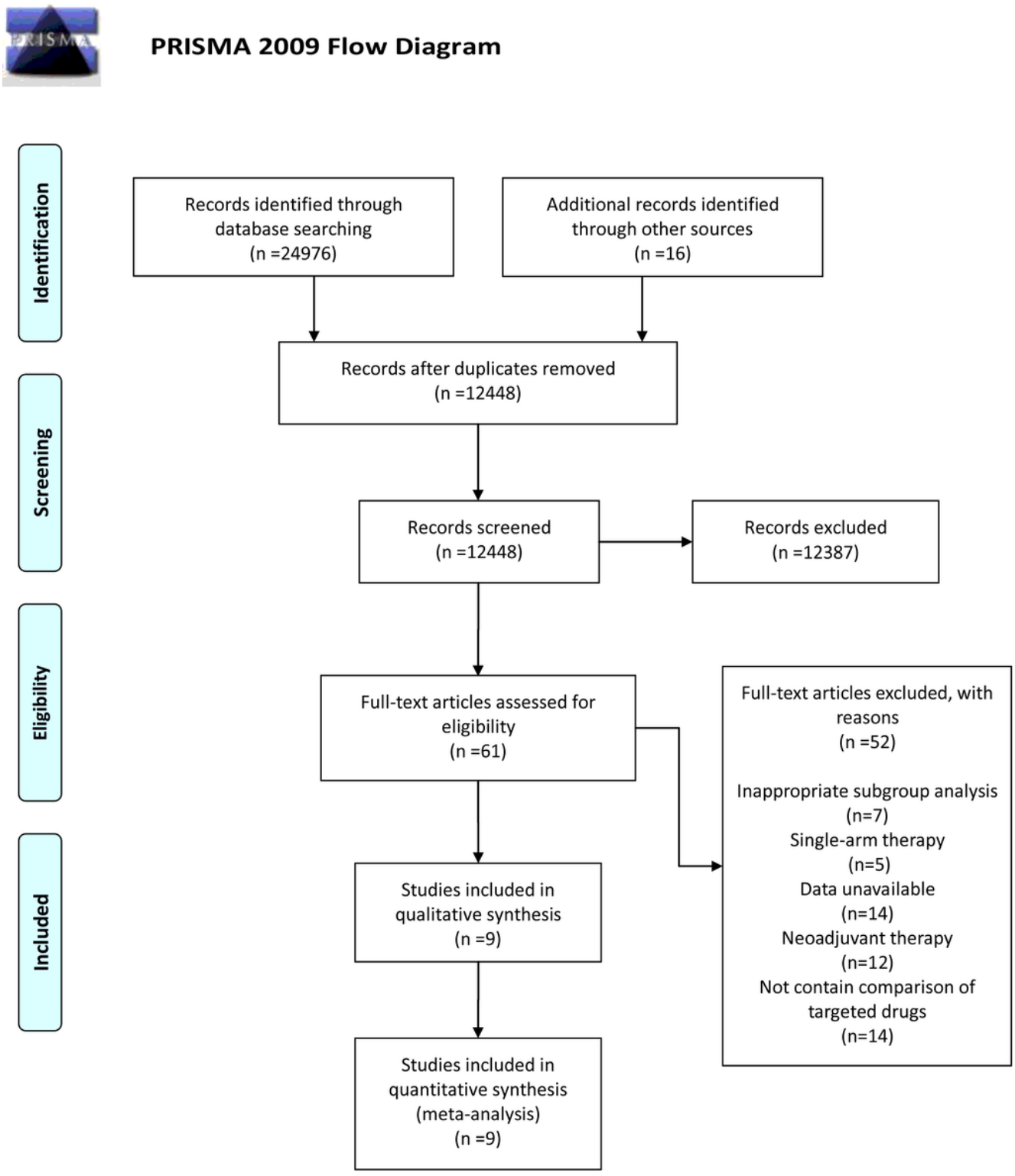

Figure 1

Flow diagram of study inclusion and exclusion.

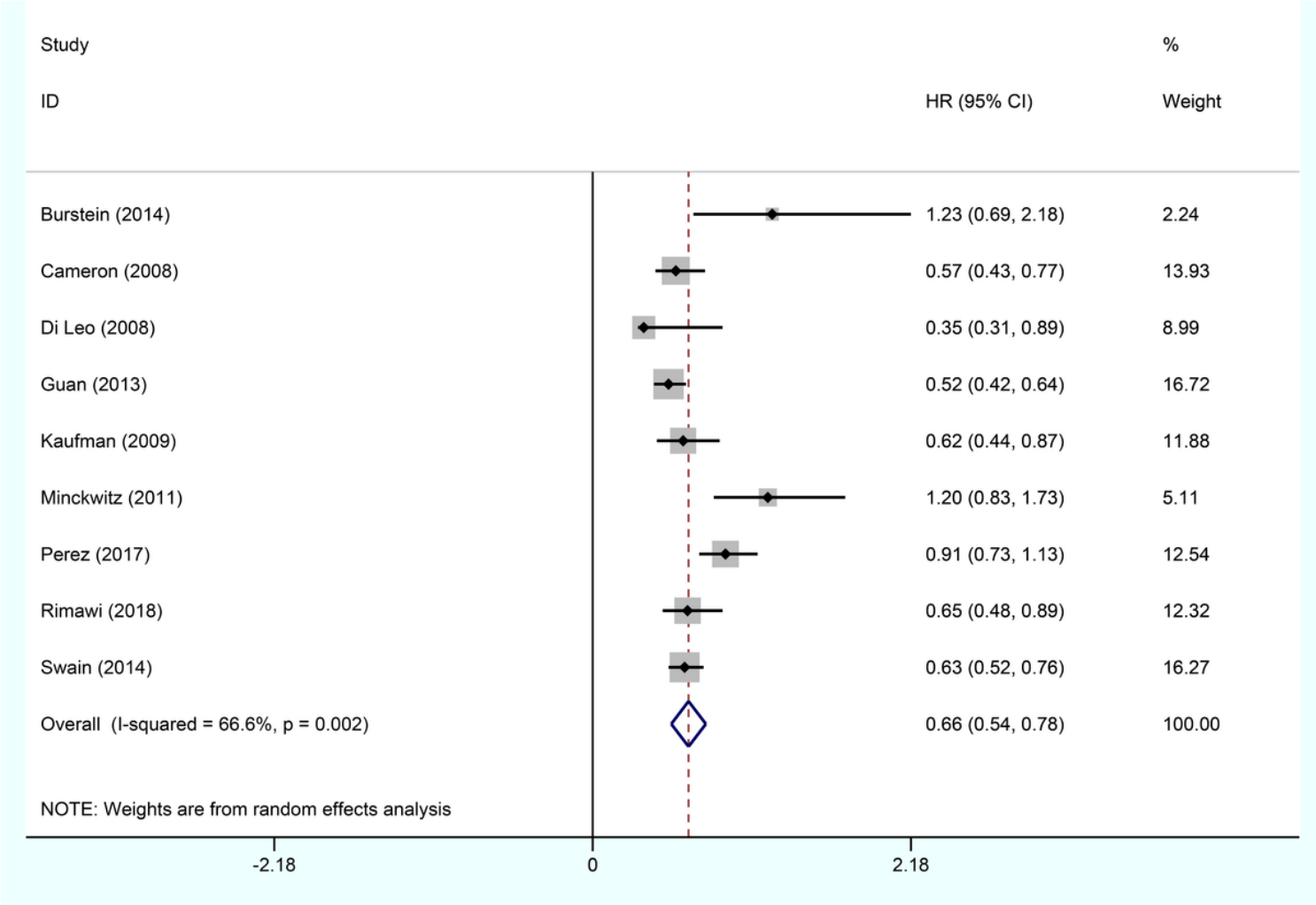

Figure 2

Forest plots of the progression-free survival (PFS) for additional anti-HER2-targeting drugs.

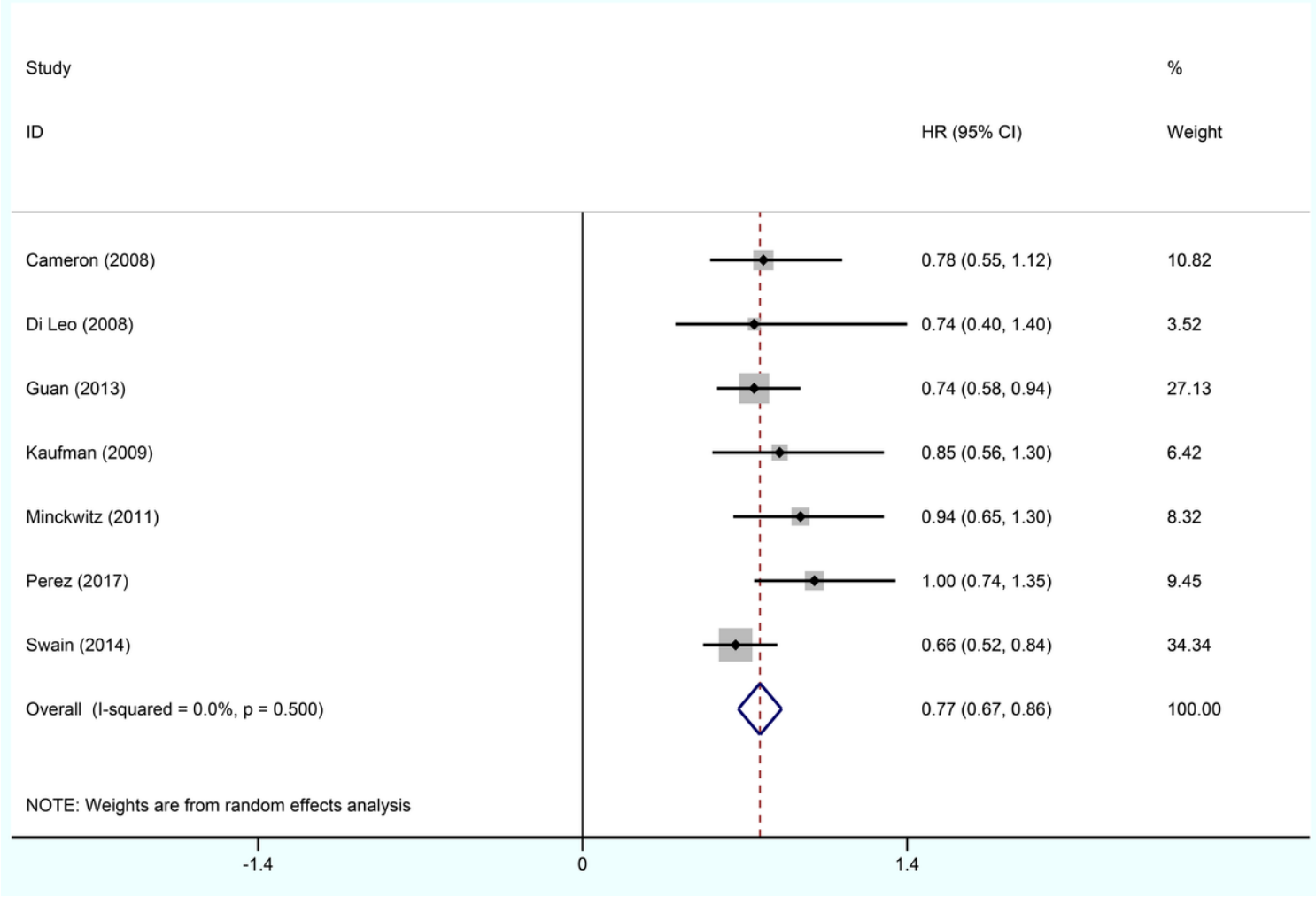

Figure 3

Forest plot of the overall survival (OS) for additional anti-HER2-targeting drugs.

Supplementary Files

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- SupplementaryTable1.doc
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