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Updated Bayesian Network Meta-Analysis of Adjuvant Targeted Treatment Regimens for Early Human Epidermal Growth Factor Receptor-2 Positive Breast Cancer

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ABSTRACT



Purpose: Combining targeted agents with adjuvant chemotherapy prolongs survival in human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients, but also increases the risk of adverse effects. The updated results of 3 randomized controlled trials (RCTs) were reported in 2019. Given the lack of adequate head-to-head pairwise assessment for anti-HER2 agents, network meta-analysis facilitates obtaining more precise inference for evidence-based therapy.

Methods: RCTs comparing at least 2 anti-HER2 regimens in an adjuvant setting for HER2-positive early-stage breast cancer (EBC) were included. Hazard ratios for overall survival (OS) and disease free survival (DFS), with respective 95% confidence intervals were pooled for assessment of efficacy. A Bayesian statistical model was used, and odds ratios (ORs) for adverse events (AEs) were used to pool effect sizes.

Results: We demonstrated that 1-year trastuzumab plus chemotherapy had increased efficacy compared to shorter or longer treatment duration. The OR of cardiac events gradually increased from 6 months to 1 and 2-year trastuzumab arms, relative to chemotherapy only. Compared to trastuzumab plus chemotherapy, dual HER2-targeting therapies increased DFS, especially for hormone receptor negative patients. Dual anti-HER2 blockade regimens revealed an increased probability of gastrointestinal reactions. As a second agent, pertuzumab showed significantly higher DFS and OS.

Conclusion: We conclude that 1-year adjuvant trastuzumab should remain as the standard treatment for HER2-positive EBC patients, as it has greater efficacy and a manageable proportion of AEs. Clinical efficacy can be increased for hormone receptor-negative tumors by including a second HER2-targeted agent to the treatment regimen. For hormone receptor-positive cases with basal disease, it is acceptable to reduce the risk of cardiotoxicity by shortening the duration of trastuzumab.

Keywords: Breast neoplasms; Drug therapy; ERBB2 protein, human; Network meta-analysis; Trastuzumab

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Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Li X,¹ Wang M,² Yu X, Guo J, Dong H; Data curation: Li X,¹ Yao L, Wang M,²; Formal analysis: Li X,¹ Yao L, Wang M,² Guo J; Funding acquisition: Wang M,¹ Guo J, Dong H; Investigation: Yao L, Li X,² Dong H; Methodology: Li X,¹ Li X,² Sun X; Project administration: Li X,² Yu X, Dong H, Sun X; Resources: Wang M,² Li X,² Yu X, Guo J; Software: Yao L, Yu X, Guo J; Supervision: Dong H; Validation: Wang M,¹ Wang M,² Sun X, Xu Y; Visualization: Sun X, Xu Y; Writing - original draft: Li X,¹ Yao L; Writing - review & editing: Wang M,¹ Xu Y.

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INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) positive breast cancer is a subtype that accounts for approximately 15%–25% of invasive breast cancer cases, and is linked to high aggressiveness and poor prognosis, even when diagnosed at an early stage [1-3]. The use of trastuzumab, a monoclonal antibody against the HER2 receptor, has been reported by several large randomized controlled trials (RCTs) (NSABP-B31, NCCTC N9831, and BCIRG-006) [4-6]. Trastuzumab has been shown to improve disease free survival (DFS) and overall survival (OS) for HER2⁺ early-stage breast cancer (EBC) patients when combined with adjuvant chemotherapy, the efficacy of which was also proven at long-term follow-up [7,8]. Following United States Food and Drug Administration approval, 1 year of trastuzumab in combination with chemotherapy became the standard therapy for HER2⁺ EBC in an adjuvant setting.

Recently, the addition of multiple classes of HER2 targeted agents, including small-molecular tyrosine kinase inhibitors (lapatinib, neratinib, and pyrotinib) and monoclonal antibodies (trastuzumab and pertuzumab), have been shown to be useful in reducing the risk of recurrence and cancer-related death for HER2⁺ EBC patients [9,10]. However, the overall effect of HER2 targeted agents was debatable, due to the presence of noticeable side effects (i.e., cardiac events caused by trastuzumab, and lapatinib-related diarrhea) [11-13]. The therapeutic efficacy, as well as the potential risk in terms of adverse events (AEs) are equally crucial in determining the most appropriate treatment strategies; however, questions remain with regards to the optimal selection of these anti-HER2 agents in an adjuvant setting.

The 11-year follow-up results from HERA trial confirmed the benefits of 1-year adjuvant trastuzumab treatment for DFS and OS; however, no additional benefits have been found as a result of prolonging the treatment duration to 2 years [14]. Three trials (FinHer, ShortHER, SOLD) compared the clinical benefit of 9-week trastuzumab treatment with standard 1-year administration, with the aim to control trastuzumab associated cardiac toxicity and lower therapeutic costs [15,16]. In the 2019 San Antonio Breast Cancer Symposium (SABCS), the updated results from APHINITY showed a 23% decline in recurrence risk in the trastuzumab plus pertuzumab group without any new cardiac events.

Two previous network meta-analyses reported an increase in treatment effectiveness by adding HER2-targeted agents into adjuvant chemotherapy for HER2⁺ EBC [17,18]. However, these studies did not systematically evaluate the comparative safety profile, or perform a subgroup analysis to observe the efficacy of HER2-targeted regimens for patients with different risk levels. Importantly, 3 updated RCT results were reported in 2019, one on the comparison of dual HER2 targeted therapy with conventional 1-year trastuzumab treatment in adjuvant therapy (APHINITY), and 2 on the influence of trastuzumab treatment duration on outcomes and cardiac safety (PHARE, PERSEPHONE) [19,20]. Thus, in the current network meta-analysis, we included the latest RCT results, and conducted direct and indirect comparisons among anti-HER2 targeted agents. We aimed to rank the postoperative treatment regimens for HER2⁺ EBC based on their relative efficacy and safety. Subgroup analysis by nodal status and hormonal receptor status was also explored.

METHODS

Search strategy

Comprehensive searches were performed using PubMed, Embase, and the Cochrane Central register of controlled trials, without restricting the year of publication. The searches included the following keywords: 'Breast neoplasms' AND 'ErbB-2 positive' AND 'Adjuvant therapy' AND 'Targeted therapy' OR 'Trastuzumab' OR 'Pertuzumab' OR 'Tyrosine kinase inhibitor (TKI)' OR 'Monoclonal antibody' OR 'Pyrotinib' OR 'Lapatinib' OR 'Tykerb' OR 'Neratinib' AND 'Randomized Clinical Trial'. The last search was updated on November 9, 2019. Some additional studies were manually searched by tracking the reference lists of pertinent original articles and reviews. Moreover, the updated results of main international congresses were also searched manually. Two reviewers independently assessed the title and abstract of the articles obtained from the literature search, and determined which articles to enroll; any disagreements were resolved by a third investigator.

Inclusion and exclusion criteria

We included phase II or III RCTs that compared the efficacy and safety between different 'chemotherapy +/- HER2-targeted agents' treatment regimens in an adjuvant setting for HER2-positive EBC. Trials that evaluated the efficacy and safety of HER2-targeted treatment with different durations were also eligible. Only prospective studies with at least 2 treatment arms, and those published in the English language were considered in this network analysis. We selected the most recent publication when trials were reported in multiple publications. We excluded trials for populations with locally advanced or metastatic HER2+ breast cancer, studies that only assessed different adjuvant chemotherapy regimens, and studies that evaluated anti-HER2 agents combined with hormonal agents. Reviews and case reports were also excluded.

Data extraction and endpoints

Data on the year of publication, sample size, median age, treatment regimens, median follow-up, outcomes, and AEs were collected by 2 independent reviewers following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, and disagreements were resolved by discussion with a third investigator. DFS and OS were the primary endpoints for these trials. The hazard ratios (HRs) and 95% confidence intervals (CIs) for DFS and OS were extracted and pooled for assessment of efficacy. The secondary endpoints included congestive heart failure (CHF), left ventricular ejection fraction (LVEF) decline, gastrointestinal events, hematological events, nervous system events, and other AEs, which were measured by odds ratios (ORs).

Definition of endpoints

DFS was defined as the duration from the date of randomization to ductal carcinoma in situ, ipsilateral invasive breast tumor recurrence, ipsilateral locoregional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, or death from any cause. Among all studies, OS was similarly defined as the time from randomization to death. AEs were graded using the National Cancer Institute Common Terminology Criteria (NCI-CTC); if AEs were not graded according to the NCI-CTC, the corresponding numbers were used. In our analysis, we defined cardiac events as symptomatic CHF and cardiac death. In trials, CHF was defined by the New York Heart Association as class III–IV, and LVEF decline usually referred to an absolute decline > 10% from the baseline, or a drop below 50%. The number of patients with grade 3 or 4 AEs, including gastrointestinal events (vomiting, nausea, and diarrhea), hematological events (neutropenia and leukopenia), and fatigue, were assessed.

Statistical methods

The quality of the included studies was conducted using the Cochrane Collaboration risk of bias tool, including 5 items: Allocation sequence, allocation concealment, blinding outcome, incomplete outcome, and selective reporting, which were ranked as high, unclear, and low risk of bias for each trial [21]. The meta-analysis was conducted using STATA version 15.0 and Review Manager version 5.3. In direct comparisons, data were pooled using the DerSimonian-Laird random effects model. The HRs for OS and DFS were extracted and pooled for assessment of efficacy. In safety assessment, all the outcomes of AEs were dichotomous variables. The ORs were used to pool effect sizes, and the results are expressed with 95% CIs. If the comparison was conducted among more than 2 studies, the statistical heterogeneity across the studies was assessed with I^2 statistics. We defined an I^2 index < 25% as low heterogeneity, 25%–50% as moderate heterogeneity, and > 50% as high heterogeneity. Network meta-analysis using a Bayesian statistical model was used to calculate the probability of each treatment arm to be the best adjuvant therapy for HER2⁺ EBC, and provide a ranking probability curve [22]. The surface under the cumulative ranking (SUCRA) was used to evaluate the effectiveness of the treatment arm, in which, SUCRA = 1 was considered the best, and SUCRA = 0 was considered the worst. Inconsistency among the results of direct and indirect comparisons was analyzed through global and local inconsistent model. The publication bias was estimated by funnel plots. All statistical tests were 2-sided, and probabilities with p -values < 0.05 were considered statistically significant.

RESULTS

Overview of literature search and trial characteristics

Following the literature search and selection, we enrolled 17 RCTs that met the eligibility criteria for HER2-positive EBC treatment (15 for efficacy outcomes and 16 for toxicity outcomes). The flowchart for the literature search is shown in **Figure 1**. Survival data of 2 trials, the B31 and the N9831, were reported together in a planned joint analysis that was published in 2014 [4]. The latest results of one of the studies (APHINITY) were not yet published; thus, presentation slides from the SABCS 2019 meeting were used as an alternative. Furthermore, the ExteNET trial only reported data on DFS [23]. The study and patient characteristics are shown in **Table 1**. Among the 43,487 patients, with median age of 48 to 56 years, who were included in our meta-analysis, 29,230 patients were treated with anthracycline and taxane-based therapy, and the remaining patients received anthracycline or taxane alone (31.7%), or other regimens (1.07%). The median follow-up duration was in the range of 42.5 to 132 months. Across the 17 trials, estrogen and/or progesterone receptor positive tumors accounted for 45%–68%. The risks of bias for each trial are demonstrated in **Supplementary Table 1**. No obvious asymmetry was displayed by the funnel plots for DFS, OS, or cardiac events (**Figure 2**). From the included studies, the 11 treatment arms we assessed in our network meta-analysis were shown in **Table 2**.

Results of direct comparisons

We made 17 direct comparisons from the included trials, and the network diagram of direct comparisons for DFS and OS is presented in **Figure 3**. The most commonly made direct comparison was chemotherapy + trastuzumab 1 year (CT + H1y) versus chemotherapy + trastuzumab ≤ 6 months (CT + H ≤ 6 m). In summary, 10,120 patients were treated with chemotherapy plus trastuzumab versus chemotherapy alone in a direct comparison within 4 RCTs; 2 involved sequential (HERA, PACS-04) and 2 involved concurrent (BCIRG-006,

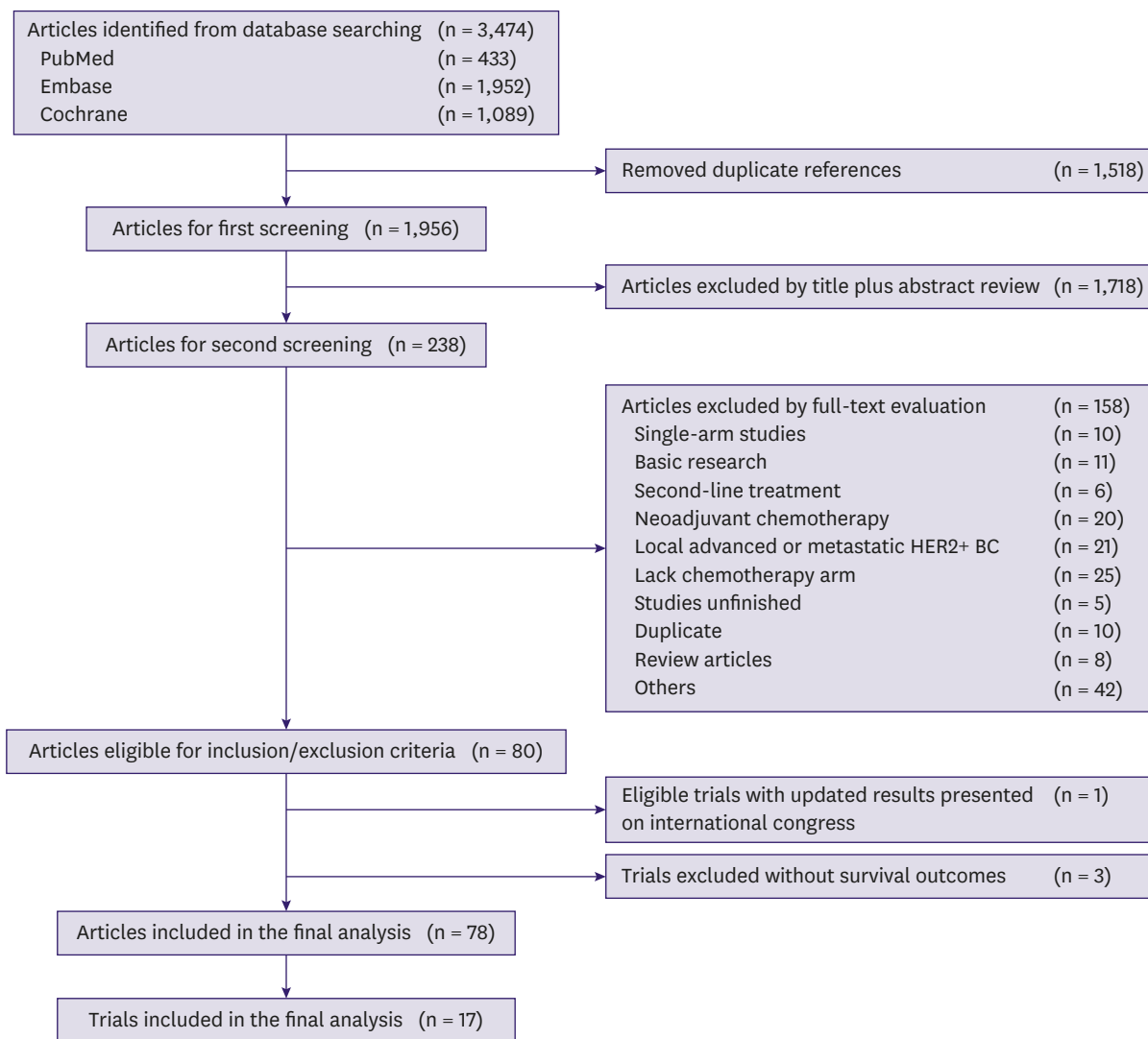


Figure 1. The flow diagram for literature search.

NCCTG-N9831+NSABP-B31) use of trastuzumab [4,5,14,24]. Four trials were conducted to investigate 1 year of trastuzumab treatment versus shorter durations. The APHINITY, ALTO, and ExteNet studies contained a dual HER2-targeted treatment arm [23,25].

The therapeutic efficacy of head-to-head comparisons in forest plots is demonstrated in **Figure 4**. The results indicated that CT plus dual blockade arms were associated with longer DFS (HR, 0.84; 95% CI, 0.74–0.94; $p = 0.238$) than the standard regimen of CT + H1y. Patients who received trastuzumab for less than 6 months had worse survival outcomes than those treated with trastuzumab for the standard 1-year duration (OS: HR, 1.16; 95% CI, 1.03–1.30; $p = 0.759$, and DFS: HR, 1.14; 95% CI, 1.02–1.27; $p = 0.213$). Improvements in OS were demonstrated by the addition of trastuzumab into CT compared to CT alone in all trials, except PACS-04 [24]. Pooled analysis confirmed a significant improvement in OS (HR, 0.62; 95% CI, 0.54–0.70; $p = 0.831$) and DFS (HR, 0.61; 95% CI, 0.55–0.68; $p = 0.595$) with concurrent addition of trastuzumab into CT compared to CT alone. However, only DFS demonstrated a statistically significant difference between CT plus trastuzumab

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

Study	Study Design	Median follow-up (mon)	Median age (yr)	HR+/N+ (%)	Sample size	Treatment arm	Arms	Frequency and Dose of HER2-targeted agents	Duration (wks)	Primary endpoints	Secondary endpoints
NSABP-B31	RCT, phase III	87	49	-	1,736	ACT ACT+H	743 947	Trastuzumab (4 mg/kg loading, 2 mg/kg q. wk).	-	Cardiac event	-
BCIRG-006	RCT, phase III	80.4	49	54/62	3,222	ACT	1,073	Trastuzumab (4 mg/kg loading, 2 mg/kg q. wk during chemotherapy and then 6 mg/kg q. 3wk).	52	DFS	OS, Safety
				54/71		ACT+H	1,074				
FinHer	RCT, phase III	62	50.9	-	232	ACT	116	Trastuzumab (4 mg/kg loading, 2 mg/kg q. wk).	9	RFS	OS, LVEF
				54/72		TC+H	1,075				
HERA	RCT, phase III	132	49	50/57	5,102	AC/TC/ACT	1,697	Trastuzumab (8 mg/kg loading, 6 mg/kg q. 3 wk).	-	DFS	OS, Cardiac safety
				51/57		AC/TC/ ACT-H	1,702				
E2198	RCT, phase II	77	49	45/100	227	ACT+H	112	Trastuzumab (4 mg/kg loading dose in week 1 followed by 2mg/kg weekly).	52	Cardiac toxicity	DFS, OS
				47/100		ACT+H	115				
HORG	RCT, phase III	51	54	64.7/74.6	481	ACT+H	241	Trastuzumab (loading dose 6 mg/kg; 4 mg/kg q. 2 wk during chemotherapy, then 6 mg/kg q. 3 wk).	52	DFS	OS, Toxicity
				68.8/83.3		ACT+H	240				
NCCTG-N9831	RCT, Phase III	110.4	49	-	1,944	ACT	664	Trastuzumab (4 mg/kg loading, 2 mg/kg q. wk).	-	DFS	-
				66(ER)/47(PR)/40		ACT+H	710				
ShortHER	RCT, phase III	72	55	68/47	1,253	ACT+H	627	Trastuzumab (8 mg/kg loading dose at 1st cycle, and 6 mg/kg thereafter, q. 3 wk for 18 doses).	52	DFS, OS	Failure Rate, Cardiac Events
				68/46		ACT+H	626				
SOLD	RCT, phase III	62.4	56	66(ER)/46(PR)/41	2,176	ACT+H	1,085	Trastuzumab (iv.first dose 4mg/kg, subsequently 2mg/kg weekly or first dose 8 mg/kg, subsequently 6 mg/kg q. 3 wk) or (subcutaneously 600 mg regardless of body weight q. 3 wk during chemotherapy, then either iv. first dose 8 mg/kg, subsequently 6 mg/kg or subcutaneously 600mg regardless of body weight q. 3 wk 14 times).	9	DFS	DDFS, OS, Cardiac safety
				66(ER)/47(PR)/40		ACT+H	1,089				
NCCTG-N9831+NSABP-B31	RCT, phase III	100.8	-	54.8/92.6	4,046	ACT	2,018	Trastuzumab (initial loading dose 4 mg/kg, then 2 mg/kg weekly).	52	Cardiac event	-
				54.7/93.4		ACT+H	2,028				
PACS-04	RCT, phase III	47	48	67/100	528	AC/AT	268	Trastuzumab (8 mg/kg loading, 6 mg/kg q. 3 wk).	-	DFS	Safety, OS, EFS
				58/100		AC/AT-H	260				
APHINITY	RCT, phase III	45.4	-	64.3/62.4	4,805	ACT/TC+H	2,402	Trastuzumab (8 mg/kg.iv as a loading dose, followed by 6 mg/kg.iv q. 3 wk) plus placebo (840 mg.iv as a loading dose, followed by 420 mg.iv q. 3 wk).	52	iDFS	OS, DFS, RFS, DRFS
				64/62.6		ACT/TC+H+P	2,400				
PHERSEPHONE	RCT, phase III	64.8	56	69/42	4,089	AC/TC/ACT+H	2,045	Trastuzumab (initial loading dose of 8 mg/kg followed by 6 mg/kg q. 3 wk intravenously or subcutaneously 600 mg).	52	DFS	OS, Cardiac Events,
				69/40		AC/TC/ACT+H	2,043				

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Table 1. (Continued) Characteristics of the trials included in network meta-analysis

Study	Study Design	Median follow-up age (yr) (mon)	Median age (yr)	HR+/N+(%)	Sample size	Treatment arm	Arms	Frequency and Dose of HER2-targeted agents	Duration (wks)	Primary endpoints	Secondary endpoints	
PHARE	RCT, phase III	42.5	54	60.4/44.6	3,380	AC/TC/ACT + H	1,690	Trastuzumab (initial loading dose of 8 mg/kg followed by 6 mg/kg q, 3 wk intravenously or subcutaneously 600 mg).	52	DFS	OS, Cardiac safety	
			55	61.5/45.3		1,690	AC/TC/ACT + H			26		
ALITTO	RCT, phase III	54	51	57/51	8,381	ACT/TC + H	2,097	Trastuzumab (4 mg/kg once and then 2 mg/kg weekly during chemotherapy or 8 mg/kg once and then 6 mg/kg q, 3 wk).	52	DFS	OS, cardiac safety	
				57/52		2,100	ACT/TC + L		Oral lapatinib (750 mg/day during chemotherapy and 1,500 mg/day when given alone).	52		
				57/51		2,093	ACT/TC + H + L		Trastuzumab (12 weekly dose) plus Lapatinib (750 mg/day during chemotherapy, with an escalation to 1,000mg/day at chemotherapy completion).	52		
				58/52		2,091	ACT/TC + H-L		Trastuzumab (12 weekly dose) followed after a 6-wk washout by oral Lapatinib (1,500 mg/day, 34 wk).	52		
TEACH	RCT, phase III	47.4	52	59/54	3,161	AC/TC/ACT + L	1,576	Oral placebo (1,500 mg) daily.	52	DFS	OS, Toxic effects	
			51	59/54		1,571	AC/TC/ACT + L		Oral lapatinib (1,500 mg) daily.	52		
ExteNet	RCT, phase III	62.4	52	57/77	2,840	AC/TC/ACT + H	1,420	Oral neratinib (240 mg) or placebo daily, administered after chemotherapy and trastuzumab	52	iDFS	DFS, DDFS, OS, Safety	
				57/77		AC/TC/ACT + H-N	1,420					

HR+ = hormone receptor positive; N+ = lymph node positive; RCT = randomized clinical trial; ACT = anthracycline, cyclophosphamide- and taxane-based chemotherapy regimen; TC = taxane-based chemotherapy regimen; AC = anthracycline based chemotherapy regimen; H = trastuzumab; L = lapatinib; N = neratinib; P = pertuzumab; + = concurrently administration; - = sequentially administration; q, wk = every week; q, 3 wk = every 3 weeks; q, 2 wk = every 2 weeks; DFS = disease free survival; OS = overall survival; DDFS = distant disease free survival; iDFS = invasive disease free survival; EFS = event free survival; RFS = recurrence free survival; LVEF = left ventricular ejection fraction.

Table 2. The treatment arms and corresponding abbreviation assessed in network meta-analysis

Arm	Treatment regimens	Abbreviation
1	Chemotherapy only	CT
2	Chemotherapy + trastuzumab 1 year	CT + H1y
3	Chemotherapy + trastuzumab ≤ 6 months	CT + H ≤ 6 m
4	Chemotherapy → trastuzumab 1 year (sequential to chemotherapy)	CT-H1y
5	Chemotherapy → trastuzumab 2 year (sequential to chemotherapy)	CT-H2y
6	Chemotherapy + trastuzumab 1 year + pertuzumab (concomitant with trastuzumab)	CT + H + P
7	Chemotherapy + lapatinib 1 year	CT + L
8	Chemotherapy + trastuzumab 1 year + lapatinib (concomitant with trastuzumab)	CT + H + L
9	Chemotherapy + trastuzumab 3 months → lapatinib 9 months (sequential to trastuzumab)	CT + H-L
10	Chemotherapy (taxane plus carboplatin) + trastuzumab 1 year	TC + H
11	Chemotherapy + trastuzumab 1 year → neratinib 1 year (sequential to trastuzumab)	CT + H-N

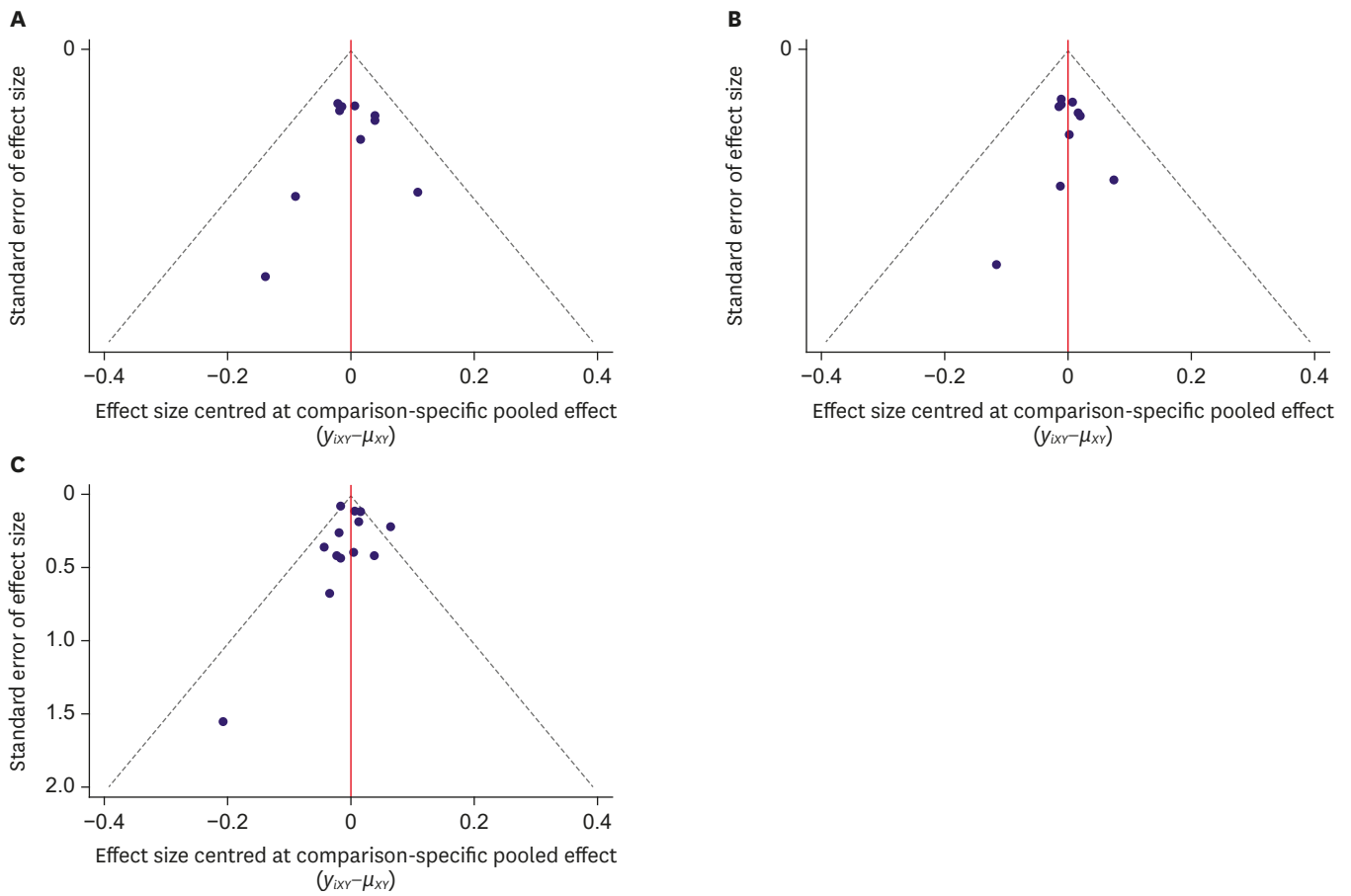


Figure 2. Funnel plot for publication bias. (A) Disease free survival. (B) Overall survival. (C) Cardiac safety.

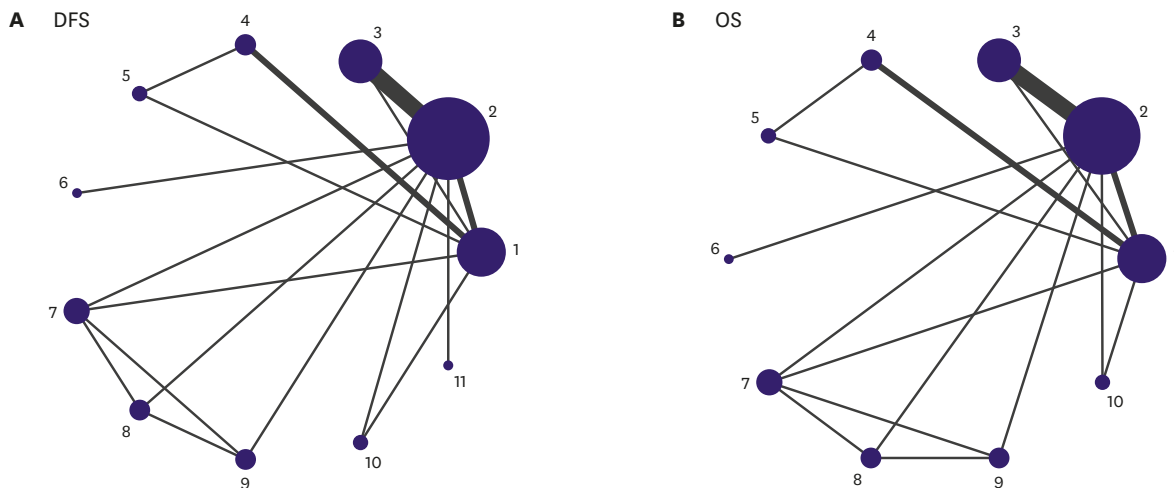
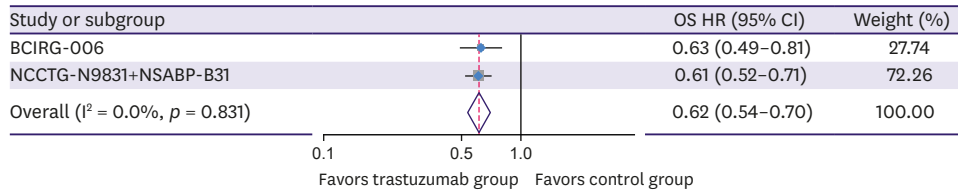
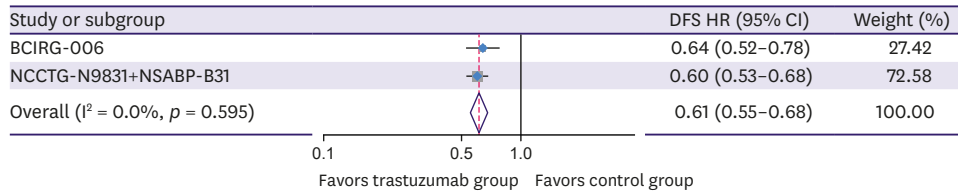
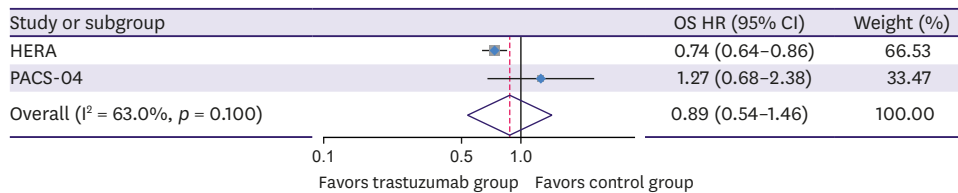
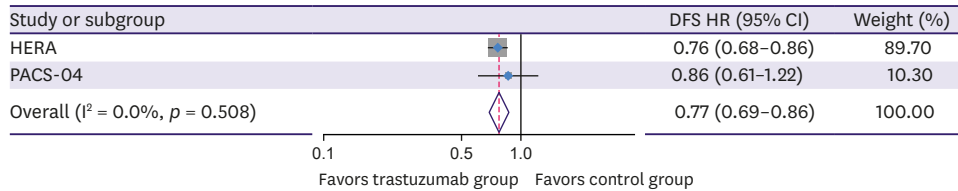


Figure 3. Networks diagram of trials comparing DFS and OS of different adjuvant anti-human epidermal growth factor receptor 2 therapies. Each link represents direct comparison between the 2 nodes and the width of that represents the number of studies for the particular comparison. The size of each node is proportional to the total sample size. Arm 1, chemotherapy only; arm 2, chemotherapy + trastuzumab 1 year; arm 3, chemotherapy + trastuzumab \leq 6 months; arm 4, chemotherapy \rightarrow trastuzumab 1 year (sequential to chemotherapy); arm 5, chemotherapy \rightarrow trastuzumab 2 year (sequential to chemotherapy); arm 6, chemotherapy + trastuzumab 1 year + pertuzumab (concomitant with trastuzumab); arm 7, chemotherapy + lapatinib 1 year; arm 8, chemotherapy + trastuzumab 1 year + lapatinib (concomitant with trastuzumab); arm 9, chemotherapy + trastuzumab 3 months \rightarrow lapatinib 9 months (sequential to trastuzumab); arm 10, chemotherapy (taxane plus carboplatin) + trastuzumab 1 year; arm 11, chemotherapy + trastuzumab 1 year \rightarrow neratinib 1 year (sequential to trastuzumab). DFS = disease free survival; OS = overall survival.

A CT + H1y vs. CT



B CT → H1y vs. CT



C CT + H ≤ 6 m vs. CT + H1y

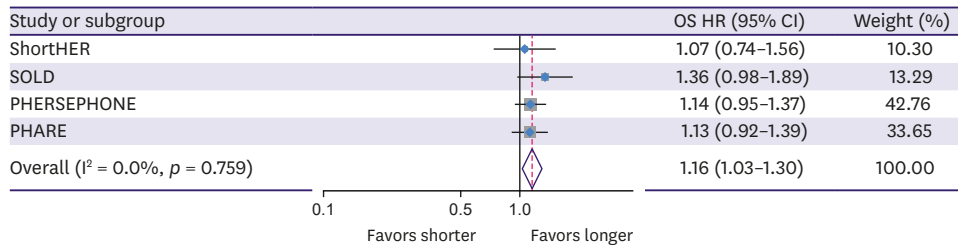
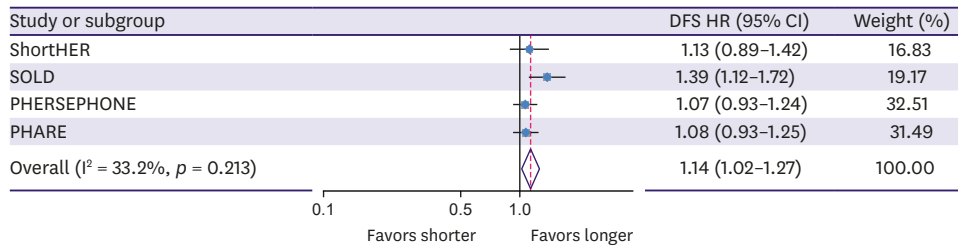


Figure 4. Pooled results of direct comparisons. (A) Results of DFS and OS comparing chemotherapy plus 1-year trastuzumab concurrently versus chemotherapy alone. (B) Results of DFS and OS comparing chemotherapy plus 1-year trastuzumab sequentially versus chemotherapy alone. (C) Results of DFS and OS comparing shorter duration versus 1 year of adjuvant trastuzumab. (D) Results of DFS and OS comparing dual HER2 blockade regimens versus traditional 1-year adjuvant trastuzumab. ALTO trial was divided into 2 parts when driving for direct comparison between dual HER2 blockade and chemotherapy plus 1-year trastuzumab therapy. ALTO 1: chemotherapy + trastuzumab 1 year + lapatinib (concomitant with trastuzumab) vs. chemotherapy plus 1-year trastuzumab therapy; ALTO 2: chemotherapy + trastuzumab 3 months → lapatinib 9 months (sequential to trastuzumab) vs. chemotherapy plus 1-year trastuzumab therapy. OS = overall survival; DFS = disease free survival; CI = confidence interval; HR = hazard ratio; CT = chemotherapy only; H = trastuzumab; + = concurrently administration; → = sequentially administration; m = months; y = year. (continued to the next page)

D Dual HER2 blockade vs. CT + H1y

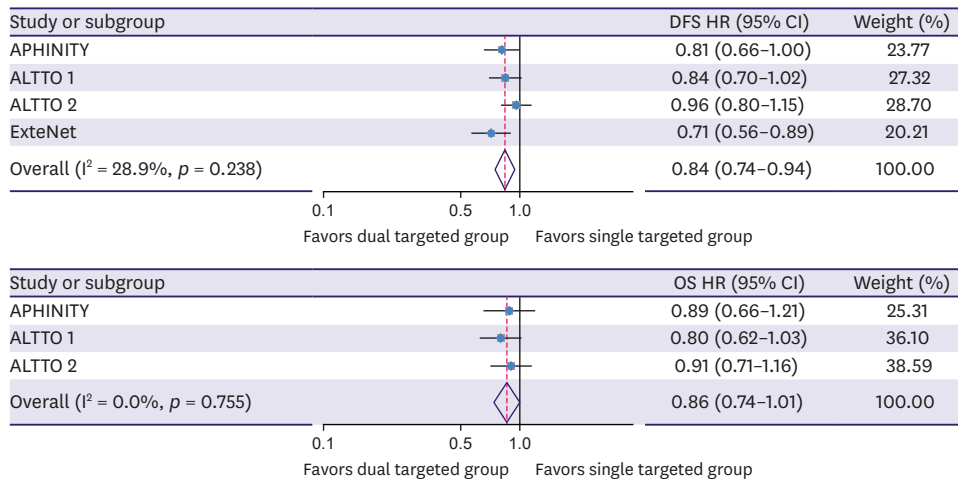


Figure 4. (Continued) Pooled results of direct comparisons. (A) Results of DFS and OS comparing chemotherapy plus 1-year trastuzumab concurrently versus chemotherapy alone. (B) Results of DFS and OS comparing chemotherapy plus 1-year trastuzumab sequentially versus chemotherapy alone. (C) Results of DFS and OS comparing shorter duration versus 1 year of adjuvant trastuzumab. (D) Results of DFS and OS comparing dual HER2 blockade regimens versus traditional 1-year adjuvant trastuzumab. ALTTO trial was divided into 2 parts when driving for direct comparison between dual HER2 blockade and chemotherapy plus 1-year trastuzumab therapy. ALTTO 1: chemotherapy + trastuzumab 1 year + lapatinib (concomitant with trastuzumab) vs. chemotherapy plus 1-year trastuzumab therapy; ALTTO 2: chemotherapy + trastuzumab 3 months → lapatinib 9 months (sequential to trastuzumab) vs. chemotherapy plus 1-year trastuzumab therapy. OS = overall survival; DFS = disease free survival; CI = confidence interval; HR = hazard ratio; CT = chemotherapy only; H = trastuzumab; + = concurrently administration; → = sequentially administration; m = months; y = year.

sequentially and CT alone (HR, 0.77; 95% CI, 0.69–0.86; $p = 0.508$); no significant difference was observed for OS, for which an estimate consistent with large heterogeneity ($I^2 > 50\%$) was found. Subgroup analyses showed a significant increase in DFS with a dual blockade arm for the hormone receptor negative subgroup (HR, 0.79; 95% CI, 0.64–0.97; $p = 0.720$) (**Supplementary Figure 1A**). There were no interactions by hormone receptor status in the improvement of DFS and OS in the CT + H arm compared to CT alone (**Supplementary Figure 1B**). Compared to shorter duration arms, 1-year CT + H showed more DFS benefits in the 1–3 positive lymph nodes subgroup (HR, 1.28; 95% CI, 0.95–1.71; $p = 0.069$) than in the node negative subgroup (HR, 1.14; 95% CI, 0.97–1.34; $p = 0.607$), as well as in the hormone receptor negative subgroup (HR, 1.21; 95% CI, 0.98–1.51; $p = 0.158$) than in the hormone receptor positive subgroup (HR, 1.07; 95% CI, 0.91–1.27; $p = 0.240$), although the benefits were not statistically significant (**Supplementary Figure 1C and D**).

Forest plots for the direct comparisons of AEs are shown in **Supplementary Figure 2**. ORs and the I^2 -value of AEs for the 4 main direct comparisons are summarized in **Table 3**. A lower incidence of cardiac events (OR, 0.51; 95% CI, 0.38–0.69; $p < 0.001$), nausea (OR, 0.54; 95% CI, 0.31–0.93; $p = 0.030$), and fatigue (OR, 0.45; 95% CI, 0.36–0.57; $p < 0.001$) was found in CT + H ≤ 6 m compared to CT + H1y. No significant difference in hematological events and gastrointestinal events was found between the CT + H ≤ 6 m and CT + H1y treatment arms. Similar results were found in CT → H1y versus CT, and the risk of cardiac events was greater in patients treated with trastuzumab (OR, 4.84; 95% CI, 3.30–7.11; $p < 0.001$). The ORs of cardiac events (OR, 2.09; 95% CI, 1.68–2.60; $p < 0.001$), neutropenia (OR, 1.45; 95% CI, 1.21–1.75; $p < 0.001$), leukopenia (OR, 1.41; 95% CI, 1.19–1.68; $p < 0.001$), and vomiting (OR, 1.89; 95% CI, 1.22–2.93; $p = 0.004$) were improved with the administration of trastuzumab for 1 year compared to CT alone. The dual anti-HER2 blockade arm had an increased probability of gastrointestinal reactions, including diarrhea (OR, 8.72; 95% CI, 2.46–30.83; $p < 0.001$), vomiting (OR, 9.69; 95% CI, 3.84–24.44; $p < 0.001$), and nausea (OR, 13.23; 95% CI, 3.13–55.83; $p < 0.001$) compared

Table 3. ORs and I²-value of adverse events for main direct comparisons

Outcome	No. of studies	Events	Total	Events	Total	OR (95% CI)	p-value	I ² (%)
		CT + H1y		CT				
Cardiac events	4	280	4,759	142	4,498	2.09 (1.68–2.60)	< 0.001	0%
Neutropenia	1	764	1,068	665	1,050	1.45 (1.21–1.75)	< 0.001	
Leukopenia	1	644	1,068	544	1,050	1.41 (1.19–1.68)	< 0.001	
Vomiting	1	60	1,068	32	1,050	1.89 (1.22–2.93)	0.004	
Nausea	1	61	1,068	62	1,050	0.97 (0.67–1.39)	0.850	
Diarrhea	1	72	1,068	65	1,050	1.10 (0.77–1.55)	0.610	
Fatigue	1	77	1,068	73	1,050	1.04 (0.75–1.45)	0.820	
		CT → H1y		CT				
Cardiac events	1	146	2,532	33	2,629	4.84 (3.30–7.11)	< 0.001	0%
		CT + H ≤ 6 m		CT + H1y				
Cardiac events	4	472	5,445	759	5,450	0.51 (0.38–0.69)	< 0.001	79%
Neutropenia	1	232	626	218	627	1.10 (0.88–1.39)	0.400	
Vomiting	1	12	2,044	16	2,044	0.75 (0.35–1.59)	0.450	
Nausea	1	20	2,044	37	2,044	0.54 (0.31–0.93)	0.030	
Diarrhea	2	62	2,670	82	2,671	0.75 (0.54–1.05)	0.090	0%
Fatigue	1	117	2,044	243	2,044	0.45 (0.36–0.57)	< 0.001	
		Dual HER2 blockade		CT + H1y				
Cardiac events	4	388	7,909	422	7,965	0.86 (0.51–1.44)	0.560	92%
Neutropenia	1	385	2,364	377	2,405	1.05 (0.90–1.22)	0.570	
Leukopenia	NA	NA	NA	NA	NA	NA	NA	NA
Vomiting	1	47	1,408	5	1,408	9.69 (3.84–24.44)	< 0.001	
Nausea	1	26	1,408	2	1,408	13.23 (3.13–55.83)	< 0.001	
Diarrhea	4	1,209	7,909	167	7,965	8.72 (2.46–30.83)	< 0.001	98%
Fatigue	1	23	1,408	6	1,408	3.88 (1.58–9.56)	0.003	

The reference of OR is treatment arm in the right column. The OR was utilized for pooling effect sizes by the DerSimonian-Laird random effects model. I² statistics evaluated the effect of heterogeneity in the studies' results, the values above 50% indicates large heterogeneity, values of 25–50% indicates modest heterogeneity, and values below 25% indicates low heterogeneity. All statistical tests were 2-sided. CI = confidence interval; OR = odds ratio; CT = chemotherapy only; H = trastuzumab; + = concurrently administration; → = sequentially administration; m = months; y = year; NA = not applicable.

to single targeted therapy. Whereas, the addition of a second anti-HER2 targeted agent did not improve the rate of cardiac events (OR, 0.86; 95% CI, 0.51–1.44; *p* = 0.560).

Network meta-analysis based on a Bayesian model

Survival outcome

A total of 38 indirect comparisons were obtained from the eligible trials. The results of possible pairwise comparisons are presented in the form of HR and corresponding 95% CI calculated by Bayesian network meta-analysis (Table 4). Comparison among the HRs of different trastuzumab-containing chemotherapy regimens (single-targeted regimens with trastuzumab) included in this network favored the 1-year CT + H arm (DFS: HR, 0.61; 95% CI, 0.51–0.74; OS: HR, 0.64; 95% CI, 0.53–0.79), followed by CT + H ≤ 6 m (DFS: HR, 0.63; 95% CI, 0.51–0.78, OS: HR, 0.65; 95% CI, 0.51–0.83), and CT → H2y (DFS: HR, 0.76; 95% CI, 0.59–1.02, OS: HR, 0.70; 95% CI, 0.54–0.95). Among different dual blockade regimens, chemotherapy + trastuzumab 1 year → neratinib 1 year (sequential to trastuzumab) (CT + H-N) showed a significantly increased DFS (HR, 0.7; 95% CI, 0.50–0.97) over the single targeted arm, while chemotherapy + trastuzumab 1 year + lapatinib (concomitant with trastuzumab) (CT + H + L) was associated with a relatively higher OS benefit (HR, 0.79; 95% CI, 0.56–1.11) than others, although this was not statistically significant. The 1-year CT + H arm showed a significant advantage in OS (HR, 0.75; 95% CI, 0.57–0.96) compared to the 1-year chemotherapy + lapatinib 1 year (CT + L) regimen. All these findings reinforced the conclusions of direct comparisons. Analyses of global and local inconsistency were also conducted, and the results showed no significant inconsistency in DFS ($\chi^2 = 3.05$, *p* = 0.549) or OS ($\chi^2 = 2.43$, *p* = 0.658) (Supplementary Figure 3).

Table 4. Estimated HRs or ORs and CIs calculated by Bayesian network meta-analysis

		OS										
DFS	CT	1.30 (0.92-1.80)	NA	1.56 (1.27-1.89)	1.54 (1.20-1.96)	1.31 (0.96-1.63)	1.42 (1.06-1.86)	1.64 (1.15-2.23)	1.17 (0.86-1.52)	1.98 (1.34-2.83)	1.73 (1.19-2.46)	
	0.78 (0.58-1.02)	TC + H	NA	1.20 (0.86-1.77)	1.18 (0.83-1.81)	1.00 (0.66-1.49)	1.10 (0.72-1.69)	1.25 (0.82-1.94)	0.90 (0.58-1.38)	1.51 (0.95-2.41)	1.32 (0.85-2.18)	
	0.44 (0.29-0.63)	0.57 (0.36-0.87)	CT + H-N	NA	NA	NA	NA	NA	NA	NA	NA	
	0.61 (0.51-0.74)	0.79 (0.62-1.07)	1.42 (1.03-2.02)	CT + H1y	0.98 (0.85-1.16)	0.83 (0.57-1.14)	0.90 (0.64-1.28)	1.05 (0.79-1.36)	0.75 (0.57-0.96)	1.26 (0.90-1.77)	1.10 (0.80-1.53)	
	0.63 (0.51-0.78)	0.80 (0.60-1.12)	1.45 (1.02-2.11)	1.03 (0.88-1.17)	CT + H ≤ 6 m	0.84 (0.57-1.18)	0.92 (0.63-1.33)	1.06 (0.76-1.44)	0.76 (0.56-1.01)	1.28 (0.88-1.85)	1.12 (0.79-1.61)	
	0.76 (0.62-1.00)	0.98 (0.71-1.51)	1.77 (1.17-2.84)	1.26 (0.94-1.70)	1.20 (0.91-1.74)	CT-H1y	1.09 (0.85-1.47)	1.25 (0.84-1.95)	0.90 (0.62-1.33)	1.51 (0.97-2.44)	1.33 (0.87-2.12)	
	0.76 (0.59-1.02)	0.98 (0.69-1.52)	1.75 (1.12-2.90)	1.27 (0.91-1.73)	1.22 (0.88-1.76)	1.01 (0.75-1.29)	CT-H2y	1.15 (0.74-1.76)	0.82 (0.55-1.20)	1.38 (0.87-2.20)	1.22 (0.77-1.91)	
	0.54 (0.40-0.77)	0.70 (0.49-1.07)	1.26 (0.84-1.98)	0.88 (0.68-1.18)	0.86 (0.65-1.20)	0.69 (0.46-1.04)	0.70 (0.47-1.09)	CT + H + P	0.72 (0.49-1.03)	1.21 (0.80-1.88)	1.05 (0.70-1.62)	
	0.75 (0.61-0.98)	0.97 (0.72-1.42)	1.76 (1.20-2.73)	1.26 (0.99-1.56)	1.20 (0.95-1.60)	1.00 (0.71-1.37)	0.99 (0.69-1.42)	1.43 (0.98-2.00)	CT + L	1.69 (1.21-2.34)	1.48 (1.08-2.06)	
	0.52 (0.38-0.69)	0.66 (0.45-0.99)	1.16 (0.76-1.85)	0.84 (0.62-1.09)	0.82 (0.59-1.12)	0.67 (0.44-0.95)	0.67 (0.43-0.98)	0.94 (0.62-1.35)	0.67 (0.50-0.86)	CT + H + L	0.88 (0.62-1.27)	
	0.56 (0.43-0.78)	0.73 (0.52-1.10)	1.30 (0.88-2.12)	0.94 (0.70-1.22)	0.90 (0.68-1.27)	0.75 (0.50-1.08)	0.74 (0.49-1.12)	1.07 (0.71-1.54)	0.75 (0.57-0.98)	1.11 (0.84-1.54)	CT + H-L	
	Cardiac event	CT	1.16 (0.64-2.08)	NA	0.46 (0.32-0.64)	0.88 (0.56-1.36)	0.23 (0.14-0.37)	0.14 (0.07-0.26)	0.39 (0.19-0.79)	0.88 (0.54-1.48)	0.43 (0.23-0.82)	1.00 (0.50-1.96)
	0.86 (0.48-1.56)	TC + H	NA	0.39 (0.22-0.70)	0.75 (0.41-1.47)	0.20 (0.10-0.41)	0.12 (0.05-0.27)	0.34 (0.15-0.80)	0.76 (0.38-1.57)	0.37 (0.17-0.87)	0.86 (0.37-2.01)	
	NA	NA	CT + H-N	NA	NA	NA	NA	NA	NA	NA	NA	
	2.17 (1.56-3.16)	2.54 (1.43-4.50)	NA	CT + H1y	1.91 (1.45-2.64)	0.51 (0.30-0.86)	0.30 (0.14-0.60)	0.86 (0.47-1.61)	1.92 (1.19-3.20)	0.94 (0.53-1.74)	2.16 (1.18-4.19)	
1.14 (0.73-1.78)	1.33 (0.68-2.46)	NA	0.52 (0.38-0.69)	CT + H ≤ 6 m	0.27 (0.14-0.48)	0.16 (0.07-0.32)	0.45 (0.23-0.89)	1.01 (0.56-1.77)	0.49 (0.25-0.95)	1.14 (0.56-2.26)		
4.27 (2.70-6.90)	4.97 (2.41-10.12)	NA	1.95 (1.16-3.34)	3.76 (2.08-6.91)	CT-H1y	0.59 (0.31-1.03)	1.69 (0.74-3.82)	3.79 (1.97-7.40)	1.85 (0.85-4.02)	4.27 (1.94-9.50)		
7.23 (3.91-14.43)	8.47 (3.66-20.48)	NA	3.33 (1.67-7.05)	6.34 (3.09-14.29)	1.70 (0.97-3.20)	CT-H2y	2.86 (1.15-7.59)	6.39 (2.95-14.93)	3.14 (1.30-8.01)	7.24 (2.94-18.95)		
2.54 (1.26-5.16)	2.96 (1.24-6.88)	NA	1.17 (0.62-2.14)	2.22 (1.12-4.42)	0.59 (0.26-1.36)	0.35 (0.13-0.87)	CT + H + P	2.24 (1.00-4.93)	1.09 (0.47-2.58)	2.52 (1.06-6.17)		
1.13 (0.68-1.84)	1.32 (0.64-2.65)	NA	0.52 (0.31-0.84)	0.99 (0.57-1.79)	0.26 (0.14-0.51)	0.16 (0.07-0.34)	0.45 (0.20-1.00)	CT + L	0.49 (0.26-0.90)	1.13 (0.59-2.12)		
2.31 (1.22-4.41)	2.70 (1.15-5.93)	NA	1.07 (0.57-1.90)	2.04 (1.05-3.99)	0.54 (0.25-1.17)	0.32 (0.12-0.77)	0.92 (0.39-2.15)	2.05 (1.11-3.85)	CT + H + L	2.32 (1.20-4.49)		
1.00 (0.51-1.98)	1.17 (0.50-2.67)	NA	0.46 (0.24-0.85)	0.88 (0.44-1.79)	0.23 (0.11-0.52)	0.14 (0.05-0.34)	0.40 (0.16-0.95)	0.89 (0.47-1.68)	0.43 (0.22-0.84)	CT + H-L		

Upper: HR and 95% CIs for survival outcome (DFS and OS). Lower: ORs and corresponding 95% CIs for cardiotoxicity. The green color indicates the comparisons between different trastuzumab-containing chemotherapy regimens and chemotherapy alone. The yellow color indicates the comparisons between different dual blockade regimens and traditional 1-year trastuzumab plus chemotherapy. The blue color indicates the comparisons among different duration of trastuzumab added into adjuvant chemotherapy. The references of HRs for green color and yellow color are chemotherapy alone and traditional 1-year trastuzumab plus chemotherapy, respectively. Comparing HRs between each treatment arm with the same reference indicates the option that most effectively improves DFS or OS. HR = hazard ratio; CI = confidence interval; OR = odds ratio; OS = overall survival; DFS = disease free survival; NA = not applicable; CT = chemotherapy only; TC = taxane-based chemotherapy regimen; H = trastuzumab; L = lapatinib; N = netatinib; P = pertuzumab; + = concurrently administration; → = sequentially administration; m = months; y = year.

Toxicity outcome

With regards to the toxicity outcome, a limited number of studies provided data on the estimation of hematological and gastrointestinal events; thus, only the presence of cardiac events could be evaluated by the Bayesian model. ORs and corresponding 95% CIs for the cardiotoxicity observed in 10 treatment arms (except for arm 11) are shown in **Table 4**. Of the entire pairwise comparisons, 29 showed significant differences. The addition of adjuvant trastuzumab to chemotherapy regimens improved the incidence of cardiac events compared to chemotherapy only, either a 2- or 1-year duration (CT → H2y: OR, 7.23; 95% CI, 3.91-14.43;

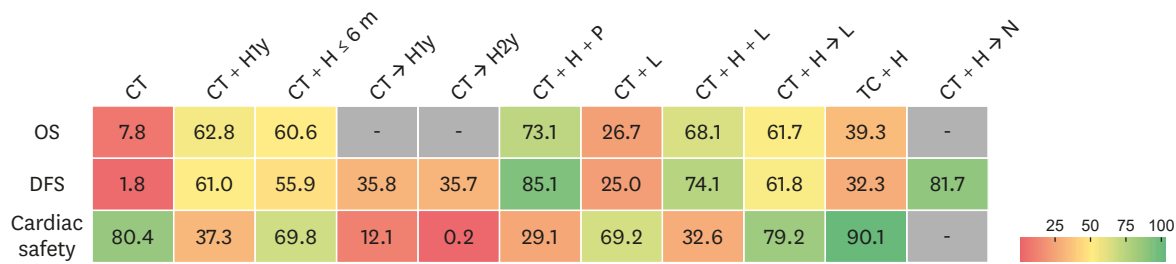


Figure 5. Heatmap graph of SUCRA. The SUCRA values shown in each box are in proportion to the probability of each treatment arm to be the best option with more survival efficacy and fewer cardiac events. The green color represents higher SUCRA value and the red color is reverse. SUCRA = surface under the cumulative ranking; OS = overall survival; DFS = disease free survival; CT = chemotherapy only; H = trastuzumab; L = lapatinib; N = netatinib; P = pertuzumab; TC = taxane-based chemotherapy regimen; + = concurrently administration; → = sequentially administration; m = months; y = year.

CT → H1y: OR, 4.27; 95% CI, 2.70–6.90; CT + H1y: OR, 2.17; 95% CI, 1.56–3.16). Considering the duration, longer-term use of trastuzumab increases cardiotoxicity. CT plus 1-year adjuvant trastuzumab therapy increased the risk of cardiotoxicity more than shorter-term (less than 6 months) trastuzumab (OR, 1.91; 95% CI, 1.45–2.64). The CT → H2y regimen was associated with a significantly higher risk of cardiotoxicity than the CT + H1y regimen (OR, 3.33; 95% CI, 1.67–7.05) and the CT + H ≤ 6 m regimen (OR, 6.34; 95% CI, 3.09–14.29). There were no global or local inconsistencies in the analysis of cardiac events ($\chi^2 = 3.57, p = 0.735$) (**Supplementary Figure 4**).

Ranking of treatment arms by efficacy and safety

According to SUCRA (**Figure 5**), the arm with highest probability to be the most effective treatment regimen in terms of OS was chemotherapy + trastuzumab 1 year + pertuzumab (concomitant with trastuzumab) (CT + H + P) (SUCRA = 73.1), followed by CT + H + L (SUCRA = 68.1), and CT + H1y (SUCRA = 62.8). A similar result was seen with regards to DFS, for which CT + H-N also showed an excellent result (SUCRA = 81.7). CT alone and CT + L had less chance to become the best arm according to their low SUCRA values for OS (SUCRA = 7.8 and 26.7, respectively) and DFS (SUCRA = 1.8 and 25, respectively). chemotherapy (taxane plus carboplatin) + trastuzumab 1 year, CT alone, and chemotherapy + trastuzumab 3 months → lapatinib 9 months (sequential to trastuzumab) had the best results for cardiac safety (SUCRA = 90.1, 80.4, and 79.2, respectively), and CT → H2y and CT → H1y had the worst (SUCRA = 0.2 and 12.1, respectively). The eleven treatment arms which formed the network are ranked in **Table 5**. In terms of OS, the results demonstrated that CT + H + P had the highest probability to be the rank 1 (39.9%), CT + H + L to be the rank 2 (21%), and CT + H1y to be the rank 3 (26.9%). For DFS, CT + H + P and CT + H-N are probably the best option for HER2⁺ EBC treatment (with 41.4% and 34.8%, respectively of posterior probability of rank 1), followed by CT + H + L (with 22.6% and 21.7% of posterior probability of rank 2 and rank 3, respectively). Furthermore, the CT → H2y regimen was considered as the worst one in terms of cardiac safety with 98.5% of posterior probabilities, followed by the CT → H1y regimen (90.1% of posterior probabilities of the second worst one).

DISCUSSION

We updated previous network meta-analyses by combining newly published RCTs for HER2-targeted therapies in the postoperative treatment of HER2⁺ EBC. This network analysis derived direct head-to-head and indirect comparisons to help doctors and patients to select

Table 5. Ranking for OS, DFS, and cardiac safety

	Arm											
	1	2	3	4	5	6	7	8	9	10	11	
OS												
Rank												
1	0	3.4	10.5	-	-	39.9	0.6	21.4	14.6	9.4	-	
2	0.1	16.8	17.7	-	-	15.8	1.3	21	18.5	8.8	-	
3	0.2	26.9	18.3	-	-	11.1	3.8	16.5	16.1	7.1	-	
4	0.7	29	18	-	-	9.1	6.2	13.8	15	8.2	-	
5	2.4	17.6	17.2	-	-	8.4	13	14.1	16.5	10.9	-	
6	8.2	5.2	12	-	-	7.2	29.6	8.7	11.9	17.1	-	
7	26.7	1	5.1	-	-	5.4	32.8	3.3	5.1	20.6	-	
8	61.7	0	1.2	-	-	3	12.7	1.2	2.3	17.8	-	
DFS												
Rank												
1	0	0.2	1.2	1.7	2.3	41.4	0	12.4	4.5	1.5	34.8	
2	0	2.7	6	3.4	3.4	24.7	0	22.6	10.6	2.5	24.1	
3	0	12.6	11.6	4.5	5	11.7	0.3	21.7	16.4	3.6	12.8	
4	0	23.5	14.7	5	4.7	7.7	0.7	14.5	16.5	4	8.8	
5	0	29.2	17.3	5.5	5.8	4.8	1.9	10.5	13.5	5.4	5.9	
6	0	20.3	20	7.6	6.9	4.2	5	8.2	15.2	7.5	5.1	
7	0	8.3	13.6	13.3	13	2.5	14.8	5.5	11.2	13.8	4	
8	0.1	2.6	9.6	19.1	17.3	1.8	22.1	3.1	6.6	15.3	2.3	
9	1.4	0.6	4.6	21.2	19.9	0.8	27	1.2	4.4	17.6	1.3	
10	14.5	0	1.5	15.8	17.7	0.4	26.3	0.2	1.2	21.7	0.7	
11	84	0	0	3	4	0	1.8	0	0	7	0.1	
Cardiac safety												
Rank												
1	11.9	0	4.6	0	0	0	5.5	0	23.6	54.3	-	
2	33.5	0	12.3	0	0	0	11.7	0	21.4	21.1	-	
3	28.1	0	22.8	0	0	0	19.3	0	18.5	11.3	-	
4	19.2	0	27.7	0	0	0.1	27.7	0.1	17.5	7.7	-	
5	7.4	0.2	32.1	0	0	0.8	35	0.4	18.6	5.5	-	
6	0	45.4	0.4	0.1	0	20	0.6	33	0.4	0.1	-	
7	0	44.8	0	0.9	0	25.4	0	28.8	0	0	-	
8	0	9.7	0	7.7	0	47.9	0	34.7	0	0	-	
9	0	0	0	90.1	1.5	5.6	0	2.8	0	0	-	
10	0	0	0	1.2	98.5	0.3	0	0.1	0	0	-	

Each value represents the probability of each arm to be a specific rank. Green color represents higher probability, conversely, red color represents lower. All statistical tests were 2-sided. The 2 trials (HERA and PACS-04) included in the comparison between chemotherapy followed by 1-year trastuzumab and chemotherapy alone (CT-H1y vs. CT) have been found to have high heterogeneity ($p = 63%$) in the analysis for OS efficacy, thus they were excluded from the ranking. Arm 1, chemotherapy only; arm 2, chemotherapy + trastuzumab 1 year; arm 3, chemotherapy + trastuzumab ≤ 6 months; arm 4, chemotherapy → trastuzumab 1 year (sequential to chemotherapy); arm 5, chemotherapy → trastuzumab 2 year (sequential to chemotherapy); arm 6, chemotherapy + trastuzumab 1 year + pertuzumab (concomitant with trastuzumab); arm 7, chemotherapy + lapatinib 1 year; arm 8, chemotherapy + trastuzumab 1 year + lapatinib (concomitant with trastuzumab); arm 9, chemotherapy + trastuzumab 3 months → lapatinib 9 months (sequential to trastuzumab); arm 10, chemotherapy (taxane plus carboplatin) + trastuzumab 1 year; arm 11, chemotherapy + trastuzumab 1 year → neratinib 1 year (sequential to trastuzumab). OS = overall survival, DFS = disease free survival.

the optimal HER2-targeted regimen in an adjuvant setting, based on the trade-off between clinical benefits and cardiac safety. A previous network meta-analysis conducted by Shen et al. [17] compared the effect of currently approved adjuvant H-containing chemotherapies on OS, EFS, and cardiotoxicity among patients with early-stage HER2⁺ primary breast cancer. Subsequently, Debiasi drove another network meta-analysis that included more recently developed HER2-targeted agents, and evaluated their efficacy for HER2⁺ EBC in adjuvant or neoadjuvant chemotherapy. However, none of these previous studies analyzed whether a shorter duration of trastuzumab treatment reduced the risk of AEs. Furthermore, neither of the abovementioned studies performed a subgroup analysis to observe which group of patients was most likely to benefit from different HER2-targeted regimens.

We demonstrate profound improvements in DFS and OS with the use of 1 year of trastuzumab compared to CT alone for the total, hormone receptor-positive, and hormone receptor-negative populations. In terms of clinical efficacy, a significant advantage of 1-year adjuvant trastuzumab treatment over shorter treatment durations (6 months or 9 weeks) and a 2-year treatment duration was shown in the Bayesian model. Compared to CT + H < 6 m, the effect of 1-year trastuzumab on DFS was more pronounced in the hormone receptor-negative population, although the magnitude was not significantly different from those with hormone receptor-positive tumors. Compared to adjuvant chemotherapy only, the addition of trastuzumab improved the incidence of cardiac events, while the CT → H2y regimen was associated with significantly higher risk than the CT + H1y regimen and the CT + H ≤ 6 m regimen. CT plus 1-year duration of trastuzumab therapy increased the risk of cardiotoxicity compared to shorter-term (less than 6 months) trastuzumab therapy, both in direct and indirect comparisons. These results suggested that long-term trastuzumab treatment might lead to higher incidence of cardiac events. Furthermore, CT plus dual blockade increased DFS compared to the standard CT + H1y regimen, but showed no significant improvement in cardiac events. Furthermore, the hormone receptor-negative subgroup showed a significant improvement in DFS from dual blockade treatment compared to single targeted therapy. Therefore, CT + H1y should remain as the standard treatment according to its favorable efficacy and manageable risk of cardiotoxicity in HER2-positive EBC patients. Patients with hormone receptor-negative primary tumors may benefit from greater clinical efficacy by combining a second HER2-targeted agent. Among hormone receptor-positive HER2⁺ patients with previously basal disease, elderly, or patients who cannot afford a full year of trastuzumab treatment, it is acceptable and reasonable to reduce the risk of cardiotoxicity and save the medical expenses through shortening the duration of trastuzumab treatment.

A robust body of evidence has demonstrated that chemotherapy plus trastuzumab form the backbone in the adjuvant setting for HER2⁺ EBC patients [26,27]. The addition of trastuzumab could reduce the risk of recurrence and death by approximately 40%. The BCIRG-006, HERA, NSABP-B31, and NCCTG-N9831 trials have showed significant benefit of 1-year adjuvant trastuzumab, and a 1-year duration was well established as a standard treatment duration due to these pivotal licensing trials. However, the optimal duration for adjuvant trastuzumab remained unclear. In 2006, the FinHer trial reported that 9-week trastuzumab administered concomitantly with chemotherapy led to a significant improvement in DFS compared to chemotherapy alone (HR, 0.29; 95% CI, 0.13–0.64; $p = 0.002$) [15]. The results encouraged interest in whether shorter trastuzumab treatment durations could bring benefits that were equal to, or greater than those observed with the standard duration. A series of non-inferiority studies (SOLD, Short-HER, E2198, HORG, and PHARE) were performed with the aim to determine the feasibility of a shorter duration (9 weeks, 12 weeks, or 6 months) of adjuvant trastuzumab. However, none of these trials reached the pre-specified margin of non-inferiority, which failed to demonstrate the non-inferiority for shorter duration treatment regimens. Since different frequencies and doses of trastuzumab can be a source of heterogeneity, the results of E2198 and HORG were not used for calculation in the direct comparison between shorter and longer treatment durations in this study. The PERSEPHONE trials were devised to assess 6-month versus 1-year trastuzumab treatment, possessing similar design and same endpoint with the PHARE trial, but reached opposite results. This discordance was derived from the pre-specified endpoint values. The updated conclusions of the PERSEPHONE trial were presented in June 2019, with a median follow-up of 5.4 years, and showed a HR of 1.07 (95% CI, 0.93–1.24) which was similar to the final analysis of the PHARE trial (HR, 1.08; 95% CI, 0.93–1.25). The PHARE trial considered 2% as non-inferiority

margin and set 1.15 on the HR scale, therefore didn't show non-inferiority. Whereas the PERSEPHONE trial with a 3% non-inferiority margin and 1.29 HR boundary was the only clinical trial to provide a positive result and show 6-month treatment was non-inferior to the standard duration of care. Therefore, the PERSEPHONE trial contained a considerable debate. A meta-analysis in 2018 evaluated 5 RCTs to compare 1-year duration of adjuvant trastuzumab versus a shorter duration in HER2⁺ EBC patients. The study claimed that a 1-year duration was associated with significantly better DFS (HR, 1.19; 95% CI, 1.08–1.3; $p < 0.001$) and OS (HR, 1.22; 95% CI, 1.07–1.39; $p = 0.003$). Moreover, a shorter duration was related to a lower risk of cardiac events (RR, 0.4; 95% CI, 0.32–0.49; $p < 0.001$) [28].

In our study, we suggested that patients may benefit more from CT with dual HER2 blockade, regardless of whether pertuzumab, lapatinib, or neratinib was used as a second agent, than CT with trastuzumab only (Tables 4 and 5, and Figure 5). Subgroup analysis showed that hormone receptor-negative patients could benefit more from dual blockade treatments; however, addition of a second anti-HER2 targeted agent increased the probability of gastrointestinal reactions, including diarrhea, vomiting, and nausea compared to single targeted therapy, without improving the rate of cardiac events. Therefore, hormone receptor-negative patients could receive a second targeted agent under the premise of gastrointestinal reaction prevention to reinforce clinical efficacy and improve long-term prognosis. Among dual blockade treatment regimens, CT + H-N showed significantly higher DFS, while CT + H + L showed higher OS benefit. SUCRA in indirect comparisons indicated that CT + H + P was probably the most effective strategy in terms of both DFS and OS, with posterior probabilities of these regimes. Previous investigations have proven that dual anti-HER2 blockade could improve the pathological complete response rate (pCR) in neoadjuvant settings, and survival outcomes in the adjuvant scenarios of metastasis or advanced HER2⁺ breast cancer. Furthermore, the APHINITY and ExteNET trials have brought powerful evidence for the efficacy and safety of dual-targeted therapy for EBC. In SABCs 2019, the updated results of the APHINITY trial still showed positive results in the 6-year follow-up, in which the invasive DFS (iDFS) rate was 90.6% and 87.8% for the pertuzumab and placebo groups, respectively. With regards to safety, diarrhea was more frequent in the pertuzumab group, whereas cardiac events were infrequent; this further supported the combination of trastuzumab and pertuzumab as a feasible adjuvant treatment for HER2-positive EBC patients. Our findings were perhaps unexpected, owing to the negative outcome of the ALTTO trial [25,29,30], in which the addition of lapatinib in adjuvant targeted therapy showed no significant improvement in survival outcomes, and increased toxicity. However, we should consider that the enrollment of low-risk participants might lead to fewer AEs, and even cause conservative biases. Considering that our study diluted the results from ALTTO, we further applied network meta-analysis that excluded the 2 dual targeted arms in ALTTO (Supplementary Data 1), the result of which could still support our conclusions of the indirect comparison among HER2 targeted therapies. Future results of current studies over a longer follow-up period, and mounting rigorous explorations are warranted to provide powerful evidence to validate the recommendation for dual anti-HER2 blockade therapy in this circumstance.

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that incorporates the anti-HER2 properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1, which is used in the intensive adjuvant treatment for metastatic breast cancer and HER2⁺ EBC. The KATHERINE study enrolled 1486 HER2⁺ non-pCR patients (remnant invasive tumors within breast and/or axillary lymph nodes) after receiving neoadjuvant chemotherapy, who were randomized into a trastuzumab plus chemotherapy arm or T-DM1 treatment arm for

14-cycle adjuvant therapy. The mid-term results showed that T-DM1 led to a 11.3% increase in 3-year iDFS (HR, 0.50; 95% CI, 0.39–0.64, $p < 0.001$), which suggested that T-DM1 is eligible for HER2⁺ EBC patients who have residual invasive cancer following neoadjuvant treatment. Nevertheless, the results of KATHERINE were not used for calculation in our network analysis, as T-DM1 is not currently the first line agent for neoadjuvant or adjuvant therapy, and its pharmacological mechanism is robustly different from that of trastuzumab.

Our study provided insight into the best HER2-targeted therapies for HER2-positive EBC; however, several limitations should be considered when interpreting the results. Significant heterogeneity was discovered among the included RCTs with regards to the efficacy and safety assessment of HER2-targeted therapies. This may be explained by differences in the study characteristics, including the study design, treatment regimens, sample size, and the definition of AEs. Firstly, for data organization, we integrated various chemotherapy regimens, including anthracycline-based (AC), taxane-based (TC), or anthracycline-, cyclophosphamide-, and taxane-based chemotherapy regimen (ACT); ACT was the most common adjuvant chemotherapy among all RCTs. The administered sequence of taxanes can be either simultaneous or sequential with AC. Secondly, the number of trials, and participants enrolled and assessed in our study were relatively small in some regimens, especially TC-H and dual anti-HER2 blockade targeted therapy. Most treatment arms involved at least 2 chemotherapy groups, and we grouped these cytotoxic agents as CT during analysis, because we focused on the differences between anti-HER2 targeted therapies. Furthermore, the therapeutic effects varied across different chemotherapy options, and lead to bias. Thirdly, the studies included in this meta-analysis spanned a long period (2009–2019), during which, the use of trastuzumab and supportive care varied, and were further developed. Finally, the definition of AEs differs between published investigations, and the number of patients experiencing toxicity might be over- or underestimated. The definition of LVEF thresholds, which lead to change in the number of cardiac events, may influence the ORs between different treatment regimens. Although such biases may bring slight deviations, we considered it unlikely that these would affect our final conclusions.

Our work indicates that a shorter duration of trastuzumab treatment shows less clinical efficacy than the standard 1-year regimen, whereas the former was associated with significantly lower risk of cardiac events and fatigue. Adjuvant dual anti-HER2 blockade with chemotherapy significantly improves DFS and OS compared to CT plus single targeting agents for HER2⁺ EBC, despite the increasing risk of digestive reactions. Mature OS and AEs results from ExteNET and other large RCTs of dual HER2 blockade are expected in the future. Conforming to the trend of personalized medicine, indicators encompassing the risk of recurrence, safety, basal healthy conditions, and personal preferences should be combined with systematic analysis of trials to provide evidence for clinical practice. This network meta-analysis supports that improvement of therapeutic efficacy is the main priority when selecting treatment regimens for HER2⁺ EBC patients with relatively high risk, whereas reducing the risks of serious AEs should be considered for those with lower risk or other basal disease.

SUPPLEMENTARY MATERIALS

Supplementary Data 1

Results of network meta-analysis that excluded the 2 dual targeted arms in ALTTO

[Click here to view](#)

Supplementary Table 1

Risk of bias assessment of eligible trials

[Click here to view](#)**Supplementary Figure 1**

Pooled results of subgroup analysis. (A) DFS with dual HER2 blockade arm versus CT plus 1-year trastuzumab based on hormone receptor status. (B) DFS and OS with chemotherapy plus 1-year trastuzumab versus CT alone based on hormone receptor status. (C, D) DFS with shorter duration versus 1 year of trastuzumab based on hormone receptor status and nodal status respectively. ALTTO trial was divided into 2 parts when driving for direct comparison between dual HER2 blockade and chemotherapy plus 1-year trastuzumab therapy. ALTTO 1: chemotherapy + trastuzumab 1 year + lapatinib (concomitant with trastuzumab) vs. chemotherapy plus 1-year trastuzumab therapy; ALTTO 2: chemotherapy + trastuzumab 3 months → lapatinib 9 months (sequential to trastuzumab) vs. chemotherapy plus 1-year trastuzumab therapy.

[Click here to view](#)**Supplementary Figure 2**

Pooled results of direct comparisons of AEs. (A) Results of AEs a-g comparing chemotherapy plus 1-year trastuzumab concurrently versus chemotherapy alone. (B) Results of AEs (a-g) comparing shorter duration versus 1 year of adjuvant trastuzumab. (C) Results of AEs (a-f) comparing dual HER2 blockade regimens versus traditional 1-year adjuvant trastuzumab. ALTTO trial was divided into 2 parts when driving for direct comparison between dual HER2 blockade and chemotherapy plus 1-year trastuzumab therapy. ALTTO 1: chemotherapy + trastuzumab 1 year + lapatinib (concomitant with trastuzumab) vs. chemotherapy plus 1-year trastuzumab therapy; ALTTO 2: chemotherapy + trastuzumab 3 months → lapatinib 9 months (sequential to trastuzumab) vs. chemotherapy plus 1-year trastuzumab therapy.

[Click here to view](#)**Supplementary Figure 3**

Analyses of global and local inconsistency of DFS and OS. In global inconsistency analysis, $p < 0.05$ indicates the inconsistent model is significant, for which the consistent model could not be used. For network meta-analysis, node-slitting method was used to analyze the local inconsistency, and $p < 0.05$ indicates the significant local inconsistency.

[Click here to view](#)**Supplementary Figure 4**

Analyses of global and local inconsistency of cardiac safety. In global inconsistency analysis, $p < 0.05$ indicates the inconsistent model is significant, for which the consistent model could not be used. For network meta-analysis, nodeslitting method was used to analyze the local inconsistency, and $p < 0.05$ indicates the significant local inconsistency.

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