Dual HER-2 blockade therapy increases the risk of developing cardiac toxicities in HER-2 positive breast cancer: an up-to-date comprehensive meta-analysis

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Abstract

Background To investigate the incidence and risk of cardiac toxicities between dual HER-2 blockade and anti-HER-2 monotherapy.

Materials and Methods We searched PubMed, EMBASE and Cochrane library databases to identify relevant trials between January 1 1990 and October 31 2019. Statistical analyses were conducted to calculate the summary incidence, Petro odds radio (Peto ORs) and 95% confidence intervals (CIs) by using either random-effects or fixed-effects models.

Results A total of 16,375 patients from 15 randomized controlled trials were included for analysis; the pooled incidence of LVEF decline and CHF in dual HER-2 blocked were 4.6% and 0.9%, which was higher than that in anti-HER-2 monotherapy (3.2% and 0.7%, respectively). Dual HER-2 blockade therapy in breast cancer patients significantly increased the risk of developing LVEF decline (OR:1.19, 95%CI: 1.02-1.40, p=0.031) and CHF (OR:1.45, 95%CI: 1.00-2.11, p=0.049) when compared to anti-HER2 monotherapy. Sub-group analysis showed that addition of dual HER-2 blockade to adjuvant treatment for breast cancer significantly increased the risk of developing LVEF decline (p=0.048) and CHF (p=0.005). In addition, dual HER-2 blockade in breast cancer patients significantly increased the risk of developing LVEF decline (p=0.004) when compared to lapatinib alone, but not for CHF (p=0.11, respectively).

Conclusion Dual HER-2 targeted therapy in HER-2 positive breast cancer significantly increase the risk of developing LVEF and CHF when compared to anti-HER-2 alone, though the overall incidence of cardiac toxicities is very low. Physicians should be aware of this risk and provide close monitoring during the administration of dual HER-2 targeted therapy.

Introduction

During the past decades, the increased knowledge of biological mechanisms involving tumor proliferation and progression has led to the introduction of novel approaches for the treatment of cancer. The epidermal growth factor receptor (EGFR) family of transmembrane receptor tyrosine kinases is one such therapeutic target, which is overexpressed or mutated in multiple cancers[1, 2]. Unlike other members of EGFR family, HER2/ErbB2 is a non-ligand-binding member of this family and exerts its activity through heterodimerization with other EGFR family members(EGFR, HER3,HER4)[3, 4]. And HER2 overexpression could also lead to HER2 dimerization and constitutive activation in the absence of ligand. Initially, HER2 overexpression is found in approximately 15–20% of breast cancer[5], then its overexpression was also detected in a subsets of many other cancer types, such as gastric[6], lung[7] or colorectal cancer[8]. In the last two decades, the introduction of monoclonal antibodies (MoAbs), TKIs or antibody-drug conjugates, which directly targets HER2 gene, has impressively improved the outcomes of HER-2 positive breast cancer patient in all disease stages[9–11]. Subsequently, the addition of anti-HER2 MoAbs to chemotherapy in HER-2 positive locally advanced gastric or gastro-oesophageal junction (GEJ) cancer also significantly improve overall survival. Currently, routine assessment of HER2 status in these

tumors is mandatory, and the use of anti-HER2 agents have become a standard treatment for in HER-2 positive breast or gastric or GEJ cancer.

However, nearly all patients with metastatic HER2-positive breast cancer or gastric or GEJ cancer would eventually progress on anti-HER2 therapy due to de novo or acquired resistance, potentially due to incomplete blockade of HER2 pathway. Therefore, inhibiting the HER2 signaling pathway more effectively with dual blockade approaches by using improved anti-HER2 therapies has been extensively investigated in both breast cancer and gastric or GEJ cancer, and dual HER2 blockade shows promising results in HER-2 positive breast cancer. Nevertheless, with the increasing use of dual HER2 blockade, particularly in the curative adjuvant setting, concerns regarding cardiac toxicities associated with dual anti-HER2 treatment in breast cancer patients has been increased. Therefore, there is an urgent need to clearly determine the overall incidence and risk of cardiac toxicities associated with dual HER2 blockade. Prior to the present study, Valachis A[12]. performed a meta-analysis to investigate the risk of cardiac toxicities related to dual HER2 blockade in breast cancer, and found that cardiac toxicities in anti-HER2 combination therapy was comparable to that of anti-HER2 monotherapy[12]. But the sample size in that study are relative small, and most of the included studies have updated cardiac toxicities data. In addition, more randomized controlled trials assessing efficacy and toxicities of dual HER2 blockade in breast cancer have been conducted since then. As a result, we perform the present study to comprehensively investigate the incidence and risk of cardiac toxicities associated with dual HER-2 blockade in breast cancer when compared to anti-HER2 monotherapy by using a meta-analysis.

Materials And Methods

Study design

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines 2009, the authors conducted the present systematic review and meta-analysis [13].

Data source

From January 1 1990 to October 31 2019, we searched related citations in PubMed by using the following keywords: trastuzumab, lapatinib, pertuzumab, T-DM1, neratinib, pyrotinib, anti-HER2 agents, HER2 blockade, breast cancer, breast carcinoma, clinical trial and randomized. We also performed independent searches in EMBASE and Cochrane library databases to identify relevant trials. Moreover, abstracts of dual HER-2 blockade therapy in breast cancer presented at the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) annual meetings between 2004 and 2013 were searched. Candidate prospective trials were initially screened and we only included the most comprehensive and updated trials in cases of duplicate publications.

Outcome definition

Incidence and risk of left ventricular ejection fraction (LVEF) decline and congestive heart failure (CHF) were the primary endpoints for the present study. According to the CTC-AE grading system, LVEF decline was defined as LVEF decline less than 50% or a decrease of more than 10% from baseline, while CHF defined as New York Heart Association (NYHA)

class III or IV or cardiac death. To avoid loss of information, trials reported LVEF decline more than 15% or 20% from baseline was also regarded as LVEF decline in the present analysis.

Data extraction

Two investigators (WXQ and JYC) initially performed the data extraction including the followings: Trial name, treatment setting, anti-HER2 regimen and dosage, duration of anti-HER2 therapy, concomitant therapy. Data related to the primary outcomes were also extracted including No. of LVEF decline, No. of CHF and No. of patients for safety analysis. The extracted data were cross-checked by another two investigators (CX and UC), and any discrepancies were resolved by consensus.

Study selection

Prospective randomized, controlled phase 2 or 3 trials investigating the cardiac safety of dual HER2 blockade versus anti-HER2 monotherapy (lapatinib or trastuzumab or pertuzumab or T-DM1) in breast cancer were included for analysis. For trials with multiple intervention arms (for example, three-arms trials with two anti-HER2 monotherapy arms and one combined anti-HER2 therapy arm), we merged the two relevant (anti-HER2 monotherapy) arms into one group, then compared the merged group with dual HER-2 blockade group as previously reported[12]. Additionally, we used the five-item Jadad scale including randomization, double-blinding, and withdrawals as previously described to assess the quality of included trials. the final score was reported between 0 and 5[14].

Statistical analysis

Events of cardiac toxicities (LVEF decline or CHF) and total number of breast cancer patients treated with anti-HER2 agents or dual HER-2 blockade were extracted to calculate the overall incidence and corresponding 95% confidence intervals (CIs). An appropriate statistical model (fixed or random-effect model) was used to pool the overall incidence and corresponding 95% CIs based on the heterogeneity results. Binary data of cardiac toxicities associated with dual HER-2 blockade versus anti-HER-2 monotherapy were meta-analyzed with the Peto method, because this method provided the best CI coverage and was more appropriate method for meta-analysis when dealing with low event rates(<5%) [15]. Additionally, we conducted the following prespecified subgroup analyses: the treatment setting (neoadjuvant, adjuvant and metastatic), the type of anti-HER2 therapies (dual HER2 blockade vs. trastuzumab; dual HER2 blockade vs. lapatinib), concomitant treatment (none, chemotherapy and hormonal therapy) to investigate the risk of cardiac toxicities associated with dual anti-HER2 blockade within particular groups. A statistical test with a p-value less than 0.05 was considered significant. The overall heterogeneity was assessed by using the I^2 statistic, and I^2 greater than 50% indicated high

heterogeneity. Sensitivity analysis using different statistical models was performed to assess the stability of results. Potential publication bias was checked by visual inspection of the symmetry of funnel plots and the Egger regression asymmetry test. All statistical analyses were performed by using Version 2 of the Comprehensive MetaAnalysis program (Biostat, Englewood, NJ) and Open Meta-Analyst software version 4.16.12 (Tufts University).

Results

Search results

Based on the electronic search protocol, a total of 470 studies were initially identified. of these studies, 338 did not meet the inclusion criteria and were therefore excluded. Among the remaining 132 studies, a total of 22 trials met the inclusion criteria[16-37]. Of these 22 included trials, six trials were update reports of published trials[17, 25, 26, 28, 29, 33], one trial involving gastric or GEJ carcinoma[18]. Thus finally 15 randomized controlled trials were included in this meta-analysis (figure 1). Table 1 listed the baseline characteristics of patients and studies. The quality of each included study was roughly assessed according to Jadad scale, four trials[16, 21, 34, 37] were double-blind, placebo-controlled trials, thus had a Jadad score of 5, and the remaining eleven trials were open-label controlled trials, thus had a Jadad score of 3.

Incidence of LVEF decline

A total of 7,184 patients receiving dual HER-2 blockade in 15 RCTs were available for LVEF decline analysis. There were 302 LVEF decline events among these patients. The highest incidence (8.7%; 95% CI 5.3% to 13.9%) was observed in a phase III breast cancer neoadjuvant trial of trastuzumab plus lapatinib when concomitant with paclitaxel [22], while the lowest incidence was observed in four trials in which no events of LVEF decline occurred[16, 27, 31, 37]. Using a random-effects model (χ2-based Q statistic test: Q= 31.75; p=0.004; I^2 = 55%), the summary incidence of LVEF decline in cancer patients treated with dual HER2 blockade was 4.6% (95% CI, 3.7% to 5.7%, figure 2A).

For LVEF decline associated with anti-HER2 monotherapy, the highest incidence (13.4%; 95% CI 10.2% to 17.4%) was observed in NSABP protocol B-41 trial[30], while no events of LVEF decline occurred in three trials[16, 19, 37]. Using a random-effects model (χ2-based Q statistic test: Q=108.33; p<0.001; I^2=86%), the summary incidence of LVEF decline in cancer patients treated with anti-HER2 monotherapy was 3.2% (95% CI, 2.2% to 4.6%, figure 2B).

Incidence of CHF

A total of 6,818 patients receiving dual HER-2 blockade in 14 RCTs were available for CHF analysis. There were 56 total CHF events among these patients. The highest incidence (2.0%; 95% CI 0.7 to 6.1%) was observed in a phase III breast cancer trial of trastuzumab plus lapatinib after prior trastuzumab-based therapies[33], while no events of CHF occurred in five trials. Using a fixed-effects model (χ2-based Q

statistic test: Q=8.26; p=0.82; I^2 =0%), the summary incidence of CHF in cancer patients treated with dual HER2 blockade was 0.9% (95% CI, 0.7% to 1.2%, figure 2C). As for CHF associated with anti-HER2 monotherapy, a total of 9,283 patients were included for analysis. Using a random-effects model (χ2-based Q statistic test: Q=52.77; p<0.001; I^2 =73.42%), the summary incidence of CHF in cancer patients treated with anti- HER2 monotherapy was 0.7% (95% CI, 0.4% to 1.3%, figure 2D).

Risk of LVEF decline and CHF associated with dual HER2 blockade

All of the 15 included trials reported the LVEF decline data, thus included for calculating the OR of LVEF decline associated with dual HER2 blockade. A total of 284 LVEF decline events were observed in dual HER2 blockade versus 357 LVEF decline events in anti-HER2 monotherapy. The pooled results demonstrated that the dual HER-2 blockade in cancer patients significantly increased the risk of developing LVEF decline with an OR of 1.20 (95% CI 1.02–1.41, p=0.031, Figure 3A) using a fixed-effects model (χ2-based Q statistic test: Q=22.58; p=0.091, I^2 =32.6).

A total of 14 randomized trials reported CHF data. A total of 55 CHF events were observed in dual HER2 blockade versus 57 CHF events in anti-HER2 monotherapy. The pooled results showed that the dual HER-2 blockade in cancer patients significantly increased risk of developing CHF with an OR of 1.45 (95% CI 1.00–2.11, p=0.049, Figure 3B) using a fixed-effects model (χ2-based Q statistic test: Q=12.67; p=0.53, I^2 =0).

Sensitivity analysis

Sensitivity analyses using Mantel Haenszel or Inverse Variance model showed that the risk of LVEF decline with dual HER-2 blockade was 1.19(95%CI: 1.02-1.41, p=0.031) and 1.18 (95%CI: 1.01-1.40, p=0.041). Similarly, sensitivity analyses using Mantel Haenszel or Inverse Variance model showed that the risk of CHF associated with dual HER-2 blockade was 1.48 (95%CI: 1.01-2.16, p=0.045) and 1.55(95%CI: 1.04-2.25, p=0.032) (supplemental table 1) when compared to anti-HER2 monotherapy.

Sub-group analysis

Firstly, we carried out a subgroup risk analysis stratified according to treatment settings. Our results demonstrated that risk of LVEF decline and CHF was comparable between dual HER-2 blockade and anti-HER2 monotherapy in neoadjuvant or metastatic setting (both p>0.05, table 2). However, the addition of dual HER2 blockade to adjuvant treatment in breast cancer significantly increased the risk of developing CHF (OR 2.00, 95%CI: 1.23-3.24, p=0.005) and LVEF decline (OR1.17, 95%CI: 1.00-1.38, p=0.048, table 2).

The concomitant treatment with anti-HER-2 therapy might impact the ORs of cardiac toxicities. Our combined results demonstrated that concomitant hormonal therapy with dual HER2 blockade in breast cancer significantly increased risk of developing LVEF decline in comparison with hormonal therapy plus anti-HER2 monotherapy (OR 4.51, 95%CI:1.24-16.40, p=0.022), while no concomitant treatment or concomitant chemotherapy with dual HER-2 blockade did not increase the risk of developing LVEF

decline(p=0.19 and p=0.11, respectively). As for CHF events, concomitant chemotherapy with dual HER2 blockade treatment significantly increased the risk of developing CHF when compared to anti-HER2 monotherapy plus chemotherapy (OR 1.47, 95%CI: 1.00-2.16, p=0.052), while no concomitant treatment or concomitant hormonal therapy with dual HER-2 blockade did not increase the risk of CHF (p=0.22 and p=0.59, respectively).

We also did sub-group analysis according to anti-HER-2 monotherapy. Our result showed that dual HER-2 blockade significantly increased the risk of developing LVEF decline (OR 1.49, 95%CI: 1.14-1.96, p=0.004) when compared to lapatinib, but not for CHF (OR 2.62, 95%CI: 0.90-2.94, p=0.11). In comparison with trastuzumab alone, no significantly increased risk of developing LVEF decline(p=0.37) and CHF (p=0.24, table 2) was observed in dual HER-2 blockade group.

Publication Bias

We performed Begg's funnel plot and Egger's test to detect the publication bias of literatures. No significant evidence of publication bias for LVEF decline and CHF was detected by using funnel plots (supplemental figure 1 for LVEF decline; and supplemental figure 2 for CHF), Begg's test (LVEF decline, p=0.62; CHF, p=0.53) and Egger's test (LVEF decline, p=0.38; CHF, p=0.93).

Discussion

To our best knowledge, this meta-analysis is the largest and most comprehensive meta-analysis to assess the risk of cardiac toxicities associated with dual HER2 blockade versus anti-HER2 monotherapy. A total of 16,375 patients from 15 randomized controlled trials were included for analysis. Our pooled results indicate that the overall incidence rate of LVEF decline and CHF in dual HER-2 blockade are 4.6% and 0.9%, which is higher than that of anti-HER-2 monotherapy (3.2% and 0.7%, respectively). Importantly, the present study for the first time demonstrates that dual HER-2 blockade therapy in breast cancer patients increases 19% risk of developing LVEF decline and 45% risk of developing CHF when compared to anti-HER2 monotherapy. It should be noted that patients with inadequate cardiac function would be excluded from treatment and close cardiac monitoring has been performed during the administration of anti-HER-2 agents, both of them would significantly reduced the incidence of cardiac toxicities. Although the overall incidence of cardiac toxicities is very low, a slight but significant risk of developing cardiac toxicities has been observed in dual HER-2 blockade when compared to anti-HER-2 monotherapy.

Sub-group analysis showed that addition of dual HER-2 blockade to adjuvant treatment in breast cancer significantly increased the risk of developing LVEF decline (p = 0.031) and CHF (p = 0.049), but not for neoadjuvant or metastatic settings. Additionally, cardiac toxicities associated with specific anti-HER-2 agents might be difference, which might be attributable to the unique epitopes of HER2 recognized by each antibody and differential effects on downstream signaling pathways[38]. The cardiac toxicities associated with trastuzumab seems higher than that of lapatinib. In a previous publication based on 29,000 breast cancer, the authors found that incidence severe cardiac toxicities with trastuzumab was 3.0%(95%CI: 2.41–3.64)[39], while the overall cardiac toxicities associated with lapatinib was 3.0%[40].

We therefore perform sub-group analysis based on anti-HER-2 agents, and find that dual HER-2 blockade in breast cancer patients significantly increased the risk of developing LVEF decline (p = 0.004) when compared to lapatinib alone, but not for CHF (p = 0.11, respectively). No significant difference of cardiac toxicities is found between dual HER-2 blockade and trastuzumab. Additionally, the concomitant hormonal treatment with dual HER-2 blockade in breast cancer significantly increases the risk of developing LVEF decline in comparison with hormonal therapy plus anti-HER2 monotherapy (p = 0.022), while concomitant chemotherapy with dual HER2 blockade treatment also significantly increases the risk of developing CHF when compared to anti-HER2 monotherapy plus chemotherapy (p = 0.052). Based on our finding, dual HER-2 blockade therapy in breast cancer is associated with a small but statistically significant risk of developing LVEF decline and CHF when compared with anti-HER2 monotherapy. In comparison with anti-HER-2 monotherapy, addition of dual HER-2 blockade to neoadjuvant or metastatic settings for breast cancer is safe in terms of cardiac toxicities, but not for adjuvant setting. Physicians should pay more attention to cardiac toxicities during the administration of dual HER-2 treatment when concomitant hormonal/chemotherapy treatment.

The molecular mechanisms related to cardiac toxicities induced by anti-HER2 agents, either alone or in combination, remains unknown. One potential explanation for the mechanism is the inhibition of NRG-1/HER2 signaling pathway by using anti-HER-2 agents[41]. In multiple vitro studies have demonstrated that the NRG-1/ErbB2 signaling pathway plays an important role in controlling cardiomyocytes proliferation, survival and myofibril disarray in cardiomyocytes[38].

The main strengths of this study are that clinical trials are identified by a systematic literature review with the largest and comprehensive meta-analysis to investigate the cardiac toxicities associated with dual HER-2 blockade versus anti-HER-2 monotherapy. The quality of this evidence is high because all of the included trials are prospective randomized controlled trials. However, several limitations are needed to be concerned. First of all, patients enrolled in prospective trials generally need to have adequate cardiac function, and close cardiac monitoring is implemented for all treated patients, which might underestimate the incidence of cardiac toxicities in common oncology practice. Secondly, this is a meta-analysis of published data, and lack of individual patient data prevents us from adjusting the cardiac toxicities according to previous treatment and patient variables. For example, the cardiac safety of dual HER-2 blockade in breast cancer patients with preexisting cardiovascular risk factors remains undetermined. Finally, these studies are conducted at various international institutions by different investigators and may have potential bias in reporting the types of cardiac events. In addition, the primary endpoints of the these included studies are aimed to investigate the survival benefit of anti-HER2 therapy in cancer patients, but not for cardiac toxicities related dual HER-2 blockade. Thus, the frequency of cardiac toxicities might be underreported in clinical trials.

Conclusion

Although the overall incidence of cardiac toxicities is very low, dual HER-2 targeted therapy in HER-2 positive breast cancer significantly increase the risk of developing LVEF and CHF when compared to anti-

HER-2 alone. Sub-group analysis that addition of dual HER-2 blockade to adjuvant treatment in HER-2 positive breast cancer increased the risk of developing cardiac toxicities but not for neoadjuvant or metastatic settings. Concomitant treatment with dual HER2 blockade would increase the risk of developing cardiac toxicities. Physicians should be aware of this risk and provide close monitoring during the administration of dual HER-2 targeted therapy.

Abbreviations

EGFR, epidermal growth factor receptor; MoAbs, monoclonal antibodies; GEJ, gastro-oesophageal junction; ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; NYHA, New York Heart Association; Peto ORs, Petro odds radio; CIs, confidence intervals;

Declarations

Ethics approval and consent to participate

The present study procedures were approved by the Ethical Committee of Rui Jin Hospital affiliated medicine school of Shanghai Jiao Tong University. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

Consent for publication

Not applicable.

Availability of supporting data

All data included in this study are available upon request by contact with the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' information

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Tables

Table 1 Baseline characteristics of 15 included trials

treatment setting	anti-HER-2 regimen	dosage of anti-HER-2 drugs	anti-HER-2 duration	exposure of anti-HER-2 therapy, w	concomitant therapy	No. of LVEF decline	No. of CHF
metastatic	L+T	L 1,000 mg daily+2 mg/kg weekly (loading 4 mg/kg)	Until progression or unacceptable toxicity	51.2	No	10#	3
	T	2 mg/kg weekly (loading 4 mg/kg)	Until progression or unacceptable toxicity	34.8	No	2#	1
neoadjuvant	L+T	L 1,000 mg daily+2 mg/kg weekly (loading 4 mg/kg)	18 W	NR	weekly PTX	7	2
	T	2 mg/kg weekly (loading 4 mg/kg)	18 W	NR	weekly PTX	2	0
	L	L 1500 mg weekly	18 W	NR	weekly PTX	2	1
metastatic	P+T	420 mg every 3 W (loading 840mg)+6 mg/kg q3w (loading 8 mg/kg) q3weekly	Until progression or unacceptable toxicity	72	q.3.w. docetaxel	24	6*
	T	6 mg/kg q3w (loading 8 mg/kg) q3weekly	Until progression or unacceptable toxicity	45	q.3.w. docetaxel	28	7*
neoadjuvant	P+T	420 mg/kg q3w (loading 840 mg/kg) + 6 mg/kg q3w (loading 8 mg/kg) q3weekly	12 W	NR	q.3.w. docetaxel	11	1
	P+T	420 mg/kg q3w (loading 840 mg/kg) + 6 mg/kg q3w (loading 8 mg/kg) q3weekly	12 W	NR	no		
	T	6 mg/kg q3w (loading 8 mg/kg) q3weekly	12 W	NR	q.3.w. docetaxel	2	0
	P	420 mg/kg q3w	12 W	NR	q.3.w.	7	0

		(loading 840 mg/kg)			docetaxel		
neoadjuvant	L+T	L 750 mg daily+2 mg/kg weekly (loading 4 mg/kg)	until surgery	NR	weekly PTX	15	2
	T	2 mg/kg weekly (loading 4 mg/kg)	until surgery	NR	weekly PTX	25	7
	L	L 1250 mg weekly	until surgery	NR	weekly PTX	22	7
neoadjuvant	L+T	L 1,000 mg daily+2 mg/kg weekly (loading 4 mg/kg)	26 W	NR	weekly PTX-FEC	0	0
	T	2 mg/kg weekly (loading 4 mg/kg)	26 W	NR	weekly PTX-FEC	1	0
	L	L 1,500 mg daily	26 W	NR	weekly PTX-FEC		
neoadjuvant	L+T	L 1,000 mg daily+2 mg/kg weekly (loading 4 mg/kg)	12 W	74% completed	q.3.w docetaxel-FEC	0	0
	T	2 mg/kg weekly (loading 4 mg/kg)	12 W	90.6% completed	q.3.w docetaxel-FEC	1	0
	L	L 1,000 mg daily	12 W	95.5% completed	q.3.w docetaxel-FEC		
adjuvant	L+T	L 750 mg daily+2 mg/kg weekly (loading 4 mg/kg) during chemotherapy	52W	NR	chemotherapy administration per physician's choice	103[&]	22
	T	2 mg/kg weekly (loading 4 mg/kg) during chemotherapy	52W	NR	chemotherapy administration per physician's choice	97[&]	18
	L	L 1,000 mg daily during chemotherapy	52W	NR	chemotherapy administration per physician's choice	63[&]	6
	T followed by L	2 mg/kg weekly (loading 4 mg/kg) during chemotherapy	T*12W+L*34W	NR	chemotherapy administration per physician's choice	57[&]	4

		followed by L 1500mg daily					
metastatic	T-DM1+P	3.6mg/kg q.3.w+420 mg every 3 W (loading 840mg)	Until progression or unacceptable toxicity	45	no	11[$]	-
	T	6 mg/kg q3w (loading 8 mg/kg) q3weekly	Until progression or unacceptable toxicity	45	taxanes q.3.w	17[$]	-
	T-DM1	3.6mg/kg q.3.w	Until progression or unacceptable toxicity	45	no	4[$]	-
metastatic	P+T	420 mg/kg q3w (loading 840 mg/kg) + 6 mg/kg q3w (loading 8 mg/kg) q3weekly	Until progression or unacceptable toxicity	45	capetabine 1000mg/m2 q.3.w.	15	2*
	T	6 mg/kg q3w (loading 8 mg/kg) q3weekly	Until progression or unacceptable toxicity	36	capecitabine 1250 mg/m2 q.3.w.	7	0
adjuvant	P+T	420 mg/kg q3w (loading 840 mg/kg) + 6 mg/kg q3w (loading 8 mg/kg) q3weekly	a maximum of 18 cycles	84.5% completed	chemotherapy administration per physician's choice	81	17
	T	6 mg/kg q3w (loading 8 mg/kg) q3weekly	a maximum of 18 cycles	87.4% completed	chemotherapy administration per physician's choice	75	8
metastatic	L+T	L 1,000 mg daily+6 mg/kg weekly (loading 8 mg/kg)	Until progression or unacceptable toxicity	36	aromatase inhibitor	4	0
	T	6 mg/kg q3w (loading 8 mg/kg) q3weekly	Until progression or unacceptable toxicity	18	aromatase inhibitor	2[#]	1[¶]
	L	L 1500 mg weekly	Until progression or unacceptable toxicity	24.7	aromatase inhibitor	0	1[¶]
metastatic	P+T	420 mg/kg q3w (loading 840 mg/kg) + 6	Until progression or	54	aromatase inhibitor	3	0

		mg/kg (loading mg/kg) q3weekly	q3w 8	unacceptable toxicity			
	T	6 mg/kg (loading mg/kg) q3weekly	q3w 8	Until progression or unacceptable toxicity	46.5	aromatase inhibitor	0	0
Neoadjuvant	P+T	420 mg/kg (loading 840 mg/kg) + 6 mg/kg (loading mg/kg) q3weekly	q3w 8	until surgery	NR	q.3.w. docetaxel	0	0
	T	6 mg/kg (loading mg/kg) q3weekly	q3w 8	until surgery	NR	q.3.w. docetaxel	0	0
Metastatic	T+P	NR		Until progression or unacceptable toxicity	NR	q.3.w. docetaxel	0	0
	T	NR		Until progression or unacceptable toxicity		q.3.w. docetaxel	0	0

[#] LVEF decline≥20% relative to the baseline value and below the LLN

*symptomatic LVSD

[&]LVEF decline ≥10% relative to the baseline and < LLN

[$]LVEF decline ≥50% with a ≥ 15% relative to the baseline

[¶] cardiac death

Abbreviations: T, trastuzumab; L, lapatinib; T-DM-1 Trastuzumab Emtansine; p, Pertuzumab; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; W, weekly; No, number; NR, not reported; PTX, paclitaxel; FEC, fluorouracil +epirubicin+ cyclophosphamide;

Table 2 Sub-group analysis of risk for developing LVEF decline and CHF associated with dual HER2 blockade versus anti-HER2 monotherapy

		No. of trials	Dual HER-2 blockage		Monotherapy		Peto OR (95%CI)	*P* value
			No. of LVEF decline	Total	No. of LVEF decline	Total		
		6	33	865	62	1117	0.90 (0.58-1.38)	0.64
		7	67	1518	60	1954	1.35(0.94-1.93)	0.1
		2	184	4425	235	6538	1.17(1.00-1.38)	0.048
therapy								
lockade	vs.	15	284	6799	259	6588	1.08(0.91-1.29)	0.37
lockade	vs.	6	129	2602	87	2564	1.49(1.14-1.96)	0.004
nent								
		2	21	515	23	860	1.51(0.81-2.83)	0.19
		11	256	6039	332	8390	1.15(0.97-1.36)	0.11
y		2	7	245	2	359	4.51(1.24-16.40)	0.022
		No. of trials	No. of CHF	Total	No. of CHF	Total	Peto OR (95%CI)	*P* value
		6	5	856	15	1117	0.71(0.31-1.54)	0.41
		6	11	1152	10	1240	1.15(0.52-2.63)	0.60
		2	39	4425	32	6538	2.00(1.23-3.24)	0.005
therapy								
lockade	vs.	14	55	6433	42	6230	1.26(0.86-1.84)	0.24
lockade	vs.	6	26	2602	15	2564	2.62(0.90-2.94)	0.11
nent								
		1	3	149	1	146	2.98(0.31-28.98)	0.22
		11	52	6039	54	8390	1.47(1.00-2.16)	0.052
y		2	0	245	2	359	0.57(0.074-4.44)	0.59

Abbreviation: CHF, congestive heart failure; LVEF, left ventricular ejection fraction; OR, odds ratio; No., number;

Supplemental Information Note

Supplemental figure 1: Funnel plot of publication bias for LVEF decline in the meta-analysis

Supplemental figure 2: : Funnel plot of publication bias for CHF in the meta-analysis

Figures

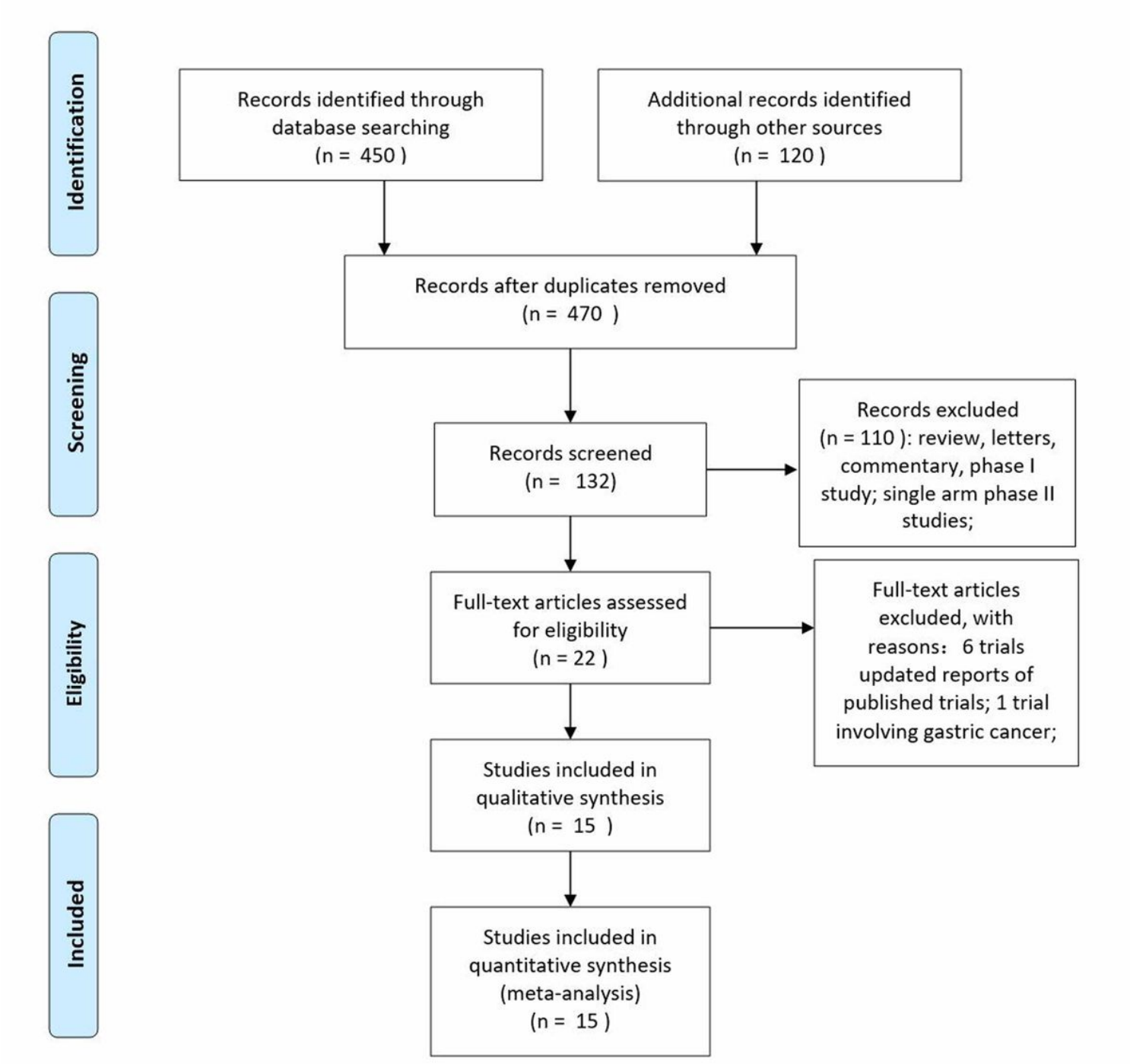

Figure 1

Flow chart of study selection in the meta-analysis

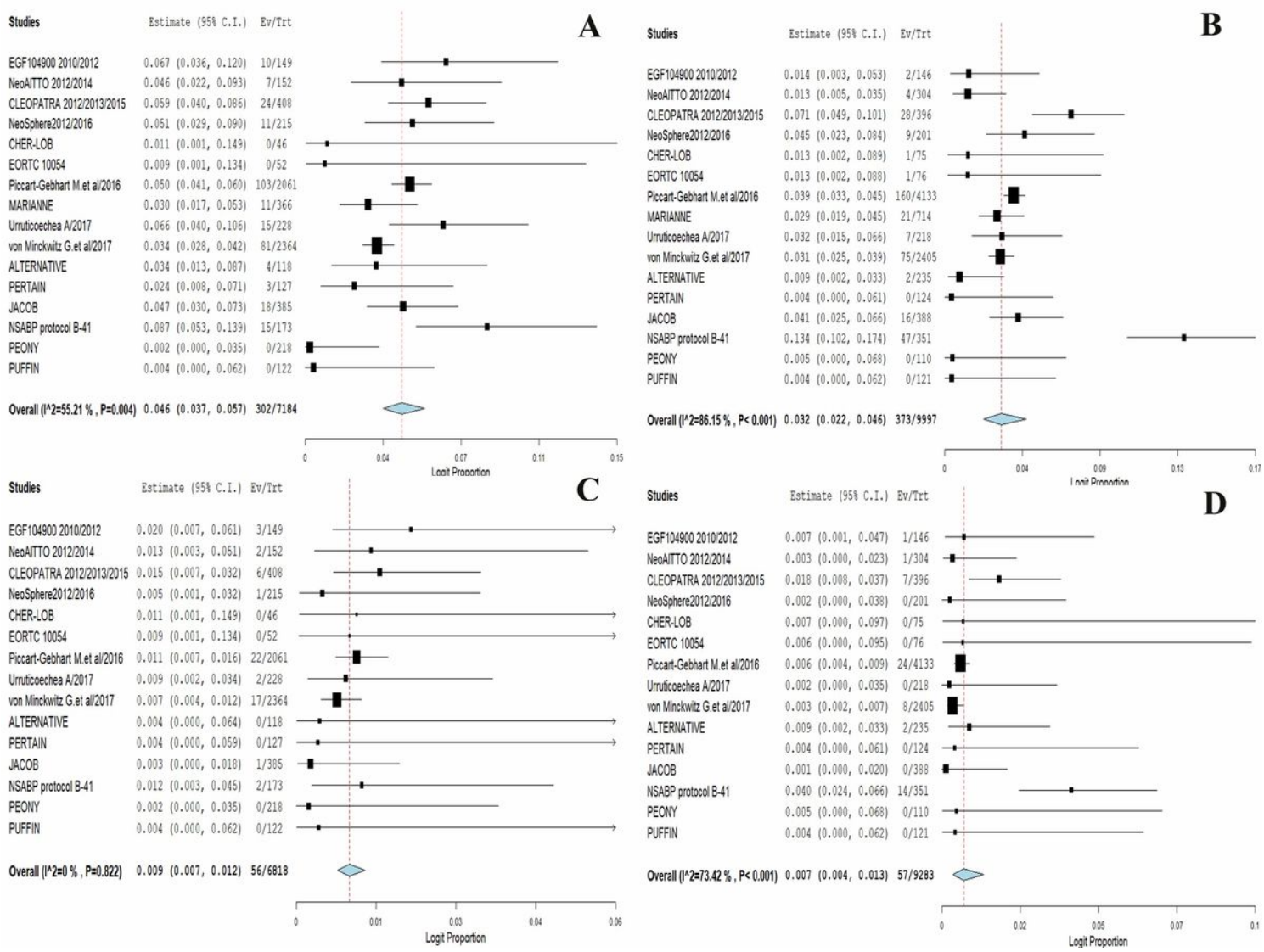

Figure 2

incidence of LVEF and CHF associated with dual HER-2 blockade and anti-HER-2 monotherapy in breast cancer

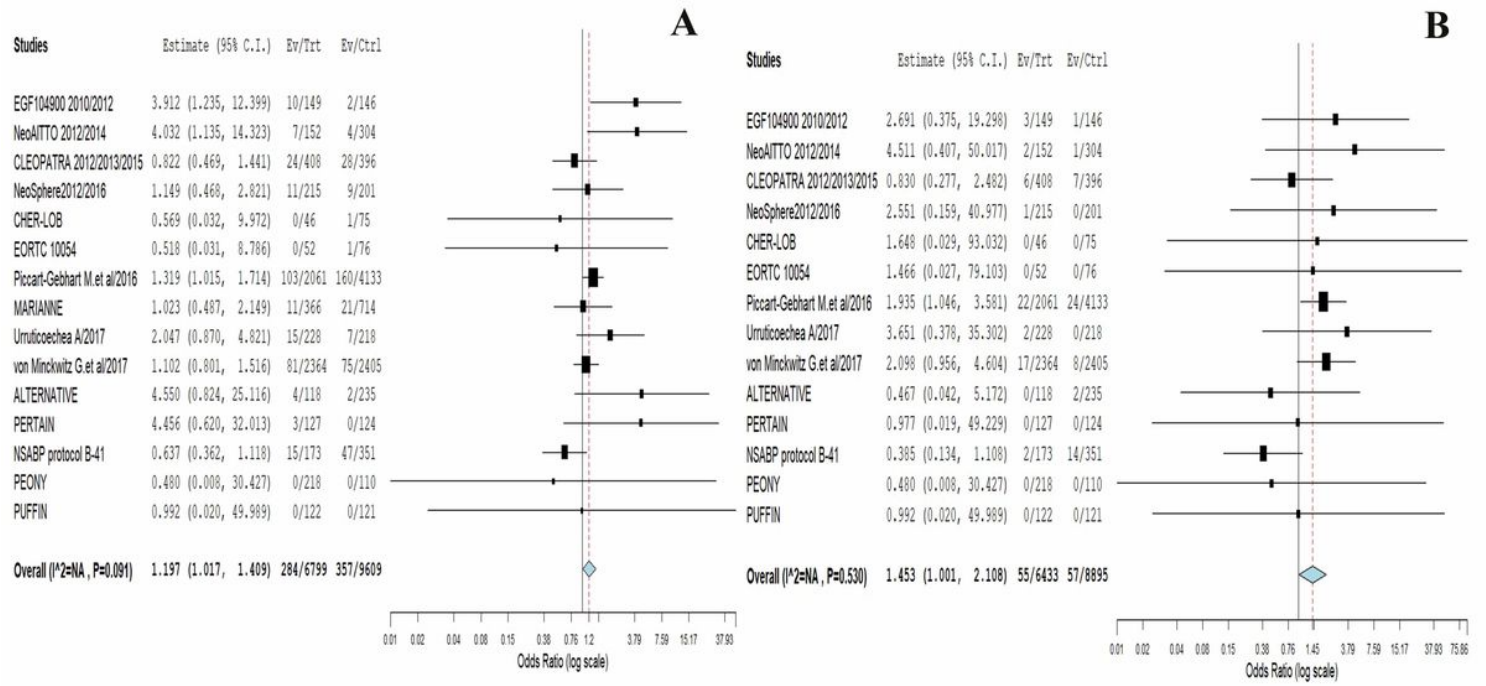

Figure 3

Risk of LVEF and CHF associated with dual HER-2 blockade versus anti-HER-2 monotherapy in breast cancer

Supplementary Files

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