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ORIGINAL RESEARCH

The efficiency and safety of trastuzumab and lapatinib added to neoadjuvant chemotherapy in Her2-positive breast cancer patients: a randomized meta-analysis

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Background: The addition of human epidermal growth factor receptor 2 (Her2) therapies to neoadjuvant chemotherapy (NAC) during treatment of Her2-positive breast cancer has been proposed as an effective way to improve the prognosis. However, the treatment outcomes of adding trastuzumab, lapatinib, or both to NAC were not unequivocal in randomized clinical trials. Based on these data, a meta-analysis was performed.

Objective: The main objective was to evaluate the efficiency and safety of trastuzumab and lapatinib added to NAC for treatment of Her2-positive breast cancer.

Methods: ClinicalTrials.gov and PubMed were searched for randomized clinical trials that compared trastuzumab, lapatinib, or both, added to NAC. The main endpoint was a pathologically complete response (pCR) rate, in breast only or in breast and lymph nodes. The drug safety and the influence of hormone-receptor status, comparing the clinical response and the rate of breast conservation, were evaluated.

Results: A total of eight publications were included in the primary analysis, designed as two or three subgroups. The cumulative cases were 2,349 and the analyses of all the clinical trials showed that the pCR rate was significantly higher in the group receiving trastuzumab than that in the group with lapatinib, either in breast only (P=0.001) or in breast and lymph nodes (P=0.0001). Similar results could be seen in comparisons of the combination versus trastuzumab group. Further studies of subgroups divided into hormone receptor-positive or-negative patients showed that the addition of trastuzumab or dual Her2-targeted therapy significantly improved the pCR rate in patients who were hormone-insensitive. Regarding the toxic effects, we found more grade 3 and 4 toxic effects, such as diarrhea, skin disorder, and hepatic biochemical changes in the lapatinib and combination groups. No temporally significant differences were found when the clinical response and the rate of breast conservation in the groups were analyzed.

Conclusion: The combination of trastuzumab and lapatinib was superior to single-agent treatment for improved pCR rate. However, combination treatment was not effective in improving the rate of breast conservation. Furthermore, a higher risk for toxicity was associated with combined administration.

Keywords: breast cancer, trastuzumab, lapatinib, human epidermal growth factor receptor, neoadjuvant, pathologically complete response

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Introduction

The overexpression of human epidermal growth factor receptor 2 (Her2) can be found in 15%–20% of breast cancer patients, which is associated with significantly shortened

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disease-free and overall survival.[1] The expression product of the *Her2* gene is a membrane spanning oncogenic protein that is processed externally at the membrane. Because of its specific overexpression in tumor cells, Her2 can be used as a target antigen for breast cancer therapy.

The use of trastuzumab, a chimeric monoclonal antibody recognizing the extracellular region of the Her2 protein, has dramatically changed the outcome of patients with Her2-amplified breast cancer.[2] Pegram et al[3] reported that when given single-therapy trastuzumab as the first-line treatment in 112 Her2-positive breast cancer patients, the total responsive rate was 23%. The responsive rate in a subgroup of patients that overexpressed Her-2 was 31%. Trastuzumab has therefore been shown to be effective when used as a single agent, or when used with other chemotherapeutic drugs.

Recently, many other inhibitors such as small molecule tyrosine-kinase inhibitors, monoclonal antibodies, and antibody–drug conjugates are emerging as additional treatments.[2] However, although these new drugs show promise, the most efficacious preoperative Her2 inhibitory agents are still being explored. Currently, the overexpression of the epidermal growth factor receptor and Her2 can be found in 20%–30% of the patients. Lapatinib is an orally bioavailable dual inhibitor of both the intracellular domain of the Her2 protein and the epidermal growth factor receptor. This dual inhibitor can effectively prevent the downstream signal transduction initiated by tyrosine kinase, thereby reducing the proliferation of tumor cells. Lapatinib was demonstrated to be beneficial in patients with Her2-positive locally advanced and metastatic breast cancer that had progressed after prior treatment with anthracycline, taxane, and trastuzumab. Because of their different mechanisms of drug actions, it may be useful to combine two drugs in order to provide improved clinically curative effects. Konecny et al[4] found synergistic interactions between two agents in Her2-positive breast cancer models. If benefits such as decreasing the primary tumor and improving tumor response to chemotherapy[5] could be achieved from neoadjuvant chemotherapy (NAC) alone, then using anti-Her2 agents together with NAC may provide a better outcome. It is therefore important to understand the efficacy and safety of a dual NAC/Her2-targeted therapy in the treatment of Her2-positive breast cancer patients. In this study, we evaluated pathologically complete response (pCR) rates when NAC was added to lapatinib, trastuzumab, or both in a meta-analysis of randomized clinical trials. We also evaluated the safety of these drugs and the influence of hormone-receptor (HR) status on treatment success. The clinical response and the rate of breast conservation were also investigated as additional parameters.

Methods

Search strategy

We carried out searches of ClinicalTrials.gov and PubMed for randomized clinical trials. The keywords used included breast cancer, trastuzumab, lapatinib, and Her2. We also used some selected studies for inclusion in the analyses.

Study criteria

The randomized Phase II or III clinical trials divided patients into groups with interventions using NAC with trastuzumab, lapatinib, or both in accordance with the inclusion criteria. Further inclusion criteria were that the patients should have Her2-positive operable breast cancer, with a primary endpoint of pCR rates. We included the chemotherapy regimen in every study and ensured homogeneity between studies.

Data extraction

After the exclusion criteria were met, eight studies met all the criteria. We extracted the following data from each eligible study: author's name, trial phase, year of publication, number of patients enrolled, chemotherapy regimens used, treatment arms, HR status, and the endpoints.

Assessment of risk of bias between included studies

The random sequence generation, sample size, blinding procedure, loss to follow-up, dropout, and intentions to treat were used to assess the risk of bias between included studies. Jadad scoring was used to assess the quality of each study.

Outcome definition

The main objective of this analysis was to determine the pCR rate after adding trastuzumab, lapatinib, or both to NAC, to estimate the efficacy of different methods in anti-Her2 therapy. Two definitions of pCR were used in the included studies, no invasive tumors in breast only, or in breast and axillary nodes. We therefore adopted both as the endpoints. Other objectives, such as evaluating the safety of the drug, the influence of HR status, comparing the clinical responses, and the rates of breast conservation were also included.

Statistical analyses

We extracted the number of patients achieving pCR and the total number in each included trial, and then estimated the odds ratio (OR) between comparable groups and the

95% confidence interval (CI). In every trial, OR was calculated to evaluate the relative advantage of a group receiving NAC plus trastuzumab, lapatinib, or both. Assuming study variations existed, we used fixed effects or random effects model to complete the data analyses.

Cochran Q (significant cutoff point: P=0.10) and I^2 (I^2>50%, strong heterogeneity) statistics were used to test the heterogeneity between studies.

All the analyses and graphs were obtained using RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, https://tech.cochrane.org).

Results

Study selection and exclusion

The primary search yielded a total of 52 relevant studies: 42 randomized clinical trials from PubMed and ten studies from additional references. The strategies used for selecting eligible studies are shown in Figure 1. Among the eliminated studies, the RC0639 study took disease-free survival and overall survival as the endpoints, not the pCR rate.[6] The clinical trial described by Davies et al[7] had a purpose inconsistent with our study.

Study characteristics

Table 1 summarizes the baseline characteristics of the eight clinical trials that met the inclusion criteria and included 2,349 patients. The characteristics of the studies show that the eight studies were randomized control trials; the number of cases ranged from 100 to 700 cases. Six trials had three groups, which compared the addition of trastuzumab versus lapatinib versus their combination added to NAC; while the other two trials compared only trastuzumab versus lapatinib. Trastuzumab was used at a 4 mg/kg loading dose followed by 2 mg/kg in another six studies, while the other two studies used an 8 mg/kg loading dose followed by 6 mg/kg. The dose of lapatinib ranged from 1,000 to 1,500 mg given daily. Regarding the combination groups, lapatinib was administered at 1,000 mg. The Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016) suggested that lapatinib was well tolerated at doses ranging

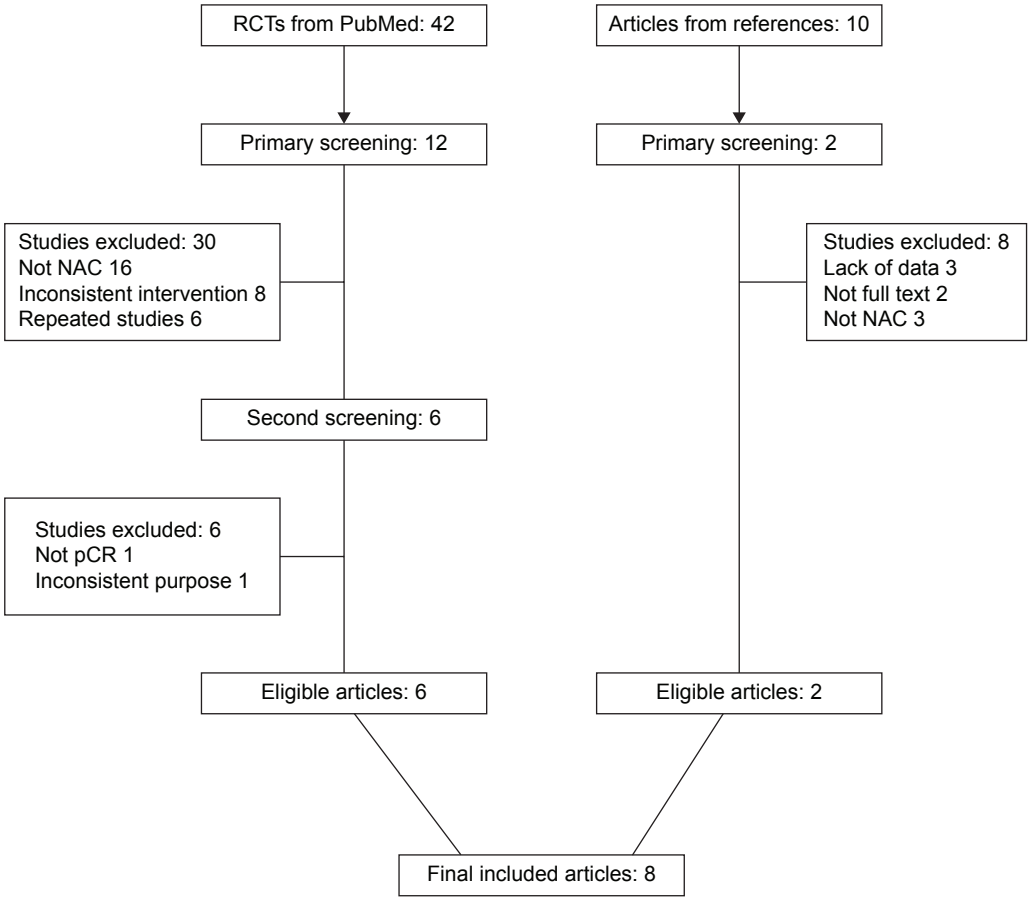


Figure 1 Flowchart of study search for the meta-analysis.
Abbreviations: NAC, neoadjuvant chemotherapy; pCR, pathologically complete response; RCTs, randomized controlled trials.

Table 1 Baseline characteristics of the eight clinical trials

Clinical trial	Recruitment period	No of patients	Her2 status	Chemotherapy	Arms	HR status (no of patients)		Anti-Her2 therapy
						Positive	Negative	
CHER-LOB[13]	August 2006–November 2010	121	IHC 3+ or FISH +	Weekly P 12 weeks→FEC ×4 (every 3 weeks), totally 26 weeks	T group	21	15	T 4 mg/kg→2 mg/kg once weekly
					L group	24	15	L 1,500 mg orally daily
					T+L group	28	18	T 4 mg/kg→2 mg/kg + L 1,000 mg orally daily
EORTC 10054[10]	October 2010–January 2013	128	IHC 3+/2+ and FISH +, or FISH + only	Doc ×3 weekly→FEC ×3 (every 3 weeks)	T group	27	26	T 4 mg/kg→2 mg/kg once weekly
					L group	15	8	L 1,000 mg orally daily
					T+L group	25	26	T 4 mg/kg→2 mg/kg + L 1,000 mg orally daily
Holmes et al[23] (2013)	August 2007–February 2010	100	IHC 3+ or FISH (ratio >2.2)	FEC ×4 (every 3 weeks)→ weekly P 12 weeks	T group	15	18	T 4 mg/kg→2 mg/kg once weekly
					L group	14	20	L 1,500 mg→1,250 mg orally daily
					T+L group	20	13	T 4 mg/kg→2 mg/kg + L 1,000 mg orally daily
GEICAM[11]	February 2009–October 2010	102	IHC 3+ or FISH +	EC ×4→doc ×4 weekly	T group	30	20	T 8 mg/kg→6 mg/kg once weekly
					L group	31	21	L 1,250 mg orally daily
GeparQuinto, GBG44[12]	November 2007–July 2010	614	HercepTest or in-situ hybridization (ratio ≥2.0)	EC ×4→doc ×4 weekly	T group	170	137	T 8 mg/kg→6 mg/kg once weekly
					L group	171	137	L 1,250 mg orally daily
NeoALTTO[14]	January 2008–May 2010	455	IHC 3+ or FISH +	Weekly P 12 weeks	T group	75	74	T 4 mg/kg→2 mg/kg once weekly
					L group	80	774	L 1,500 mg orally daily
					T+L group	77	75	T 4 mg/kg→2 mg/kg + L 1,000 mg orally daily
NSABP[24]	July 2007–June 2011	524	FISH or CISH, or IHC 3+	AC ×4→weekly P	T group	122	59	T 4 mg/kg→2 mg/kg once weekly
					L group	101	73	L 1,500 mg→1,000 mg orally daily
					T+L group	108	66	T 4 mg/kg→2 mg/kg + L 1,000 mg orally daily
CALGB 40601[27]	December 2008–February 2012	305	IHC 3+ or FISH +	Weekly P 16 weeks	T group	70	48	T 4 mg/kg→ 2 mg/kg once weekly
					L group	37	27	L 1,500 mg orally daily
					T+L group	69	48	T 4 mg/kg→ 2 mg/kg + L 1,000 mg orally daily

Abbreviations: AC, doxorubicin-cyclophosphamide; CISH, chromogenic in situ hybridization; doc, docetaxel; EC, epirubicine–cyclophosphamide; FEC, fluorouracil–epirubicine–cyclophosphamide; FISH, fluorescent in situ hybridization; Her2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; kg, kilogram; L, lapatinib; mg, milligram; No, number; P, paclitaxel; T, trastuzumab; HR, hormone receptor.

from 500 to 1,600 mg given once daily, and clinical activity was observed most frequently at 900–1,200 mg.[8] The clinical choice of dose was related to the tolerance to toxicities and there was no correlation between clinical response and different doses.

Assessment of the methodological quality

All trials had definitely established inclusion and exclusion criteria. All patients with Her2-positive breast cancer were randomized to receive different anti-Her2 therapy, including trastuzumab, lapatinib, or their combination. The anti-HER2 therapy was carried out simultaneously with NAC, and included fluorouracil–epirubicine–cyclophosphamide, epirubicine–cyclophosphamide, and doxorubicin-cyclophosphamide. HER2 amplification was confirmed by immunohistochemistry or fluorescent in situ hybridization, and HR status was recorded for every trial. Study quality was assessed using the five-item Jadad score (seven points), with a score range of 4–7 (Table 2).

The pCR rate of trastuzumab versus lapatinib

Seven trials, including 1,694 patients (n=887 in the trastuzumab group and n=807 in the lapatinib group), were analyzed for the pCR rate after addition of trastuzumab versus lapatinib compared to NAC in breast only. The absolute pCR rate was estimated to be 41% in the trastuzumab group compared to 33% in the lapatinib group. The pCR rate tended to be higher in the trastuzumab group versus the lapatinib group (OR, 1.41, 95% CI 1.14–1.73, P=0.001) (Figure 2A).

Eight trials including 1,752 patients (n=915 in trastuzumab group and n=837 in the lapatinib group) were compared for the pCR rates in breast and lymph nodes. The absolute pCR rate was estimated to be 38% in the trastuzumab group and 29% in the lapatinib group. There were significant differences between the two groups, and the probability to achieve pCR was higher for the trastuzumab group versus the lapatinib group (OR, 1.50, 95% CI 1.22–1.85, P=0.0001) (Figure 2B).

The pCR rate of the combination treatment versus trastuzumab alone

For this comparison, data were available from five trials, providing the endpoints of the rates of pCR in breast alone. Overall, 1,057 patients enrolled (n=535 in the combination group and n=522 in the trastuzumab group), and the pCR rate was significantly higher in the combination group than that in the trastuzumab group (57.6% versus 44.6%, OR, 1.70, 95% CI 1.33–2.19, $P<0.0001$) (Figure 3A).

The pCR rate in breast and lymph nodes could be obtained from five trials (1,017 patients; 510 patients treated with lapatinib plus trastuzumab and 507 patients treated with trastuzumab alone). It is noteworthy that the dual HER2-targeted combination treatment achieved the higher rate of pCR in breast and lymph nodes (54% versus 41%, OR, 1.80, 95% CI 1.39–2.32, $P<0.00001$) (Figure 3B).

Subgroup analysis: the influence of HR status

Considering that the evaluation of biomarkers is highly recommended for the best management and therapeutic decision of breast cancer patient treatment, we divided patients into subgroups according to HR status in two comparisons, although the differences were small. The result showed that HR status contributed to the efficacy of different anti-Her2 therapies. In patients with HR-negative tumors, the pCR rate for the trastuzumab group, in breast only or in breast and lymph nodes, was significantly higher than for the lapatinib group. However, there was no significant difference in patients with HR-positive tumors (Figure 2). Similar outcomes were obtained with the comparison between the combination group and the trastuzumab group (Figure 3).

The clinical response

There were six trials providing comparison data of clinical response status between patients in the trastuzumab group and the lapatinib group. Four trials provided results comparing patients treated with trastuzumab plus lapatinib versus those treated using trastuzumab only. The percentage of patients

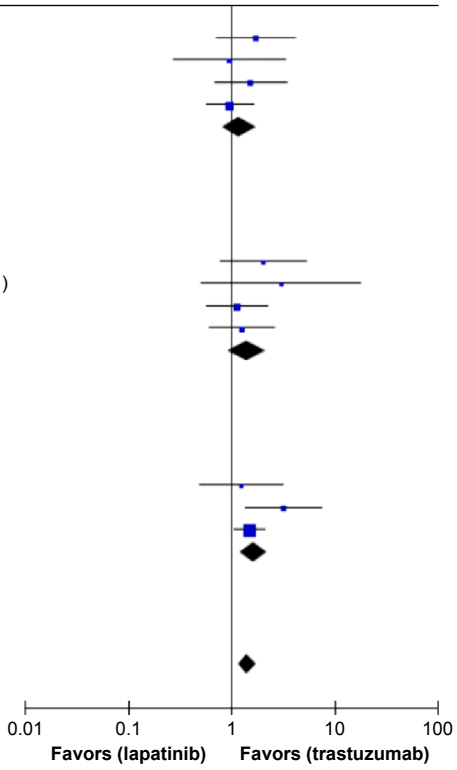
Table 2 The Jadad scale

Clinical trials	CHER-LOB[13]	EORTC 10054[10]	Holmes et al[23]	GEICAM[11]	GeparQuinto, GBG44[12]	NeoALTTO[14]	NSABP[24]	CALGB 40601[27]
Randomization	2	2	2	1	2	2	2	1
Concealment of allocation	2	2	0	0	2	2	2	0
Double blinding	2	2	2	2	2	2	2	2
Withdrawals and dropouts	0	1	1	1	1	1	1	1
Jadad score[a]	6	7	5	4	7	7	7	4

Notes: [a]Methodological quality of meditative movements studies reviewed using Jadad scoring criteria. Total score is 7. Scores 1–3 considered as low quality; Scores 4–7 considered as high quality.

A

Study or subgroup	Trastuzumab group Events	Total	Lapatinib group Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Hormone receptor-positive						
CALGB 40601[27]	28	69	10	35	5.1	1.71 (0.71, 4.10)
EORTC 10054[10]	14	27	8	15	3.2	0.94 (0.27, 3.34)
NeoALTTO[14]	17	75	13	80	6.3	1.51 (0.68, 3.37)
NSABP[24]	57	122	48	100	18.3	0.95 (0.56, 1.61)
Subtotal (95% CI)		**293**		**230**	**33.0**	**1.17 (0.81, 1.71)**
Total events	116		79			
Heterogeneity: χ^2=1.81, *df*=3 (*P*=0.61); I^2=0%						
Test for overall effect: *Z*=0.84 (*P*=0.40)						
Hormone receptor-negative						
CALGB 40601[27]	26	48	10	27	3.8	2.01 (0.76, 5.28)
EORTC 10054[10]	13	26	2	8	1.0	3.00 (0.51, 17.71)
NeoALTTO[14]	27	74	25	74	10.3	1.13 (0.57, 2.21)
NSABP[24]	36	55	43	71	8.5	1.23 (0.59, 2.56)
Subtotal (95% CI)		**203**		**180**	**23.6**	**1.39 (0.91, 2.12)**
Total events	102		80			
Heterogeneity: χ^2=1.76, *df*=3 (*P*=0.62); I^2=0%						
Test for overall effect: *Z*=1.51 (*P*=0.13)						
Hormone state unclassified						
CHER-LOB[13]	15	36	14	38	5.2	1.22 (0.48, 3.12)
GEICAM[11]	25	48	13	51	3.9	3.18 (1.36, 7.41)
GeparQuinto, GBG44[12]	105	307	80	308	34.2	1.48 (1.05, 2.10)
Subtotal (95% CI)		**391**		**397**	**43.4**	**1.60 (1.19, 2.17)**
Total events	145		107			
Heterogeneity: χ^2=3.02, *df*=2 (*P*=0.22); I^2=34%						
Test for overall effect: *Z*=3.07 (*P*=0.002)						
Total (95% CI)		**887**		**807**	**100**	**1.41 (1.15, 1.73)**
Total events	363		266			
Heterogeneity: χ^2=8.20, *df*=10 (*P*=0.61); I^2=0%						
Test for overall effect: *Z*=3.28 (*P*=0.001)						
Test for subgroup differences: χ^2=1.62, *df*=2 (*P*=0.44); I^2=0%						



B

Study or subgroup	Trastuzumab group Events	Total	Lapatinib group Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Hormone receptor-positive						
CALGB 40601[27]	27	69	9	35	5.0	1.86 (0.76, 4.56)
EORTC 10054[10]	14	27	6	15	2.5	1.62 (0.45, 5.81)
Holmes et al[23]	6	15	4	14	1.7	1.67 (0.35, 7.88)
NSABP[24]	55	121	42	100	17.1	1.15 (0.67, 1.96)
Subtotal (95% CI)		**232**		**164**	**26.4**	**1.36 (0.90, 2.06)**
Total events	102		61			
Heterogeneity: χ^2=0.97, *df*=3 (*P*=0.81); I^2=0%						
Test for overall effect: *Z*=1.46 (*P*=0.14)						
Hormone receptor-negative						
CALGB 40601[27]	24	48	8	27	3.5	2.38 (0.87, 6.46)
EORTC 10054[10]	13	26	2	8	1.0	3.00 (0.51, 17.71)
Holmes et al[23]	13	18	13	20	2.3	1.40 (0.35, 5.57)
NSABP[24]	32	55	39	71	9.7	1.14 (0.56, 2.32)
Subtotal (95% CI)		**147**		**126**	**16.6**	**1.55 (0.94, 2.58)**
Total events	82		62			
Heterogeneity: χ^2=1.96, *df*=3 (*P*=0.58); I^2=0%						
Test for overall effect: *Z*=1.71 (*P*=0.09)						
Hormone state unclassified						
CHER-LOB[13]	9	36	10	38	5.0	0.93 (0.33, 2.65)
GEICAM[11]	23	48	12	51	4.1	2.99 (1.27, 7.06)
GeparQuinto, GBG44[12]	93	307	70	308	33.3	1.48 (1.03, 2.12)
NeoALTTO[14]	40	145	30	150	14.6	1.52 (0.89, 2.62)
Subtotal (95% CI)		**536**		**547**	**57.0**	**1.55 (1.18, 2.04)**
Total events	165		122			
Heterogeneity: χ^2=3.22, *df*=3 (*P*=0.36); I^2=7%						
Test for overall effect: *Z*=3.16 (*P*=0.002)						
Total (95% CI)		**915**		**837**	**100**	**1.50 (1.22, 1.85)**
Total events	349		245			
Heterogeneity: χ^2=6.44, *df*=11 (*P*=0.84); I^2=0%						
Test for overall effect: *Z*=3.84 (*P*=0.0001)						
Test for subgroup differences: χ^2=0.29, *df*=2 (*P*=0.87); I^2=0%						

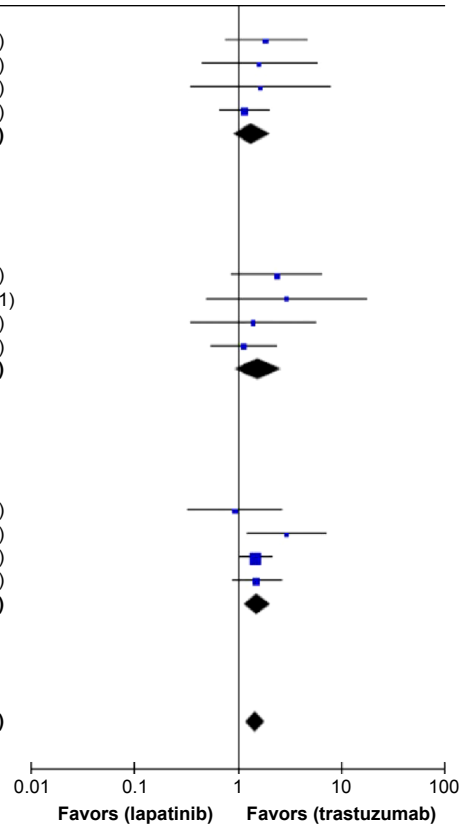
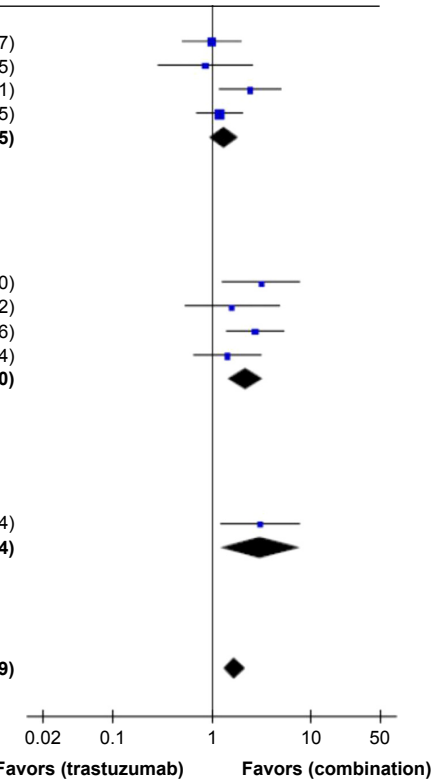


Figure 2 Forest plots of pCR rates: trastuzumab versus lapatinib, defined as no invasive disease in the breast only (**A**) or no invasive disease in the breast and lymph nodes (**B**).
Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel; pCR, pathologically complete response.

A

Study or subgroup	Combination group Events	Total	Trastuzumab group Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Hormone receptor-positive						
CALGB 40601[27]	28	69	28	69	17.5	1.00 (0.51, 1.97)
EORTC 10054[10]	12	25	14	27	7.4	0.86 (0.29, 2.55)
NeoALTTO[14]	32	77	17	75	10.6	2.43 (1.20, 4.91)
NSABP[24]	60	108	57	112	26.1	1.21 (0.71, 2.05)
Subtotal (95% CI)		**279**		**283**	**61.6**	**1.32 (0.94, 1.85)**
Total events	132		116			
Heterogeneity: χ^2=4.22, *df*=3 (*P*=0.24); I^2=29%						
Test for overall effect: *Z*=1.59 (*P*=0.11)						
Hormone receptor-negative						
CALGB 40601[27]	37	47	26	48	5.8	3.13 (1.27, 7.70)
EORTC 10054[10]	16	26	13	26	5.3	1.60 (0.53, 4.82)
NeoALTTO[14]	46	75	27	74	11.0	2.76 (1.42, 5.36)
NSABP[24]	46	63	36	55	10.9	1.43 (0.65, 3.14)
Subtotal (95% CI)		**211**		**203**	**33.0**	**2.20 (1.46, 3.30)**
Total events	145		102			
Heterogeneity: χ^2=2.52, *df*=3 (*P*=0.47); I^2=0%						
Test for overall effect: *Z*=3.80 (*P*=0.0001)						
Hormone state unclassified						
CHER-LOB[13]	31	45	15	36	5.5	3.10 (1.24, 7.74)
Subtotal (95% CI)		**45**		**36**	**5.5**	**3.10 (1.24, 7.74)**
Total events	31		15			
Heterogeneity: Not applicable						
Test for overall effect: *Z*=2.42 (*P*=0.02)						
Total (95% CI)		**535**		**522**	**100**	**1.70 (1.33, 2.19)**
Total events	308		233			
Heterogeneity: χ^2=12.12, *df*=8 (*P*=0.15); I^2=34%						
Test for overall effect: *Z*=4.20 (*P*<0.0001)						
Test for subgroup differences: χ^2=5.40, *df*=2 (*P*=0.07); I^2=63.0%						



B

Study or subgroup	Combination group Events	Total	Trastuzumab group Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Hormone receptor-positive						
CALGB 40601[27]	28	69	27	69	18.2	1.06 (0.54, 2.10)
Holmes et al[23]	15	20	6	15	1.9	4.50 (1.06, 19.11)
NSABP[24]	59	108	55	121	26.7	1.44 (0.86, 2.43)
Subtotal (95% CI)		**197**		**205**	**46.8**	**1.42 (0.96, 2.11)**
Total events	102		88			
Heterogeneity: χ^2=3.14, *df*=2 (*P*=0.21); I^2=36%						
Test for overall effect: *Z*=1.75 (*P*=0.08)						
Hormone receptor-negative						
CALGB 40601[27]	32	47	24	48	8.6	2.13 (0.93, 4.91)
Holmes et al[23]	10	13	13	18	2.9	1.28 (0.25, 6.69)
NSABP[24]	44	63	32	55	11.7	1.66 (0.78, 3.56)
Subtotal (95% CI)		**123**		**121**	**23.1**	**1.79 (1.05, 3.05)**
Total events	86		69			
Heterogeneity: χ^2=0.36, *df*=2 (*P*=0.83); I^2=0%						
Test for overall effect: *Z*=2.15 (*P*=0.03)						
Hormone state unclassified						
CHER-LOB[13]	21	45	9	36	6.0	2.63 (1.01, 6.82)
NeoALTTO[14]	68	145	40	145	24.1	2.32 (1.42, 3.78)
Subtotal (95% CI)		**190**		**181**	**30.1**	**2.38 (1.54, 3.68)**
Total events	89		49			
Heterogeneity: χ^2=0.05, *df*=1 (*P*=0.82); I^2=0%						
Test for overall effect: *Z*=3.91 (*P*<0.0001)						
Total (95% CI)		**510**		**507**	**100**	**1.80 (1.39, 2.32)**
Total events	277		206			
Heterogeneity: χ^2=6.51, *df*=7 (*P*=0.48); I^2=0%						
Test for overall effect: *Z*=4.50 (*P*<0.00001)						
Test for subgroup differences: χ^2=2.94, *df*=2 (*P*=0.23); I^2=32.0%						

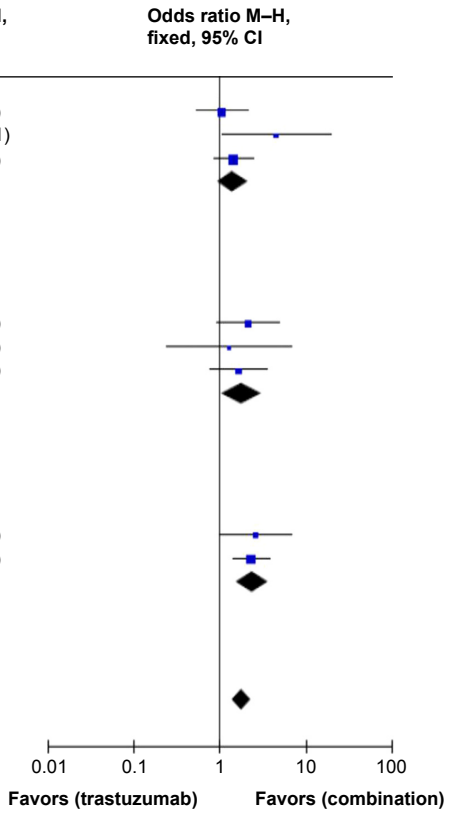


Figure 3 Forest plots of pCR rates: combination versus trastuzumab, defined as no invasive disease in the breast only (**A**) or no invasive disease in the breast and lymph nodes (**B**).

Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel; pCR, pathologically complete response.

who achieved a clinically complete response was similar in patients treated with trastuzumab or lapatinib (82.8% versus 82.4%, OR, 0.99, 95% CI 0.75–1.32, *P*=0.95) (Figure 4A). A similar result was observed for patients who were given dual Her2 block treatment or trastuzumab only (85.4% versus 82.2%, OR, 1.34, 95% CI 0.91–1.98, *P*=0.14) (Figure 4B).

The rate of breast conservation

Surgery was planned after the last chemotherapy administration and the candidates underwent breast conservation, or alternately, total mastectomy. The choice of surgery depended on the results obtained after chemical drug treatments. The rate of breast conservation between the groups showed no significant difference, either in the comparison groups of trastuzumab and lapatinib (50.5% versus 47.5%, OR, 1.812, 95% CI 0.91–1.38, *P*=0.27) (Figure 5A) or in that of the combination group and trastuzumab-alone group (45.7% versus 44.3%, OR, 1.05, 95% CI 0.79–1.40, *P*=0.73) (Figure 5B).

Toxicity studies

The main grade 3 and 4 toxic effects are summarized in Tables 3 and 4, and in Figure 6. After statistical analyses, the results showed that patients treated with lapatinib had more diarrhea, skin disorders, hepatic biochemical changes, infections, and inflammation ($P<0.05$) (Table 3, Figure 6). For the combination group, diarrhea, other digestive tract symptoms, hepatic biochemical changes, and skin disorders occurred much more than in patients treated with trastuzumab alone (Tables 3 and 4, Figure 6).

Discussion

This study provides an analysis of the efficacy and safety of adding trastuzumab, lapatinib, or both to NAC in Her2-positive breast cancer patient treatments. Previous meta-analyses performed by Hicks et al[9] showed an improvement in the pCR rate when lapatinib was combined with trastuzumab in patients receiving NAC. However, further analyses of the subgroups based on different HR status have not been performed. Furthermore, the toxic effects and breast conversation rates were not reported. In this study, we have updated the analysis by adding studies[10–12] including the GEICAM/2006-14 trial, the GeparQuinto, GBG44 trial, and the EORTC 10054 study. In addition to including the pCR rates, we included the clinical responses, toxic effects, and the rates of breast conservation in the comparison analyses.

The overall pCR rate in the dual blockade of Her2 treatment groups was above 50%, while the CALGB 40601[13] and NeoALTTO[14] studies reported 46.7% and 46.9%, respectively. The different definitions of the pCR rate and statistical

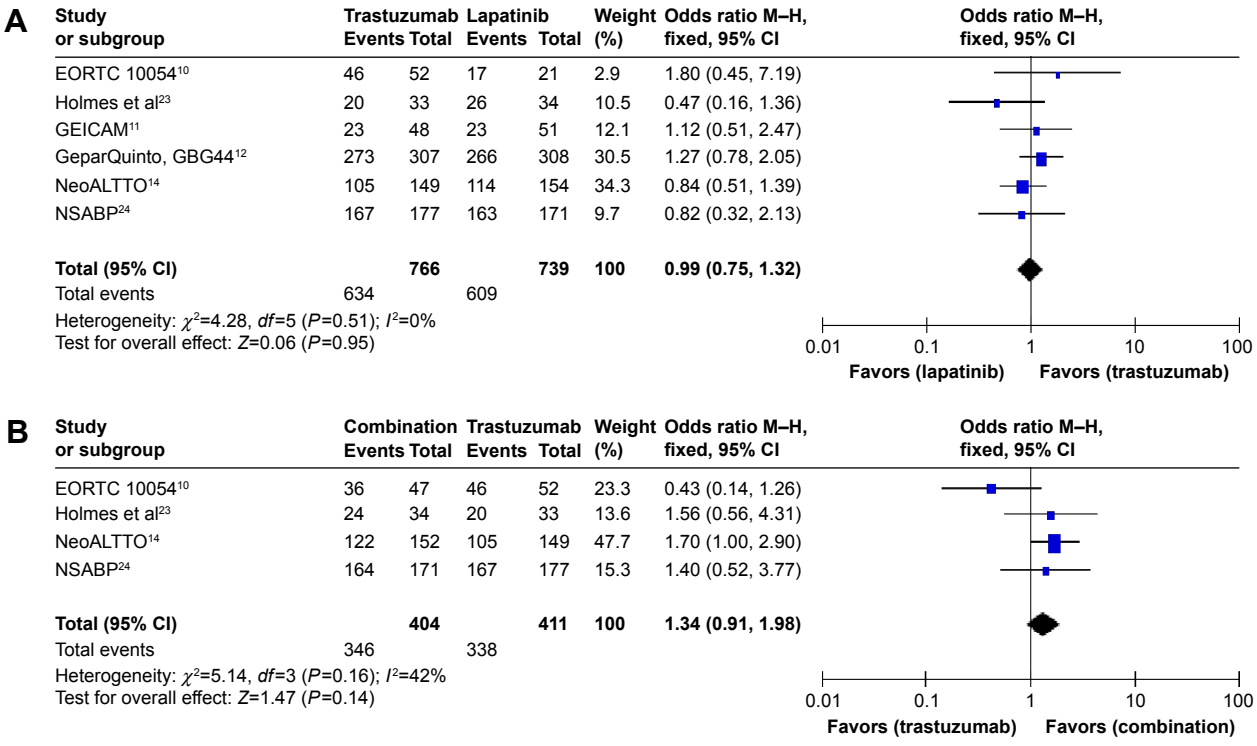


Figure 4 Forest plots of clinical complete response rates: trastuzumab versus lapatinib (**A**); combination versus trastuzumab (**B**).
Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel.

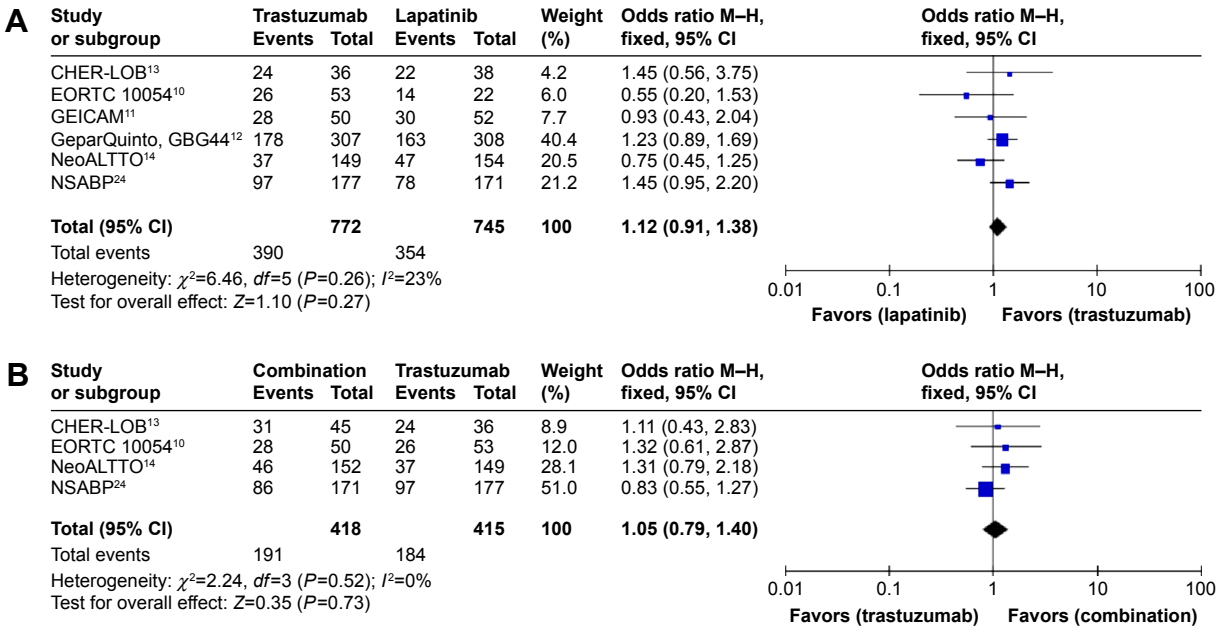


Figure 5 Forest plots of the rate of breast conservation: trastuzumab versus lapatinib (**A**); combination versus trastuzumab (**B**).
Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel.

bias might be the causes of the discrepancy in these results. In our analyses of the combination groups, the pCR rates, both in breast and in breast with lymph nodes, were 57.6% and 54% respectively, and were found to be superior to the single-agent treated groups. In addition, the pCR rate of the trastuzumab group was reported in articles that compared the effects of trastuzumab versus lapatinib. In our analyses, trastuzumab gave higher efficacy compared to lapatinib. The results suggest an advantage of adding trastuzumab to NAC as a more effective method, versus lapatinib alone, and showed elevated pCR rates either in breast or in breast and lymph nodes. These results could be explained by the lower ability of lapatinib to block the HER2 pathway, the lower drug dose of lapatinib used, and the greater ability

Table 3 Selected toxic effects in the trastuzumab group and lapatinib group

Toxic effect	Studies	Participants	Odds ratio (M–H, fixed, 95% CI)
Diarrhea	8	1,769	0.11* (0.07, 0.18)
Other digestive tract symptoms	6	1,284	0.92 (0.59, 1.44)
Febrile neutropenia	5	1,289	0.85 (0.54, 1.34)
Neutropenia	7	1,694	0.90 (0.69, 1.15)
Hepatic	8	1,769	0.60* (0.39, 0.92)
Skin disorder	7	1,703	0.14* (0.08, 0.26)
CHF	3	1,041	0.76 (0.29, 2.03)
Hemoglobin	4	1,107	0.93 (0.57, 1.50)
LVSD	4	1,143	1.66 (0.98, 2.81)
Fatigue	5	1,218	0.83 (0.55, 1.26)
Dehydration	2	417	0.25 (0.03, 2.24)
Infection and inflammation	6	1,284	0.52* (0.29, 0.94)
Neuropathy sensory	5	1,298	0.69 (0.36, 1.31)
Dyspnea	3	492	1.27 (0.34, 4.71)

Note: *$P<0.05$.
Abbreviations: CHF, congestive heart failure; CI, confidence interval; LVSD, left ventricular systolic dysfunction; M–H, Mantel–Haenszel.

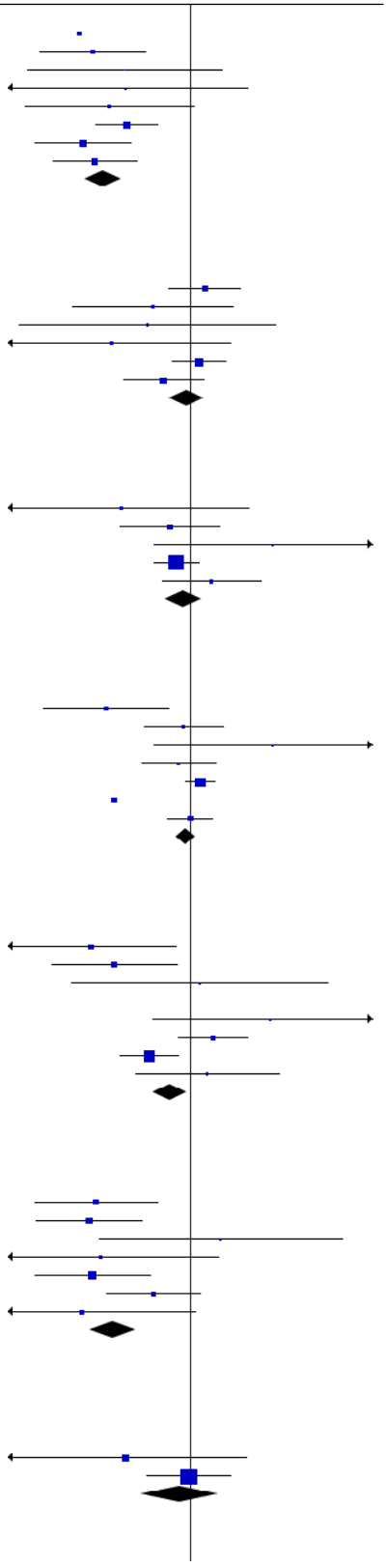
Table 4 Selected toxic effects in the combination group and trastuzumab group

Toxic effect	Studies	Participants	Odds ratio (M–H, fixed, 95% CI)
Diarrhea	6	1,135	14.38* (8.02, 25.78)
Other digestive tract symptoms	4	599	2.11* (1.17, 3.82)
Febrile neutropenia	4	517	0.92 (0.46, 1.85)
Neutropenia	5	1,053	1.37 (0.93, 2.02)
Hepatic	6	1,135	2.63* (1.51, 4.59)
Skin disorder	5	1,072	4.97* (2.56, 9.61)
CHF	2	454	0.14 (0.02, 1.17)
Hemoglobin	3	517	2.80 (0.74, 10.67)
LVSD	2	454	0.73 (0.28, 1.90)
Fatigue	3	536	1.01 (0.51, 2.01)
Dehydration	3	517	3.15 (0.32, 30.76)
Infection and inflammation	4	599	2.26 (0.82, 6.29)
Neuropathy sensory	4	771	1.97 (0.95, 4.11)
Dyspnea	3	517	0.84 (0.24, 2.96)

Note: *$P<0.05$.
Abbreviations: CHF, congestive heart failure; CI, confidence interval; LVSD, left ventricular systolic dysfunction; M–H, Mantel–Haenszel.

A

Study or subgroup	Trastuzumab Events	Trastuzumab Total	Lapatinib Events	Lapatinib Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Diarrhea						
CALGB 40601[27]	2	118	14	64	11.8	0.06 (0.01, 0.28)
CHER-LOB[13]	3	36	20	39	11.6	0.09 (0.02, 0.33)
EORTC 10054[10]	1	53	2	22	1.8	0.19 (0.02, 2.24)
Holmes et al[23]	0	32	2	34	1.6	0.20 (0.01, 4.33)
GEICAM[11]	1	50	7	52	4.4	0.13 (0.02, 1.11)
GeparQuinto, GBG44[12]	8	307	36	308	23.1	0.20 (0.09, 0.44)
NeoALTTO[14]	3	149	36	154	22.9	0.07 (0.02, 0.22)
NSABP[24]	4	178	35	173	22.9	0.09 (0.03, 0.26)
Subtotal (95% CI)		**923**		**846**	**100**	**0.11 (0.07, 0.18)**
Total events	22		152			
Heterogeneity: χ^2=4.10, *df*=7 (*P*=0.77); I^2=0%						
Test for overall effect: *Z*=9.35 (*P*<0.00001)						
Other digestive tract symptoms						
CHER-LOB[13]	20	36	18	39	18.8	1.46 (0.59, 3.62)
EORTC 10054[10]	2	53	2	22	6.6	0.39 (0.05, 2.98)
Holmes et al[23]	0	32	1	34	3.5	0.34 (0.01, 8.74)
GEICAM[11]	0	50	3	52	8.3	0.14 (0.01, 2.78)
GeparQuinto, GBG44[12]	20	307	16	308	36.5	1.27 (0.65, 2.50)
NSABP[24]	6	178	11	173	26.3	0.51 (0.19, 1.42)
Subtotal (95% CI)		**656**		**628**	**100**	**0.92 (0.59, 1.44)**
Total events	48		51			
Heterogeneity: χ^2=5.68, *df*=5 (*P*=0.34); I^2=12%						
Test for overall effect: *Z*=0.36 (*P*=0.72)						
Febrile neutropenia						
CALGB 40601[27]	0	118	1	64	4.8	0.18 (0.01, 4.45)
EORTC 10054[10]	8	53	5	22	15.0	0.60 (0.17, 2.11)
Holmes et al[23]	3	32	0	34	1.1	8.19 (0.41, 165.03)
GeparQuinto, GBG44[12]	22	307	30	308	69.4	0.72 (0.40, 1.27)
NSABP[24]	7	178	4	173	9.7	1.73 (0.50, 6.02)
Subtotal (95% CI)		**688**		**601**	**100**	**0.85 (0.54, 1.34)**
Total events	40		40			
Heterogeneity: χ^2=4.97, *df*=4 (*P*=0.29); I^2=20%						
Test for overall effect: *Z*=0.69 (*P*=0.49)						
Neutropenia						
CALGB 40601[27]	2	118	8	64	8.1	0.12 (0.02, 0.59)
EORTC 10054[10]	22	53	10	22	6.5	0.85 (0.31, 2.32)
Holmes et al[23]	3	32	0	34	0.3	8.19 (0.41, 165.03)
GEICAM[11]	10	50	13	52	8.1	0.75 (0.29, 1.91)
GeparQuinto, GBG44[12]	237	307	222	308	40.0	1.31 (0.91, 1.89)
NeoALTTO[14]	4	149	24	154	18.2	0.15 (0.05, 0.44)
NSABP[24]	29	178	28	173	18.8	1.01 (0.57, 1.78)
Subtotal (95% CI)		**887**		**807**	**100**	**0.90 (0.69, 1.15)**
Total events	307		305			
Heterogeneity: χ^2=23.24, *df*=6 (*P*=0.0007); I^2=74%						
Test for overall effect: *Z*=0.85 (*P*=0.39)						
Hepatic						
CALGB 40601[27]	1	118	6	64	14.3	0.08 (0.01, 0.70)
CHER-LOB[13]	2	36	11	39	18.5	0.15 (0.03, 0.73)
EORTC 10054[10]	1	53	0	22	1.3	1.29 (0.05, 32.78)
Holmes et al[23]	0	32	0	34		Not estimable
GEICAM[11]	3	50	0	52	0.8	7.74 (0.39, 153.71)
GeparQuinto, GBG44[12]	14	307	8	308	14.1	1.79 (0.74, 4.33)
NeoALTTO[14]	11	149	28	154	47.3	0.36 (0.17, 0.75)
NSABP[24]	3	173	2	178	3.6	1.55 (0.26, 9.41)
Subtotal (95% CI)		**918**		**851**	**100**	**0.60 (0.39, 0.92)**
Total events	35		55			
Heterogeneity: χ^2=18.08, *df*=6 (*P*=0.006); I^2=67%						
Test for overall effect: *Z*=2.32 (*P*=0.02)						
Skin disorder						
CALGB 40601[27]	2	118	10	64	17.0	0.09 (0.02, 0.44)
CHER-LOB[13]	3	36	21	39	24.6	0.08 (0.02, 0.30)
EORTC 10054[10]	2	53	0	22	0.9	2.18 (0.10, 47.36)
GEICAM[11]	0	50	4	52	5.8	0.11 (0.01, 2.04)
GeparQuinto, GBG44[12]	2	307	22	308	29.1	0.09 (0.02, 0.37)
NeoALTTO[14]	4	149	10	154	12.8	0.40 (0.12, 1.30)
NSABP[24]	0	173	7	178	9.8	0.07 (0.00, 1.16)
Subtotal (95% CI)		**886**		**817**	**100**	**0.14 (0.08, 0.26)**
Total events	13		74			
Heterogeneity: χ^2=7.77, *df*=6 (*P*=0.26); I^2=23%						
Test for overall effect: *Z*=6.43 (*P*<0.00001)						
CHF						
EORTC 10054[10]	0	53	0	22		Not estimable
GeparQuinto, GBG44[12]	0	307	2	308	26.8	0.20 (0.01, 4.17)
NSABP[24]	7	178	7	173	73.2	0.97 (0.33, 2.83)
Subtotal (95% CI)		**538**		**503**	**100**	**0.76 (0.29, 2.03)**
Total events	7		9			
Heterogeneity: χ^2=0.94, *df*=1 (*P*=0.33); I^2=0%						
Test for overall effect: *Z*=0.54 (*P*=0.59)						



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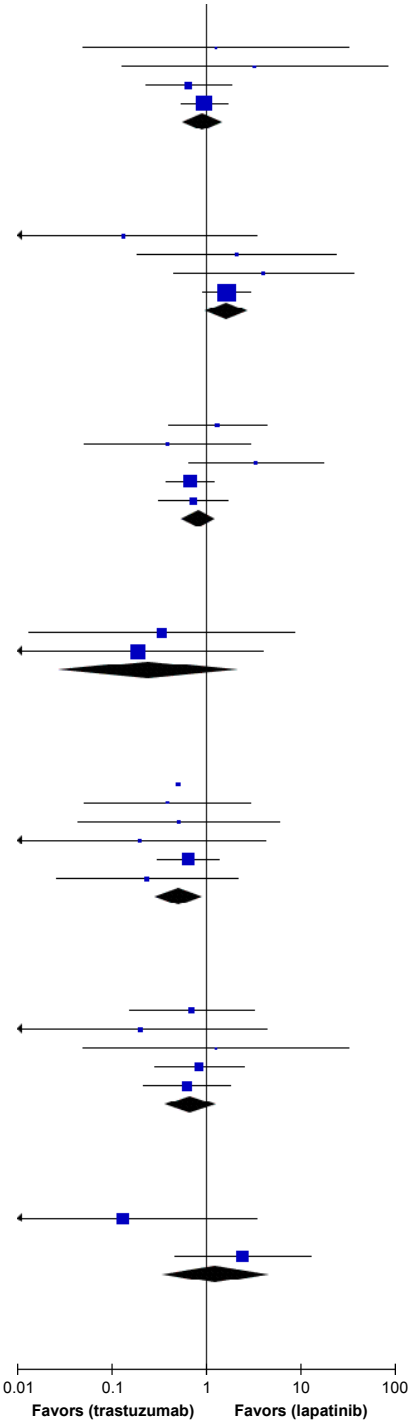
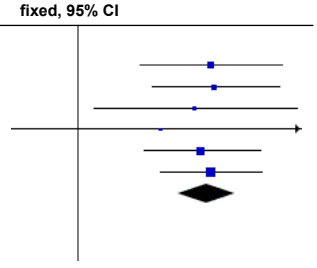


Hemoglobin							
EORTC 10054[10]	1	53	0	22	2.0	1.29 (0.05, 32.78)	
Holmes et al[23]	1	32	0	34	1.4	3.29 (0.13, 83.63)	
GeparQuinto, GBG44[12]	6	307	9	308	26.0	0.66 (0.23, 1.88)	
NSABP[24]	28	178	28	173	70.6	0.97 (0.55, 1.71)	
Subtotal (95% CI)		**570**		**537**	**100**	**0.93 (0.57, 1.50)**	
Total events	36		37				
Heterogeneity: χ^2=1.04, *df*=3 (*P*=0.79); I^2=0%							
Test for overall effect: *Z*=0.31 (*P*=0.76)							
LVSD							
EORTC 10054[10]	0	53	1	22	9.5	0.13 (0.01, 3.42)	
GEICAM[11]	2	50	1	52	4.3	2.13 (0.19, 24.20)	
GeparQuinto, GBG44[12]	4	307	1	308	4.5	4.05 (0.45, 36.47)	
NSABP[24]	35	178	22	173	81.7	1.68 (0.94, 3.00)	
Subtotal (95% CI)		**588**		**555**	**100**	**1.66 (0.98, 2.81)**	
Total events	41		25				
Heterogeneity: χ^2=2.99, *df*=3 (*P*=0.39); I^2=0%							
Test for overall effect: *Z*=1.88 (*P*=0.06)							
Fatigue							
CHER-LOB[13]	7	36	6	39	9.4	1.33 (0.40, 4.40)	
EORTC 10054[10]	2	53	2	22	5.5	0.39 (0.05, 2.98)	
GEICAM[11]	6	50	2	52	3.5	3.41 (0.65, 17.77)	
GeparQuinto, GBG44[12]	21	307	30	308	56.4	0.68 (0.38, 1.22)	
NSABP[24]	10	178	13	173	25.2	0.73 (0.31, 1.72)	
Subtotal (95% CI)		**624**		**594**	**100**	**0.83 (0.55, 1.26)**	
Total events	46		53				
Heterogeneity: χ^2=4.46, *df*=4 (*P*=0.35); I^2=10%							
Test for overall effect: *Z*=0.86 (*P*=0.39)							
Dehydration							
Holmes et al[23]	0	32	1	34	36.2	0.34 (0.01, 8.74)	
NSABP[24]	0	178	2	173	63.8	0.19 (0.01, 4.03)	
Subtotal (95% CI)		**210**		**207**	**100**	**0.25 (0.03, 2.24)**	
Total events	0		3				
Heterogeneity: χ^2=0.07, *df*=1 (*P*=0.80); I^2=0%							
Test for overall effect: *Z*=1.24 (*P*=0.21)							
Infection and inflammation							
CHER-LOB[13]	2	36	4	39	11.3	0.51 (0.09, 3.00)	
EORTC 10054[10]	2	53	2	22	8.5	0.39 (0.05, 2.98)	
Holmes et al[23]	1	32	2	34	5.9	0.52 (0.04, 5.99)	
GEICAM[11]	0	50	2	52	7.6	0.20 (0.01, 4.27)	
GeparQuinto, GBG44[12]	12	307	18	308	54.0	0.66 (0.31, 1.38)	
NSABP[24]	1	178	4	173	12.6	0.24 (0.03, 2.16)	
Subtotal (95% CI)		**656**		**628**	**100**	**0.52 (0.29, 0.94)**	
Total events	18		32				
Heterogeneity: χ^2=1.29, *df*=5 (*P*=0.94); I^2=0%							
Test for overall effect: *Z*=2.17 (*P*=0.03)							
Neuropathy sensory							
CALGB 40601[27]	4	118	3	64	16.7	0.71 (0.15, 3.29)	
CHER-LOB[13]	0	36	2	39	10.5	0.21 (0.01, 4.43)	
EORTC 10054[10]	1	53	0	22	3.0	1.29 (0.05, 32.78)	
GeparQuinto, GBG44[12]	6	307	7	308	30.5	0.86 (0.28, 2.58)	
NSABP[24]	6	178	9	173	39.2	0.64 (0.22, 1.83)	
Subtotal (95% CI)		**692**		**606**	**100**	**0.69 (0.36, 1.31)**	
Total events	17		21				
Heterogeneity: χ^2=0.91, *df*=4 (*P*=0.92); I^2=0%							
Test for overall effect: *Z*=1.13 (*P*=0.26)							
Dyspnoea							
EORTC 10054[10]	0	53	1	22	51.4	0.13 (0.01, 3.42)	
Holmes et al[23]	0	32	0	34		Not estimable	
NSABP[24]	5	178	2	173	48.6	2.47 (0.47, 12.91)	
Subtotal (95% CI)		**263**		**229**	**100**	**1.27 (0.34, 4.71)**	
Total events	5		3				
Heterogeneity: χ^2=2.47, *df*=1 (*P*=0.12); I^2=60%							
Test for overall effect: *Z*=0.36 (*P*=0.72)							
Test for subgroup differences: χ^2=109.29, *df*=13 (*P*<0.00001); I^2=88.1%							

B

Study or subgroup	Combination Events	Combination Total	Trastuzumab Events	Trastuzumab Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Diarrhea						
CALGB 40601[27]	25	117	2	118	16.6	15.76 (3.64, 68.28)
CHER-LOB[13]	28	46	3	36	14.0	17.11 (4.56, 64.18)
EORTC 10054[10]	9	50	1	53	8.5	11.41 (1.39, 93.79)
Holmes et al[23]	2	31	0	32	4.8	5.51 (0.25, 119.50)
NeoALTTO[14]	32	152	3	149	25.4	12.98 (3.88, 43.43)
NSABP[24]	46	173	4	178	30.7	15.76 (5.53, 44.89)
Subtotal (95% CI)		**569**		**566**	**100**	**14.38 (8.02, 25.78)**
Total events	142		13			
Heterogeneity: χ^2=0.56, *df*=5 (*P*=0.99); I^2=0%						
Test for overall effect: *Z*=8.95 (*P*<0.00001)						



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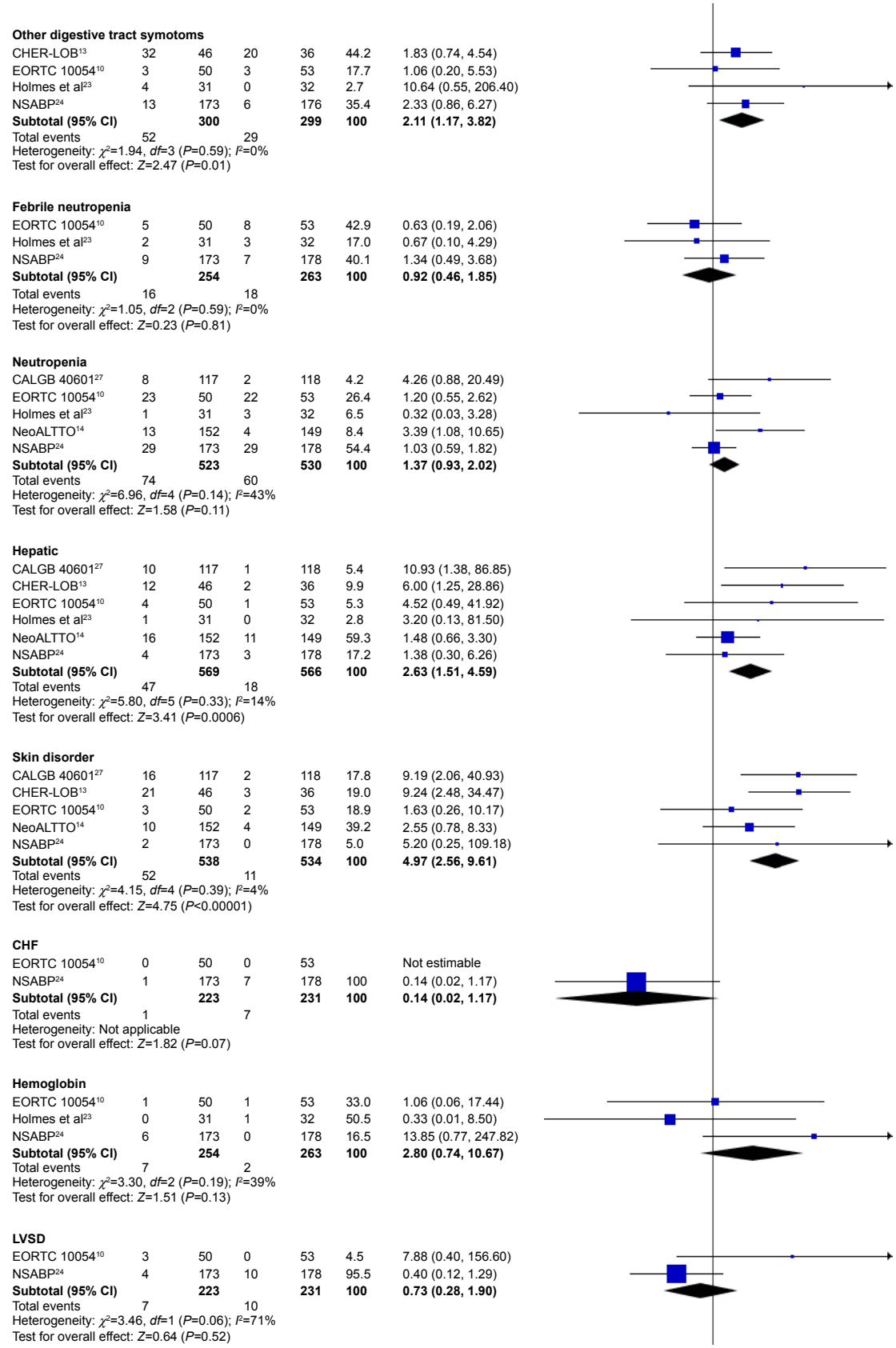

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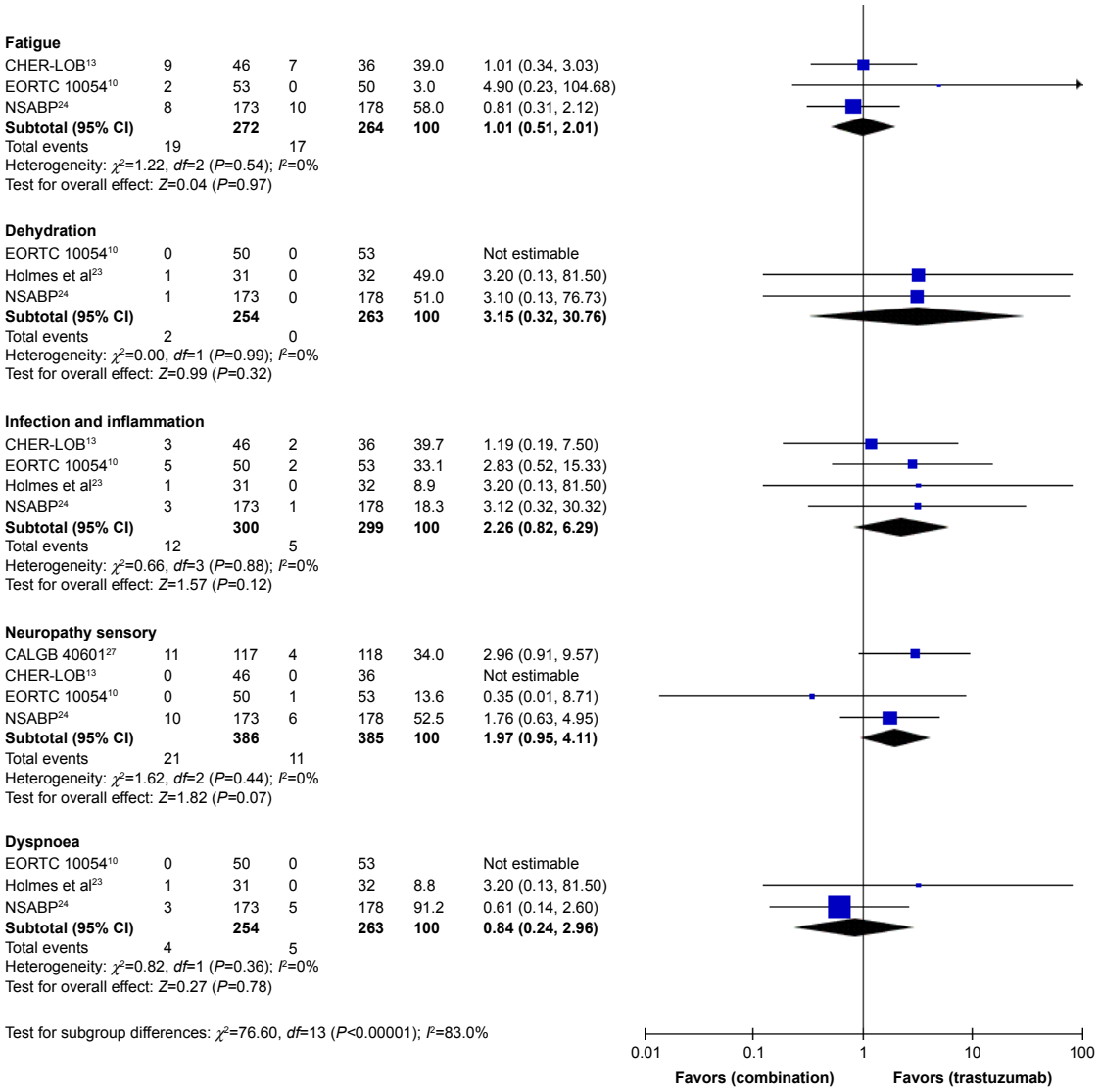

Figure 6 Forest plots of the toxic effect, trastuzumab versus lapatinib (**A**); combination versus trastuzumab (**B**).
Abbreviations: CHF, congestive heart failure; CI, confidence interval; *df*, degrees of freedom; LVSD, left ventricular systolic dysfunction; M–H, Mantel–Haenszel.

of trastuzumab to recruit immune cells that are responsible for antibody-dependent cytotoxicity[15] and inhibition of angiogenesis.[16]

The use of the dual blockade of Her2 is supported by biological and clinical data. Trastuzumab and lapatinib are well-known drugs that inhibit the function of Her2 by different mechanisms.[17] The expression product of the *Her2* gene is an oncogenic membrane-spanning protein that is processed externally at membrane sites. Because of its specific overexpression in tumor cells, it can be used as a target antigen for breast cancer therapy. Trastuzumab, a monoclonal antibody to Her2, combines with the extracellular domain of Her2,[18] thereby inducing the growth arrest of cells in G1 and the decrease of cell amplification. Regarding lapatinib, it can inhibit the tyrosine-kinase activity of both the epidermal growth factor receptor and ErbB-2 (Her2). This dual inhibitory activity can effectively prevent downstream signal transduction, thus preventing the proliferation of tumor cells. Taking the different mechanisms of drug action of trastuzumab and lapatinib into consideration, we suggest that the combination of these two drugs can provide a more optimal clinical curative effect.

Whether pCR can be used as a surrogate for disease-free survival rates in HER2-positive breast carcinomas, particularly those that are HR-positive, remains to be determined. Studies have confirmed that the higher the pCR rates,

the better the disease-free survival and overall survival can be achieved; but this effect may be limited to HR-negative tumors.[19] However, within the same group of Her2-positive patients, when accepting the same method of anti-Her2 therapy, the outcome (pCR) could vary. The differences in results obtained in the included studies were not due to statistical errors. Untch et al[12] reported that the absence of HR expression was an important predictor of pCR. Therefore, we hypothesize that a relationship between HR state and the drug effects exists. Interestingly, when we set the subgroups according to HR status, a significant difference for the pCR was found only in the HR-negative subgroups. This indicated that some relationships existed between HR and Her2, or that resistance to anti-Her2 agents existed. A previous study[20] showed impaired survival in patients with estrogen receptor-negative tumors. Estrogen receptor negativity has been reported to have a negative prognostic impact in breast cancer patients with Her2-positive tumors.[21,22] Further exploration of interactions between HR and Her2 will help to evaluate prognosis and to guide future treatment strategies.

Regarding toxicity of the drugs, some grade 3 and 4 toxic effects, such as diarrhea and skin disorder were more common in the lapatinib and dual-drug treated groups. This suggests both advantages and disadvantages to the patients, with some severe toxic effects from treatments.

Some trials reported additional operative procedures[10–12,14,23,24] for patients after NAC with anti-Her2 therapy. Although dual Her2 inhibition provides better pCR rates, this provides no significant improvement in the rate of breast conservation. Breast conservative therapy (BCT) is reported to provide long-term survival rates equivalent to those of total mastectomy.[22] Tan et al[25] performed a retrospective analysis in patients with breast malignancies and found that BCT was achieved in 85% of the patients with multifocal and multicentric breast cancer without evidence of poorer local control. Benediktsson and Perbeck[26] reported a series of 216 patients who underwent conservative mastectomy with a long follow-up (median 13 years). The 10-year frequency of local recurrence rate was 8.5% when patients accepted radio therapy according to international guidelines. Because BCT provides better cosmetic results and improves the quality of life, it is necessary to identify the indications for BCT. In our analyses, there was no relationship between anti-Her2 therapy and BCT. However, considering the limited studies included here, further investigations are needed.

Conclusion

In our study, we found that the combination of trastuzumab and lapatinib was superior to single-agent treatment for improved pCR rate. However, combination treatment was not effective in improving the rate of breast conservation. Furthermore, a higher risk for toxicity was associated with combined administration. There are limitations to this study. First, only English language literature was included. Second, although we chose only the randomized clinical trials, there was relative heterogeneity in the study, especially when it came to analyzing the toxicity effects. Finally, the chemotherapy regimens used in the included articles were not the same, and this could be a cause of the differences in reported pCR rates among the included groups. Based on clinical requirements, a larger study, including more evidence to verify the conclusions proposed here, is required.

Disclosure

The authors report no conflicts of interest in this work.

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