DOI:10.1093/jnci/dju203
First published online September 15, 2014

REVIEW

Comparative Effectiveness of Neoadjuvant Therapy for HER2–Positive Breast Cancer: A Network Meta-Analysis

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Manuscript received June 18, 2013; revised May 13, 2014; accepted June 2, 2014.

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Background The growing number of antihuman epidermal growth factor receptor-2 (HER2) agents suggests the need for defining the optimal choice of neoadjuvant therapy for HER2-positive breast cancer. This study aims to assess the efficacy and safety of neoadjuvant therapy for HER2-positive breast cancer.

Methods Randomized trials that compared different anti-HER2 regimens in the neoadjuvant setting were included. The odds ratio (OR) for pathological complete response (pCR), treatment completion, and safety was utilized for pooling effect sizes. Network meta-analysis using a Bayesian statistical model was performed to combine the direct and indirect evidence of neoadjuvant therapy for HER2-positive breast cancer. All statistical tests were two-sided.

Results A database search identified 1047 articles, with 10 studies meeting the eligibility criteria. A total of 2247 patients in seven different treatment arms were assessed. Anti-HER2 agents evaluated included trastuzumab (tzmb), lapatinib (lpnb), and pertuzumab (pzmb). Network meta-analysis showed no statistically significant difference between dual targeting treatment arms; however, lpnb reduced treatment completion due to adverse events. Patients in dual targeting arms had statistically significantly more pCR than those in other treatment arms (chemotherapy [CT] + tzmb + pzmb vs CT + tzmb, OR = 2.29, 95% credibility interval = 1.02 to 5.02, $P = .02$). The surface under the cumulative ranking probability curve indicated that CT + tzmb + pzmb had the highest probability of being the best treatment arm in terms of pCR.

Conclusions This study indicates that combining two anti-HER2 agents with CT is the most effective treatment modality in the neoadjuvant setting for HER2-positive breast cancer.

JNCI J Natl Cancer Inst (2014) 106(9): dju203 doi:10.1093/jnci/dju203

Overexpression or amplification of human epidermal growth factor receptor-2 (HER2) occurs in approximately 20% of human breast cancers and has been traditionally associated with poor prognosis (1). Trastuzumab (tzmb), an anti-HER2 agent, has demonstrated clinically significant efficacy against HER2-positive breast cancer and is considered the standard of care for adjuvant and metastatic treatment (2,3). In a recent meta-analysis, the addition of tzmb to neoadjuvant chemotherapy (CT) also improved the probability of achieving pathologically complete response (pCR) for HER2-positive breast cancer (4).

Positive efficacy outcomes with tzmb prompted the search to identify other HER2-targeted drugs capable of improving the therapeutic effects of tzmb in combination or sequential administration (5). The addition of the tyrosine kinase inhibitor lapatinib (lpnb) or monoclonal antibody pertuzumab (pzmb) to tzmb statistically significantly improved progression-free survival (PFS) compared with tzmb alone in HER2-positive metastatic breast cancer (MBC) (6,7). In addition, other anti-HER2 agents are at varying stages of clinical development (8). For example, an antibody-drug conjugate trastuzumab-DM1 (T-DM1) showed statistically significantly better PFS as compared with lpnb plus capecitabine among patients with HER2-positive MBC (9). Moreover, neratinib, a pan-HER tyrosine kinase inhibitor that irreversibly inhibits HER1 and HER2, has also shown activity against MBC (10).

The growing number of HER2-targeted agents has created the need to define the optimal neoadjuvant therapy for HER2-positive breast cancer. Although many trials have been conducted to compare treatments, it is difficult to integrate information on the relative efficacy of all tested regimens, since each trial has compared only a few treatments. Recently, a promising but much-debated extension of systematic reviews, network meta-analysis, has become increasingly popular. Network meta-analysis synthesizes information from a network of trials and combines direct and indirect evidence on the relative effectiveness of the treatments. For example, direct evidence comes from trials of A vs B, while indirect

evidence, through an "intermediate" comparator C, comes by combining trials of A vs C and of C vs B. This method helps interpret the randomized evidence from a networks of trials and can rank many different treatments, going beyond the classical focus on simple direct comparisons (11–13). This network meta-analysis has become widely employed, with the increased complexity of analyses that underpin clinical guidelines and can serve decision-making for policy makers (14). Here, we systematically assess the efficacy and safety of neoadjuvant therapy for HER2-positive breast cancer by conducting direct and indirect comparisons from multiple randomized clinical trials.

Methods

Search Strategy

Searches were performed using MEDLINE and the Cochrane Central Register of Controlled Trials without year and language restrictions, using the following search algorithm: Breast Neoplasms AND Neoadjuvant therapy AND Antibodies, Monoclonal OR Receptor, erbB-2. The last search was updated in August 2012. Because recent trials with anti-HER2 agents in a neoadjuvant setting may still be unpublished, electronic searches were also performed using the major international congress proceedings (American Society of Clinical Oncology Annual Meeting and San Antonio Breast Cancer Symposium). In addition, the reference lists of all studies fulfilling the eligibility criteria were examined for other relevant articles missed by the electronic searches.

Selection Criteria

Eligibility and exclusion criteria were prespecified. All randomized trials that compared at least two arms of different treatment regimens involving CT and/or anti-HER2 agents in patients with HER2-positive breast cancer in the neoadjuvant setting were considered. All cytotoxic CT regimens were considered eligible for the meta-analysis. If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent and informative publication was included. Using the Cochrane Collaboration risk of bias tool (15), two independent reviewers (AN and TH) assessed all studies for quality; appropriateness of allocation, blinding, and management of incomplete outcome data; and the completeness of reporting of outcomes.

Data Extraction

Data was extracted independently by two authors (AN and TH) according to a prespecified protocol, and a consensus was reached on all items. From each eligible trial, the first author, year of publication, journal, country of origin as noted in their affiliations, sample size, age, estrogen receptor/progesterone receptor status, node positivity, CT regimens, and anti-HER2 agent(s) dose/duration were recorded. Primary and secondary outcome measures were also recorded. Authors were contacted to obtain missing data. If no response was received, analysis was performed without these data.

Definition of Outcomes

The primary outcome in this study was the number of patients who achieved pCR with the number of patients treated. pCR was defined as no invasive residual cancer in the breast tissue and nodes; noninvasive breast residuals were allowed. Other definitions of pCR were substituted if not reported. Secondary objectives were the number of patients who completed the treatment as planned and the number of patients who had grade 3 or 4 adverse events, including diarrhea, neutropenia, and skin disorders, each with the number of patients treated. Adverse events were graded according to National Cancer Institute Common Terminology Criteria (NCI-CTC) version 4.0. If adverse events were not graded with the NCI-CTC, the corresponding numbers of the adverse events were used. Cardiac events, including asymptomatic events, such as left ventricular ejection fraction less than 50% or a drop of at least 10% from baseline, and symptomatic events, such as congestive heart failure or cardiac deaths, were reported separately. However, outcomes, such as overall survival and disease-free survival (DFS), were not analyzed because of insufficient data accumulation.

Statistical Methods

In direct comparisons, the odds ratio (OR) was utilized for pooling effect sizes, because all of the outcomes of interest were dichotomous variables. Data was pooled using the DerSimonian-Laird random effects model (16). Results were reported with 95% confidence intervals (CIs), and statistical significance was defined as P less than .05. All statistical tests were two-sided. If a direct comparison was based on two or more studies, statistical heterogeneity was calculated using the I^2 statistic. I^2 describes the percentage of total variation across studies that is due to heterogeneity rather than chance (17). I^2 quantifies the effect of heterogeneity in the studies' results (18). Furthermore, we defined the range: values above 50% indicative of large between-study heterogeneity, values of 25–50% indicative of modest heterogeneity, and values below 25% indicative of low heterogeneity (17).

Network meta-analysis using a Bayesian statistical model was carried out to compare the direct and indirect evidence for HER2-positive breast cancer neoadjuvant therapy by combining all the information regarding efficacy, treatment completion, and adverse events from different studies. The model applied to analyze the data is a Bayesian consistency model as described in Caldwell et al. (12). In a Bayesian framework, all parameters are treated as random variables. For each parameter of interest, its posterior distribution is being estimated using Markov chain Monte Carlo by placing suitable prior distributions (19). A hierarchical Bayesian model is a natural extension of a meta-analysis model for synthesizing comparisons between treatment pairs (13). Multivariate meta-analysis provides a solution to the multiplicity problem by summarizing simultaneously all outcomes of interest instead of conducting many separate univariate meta-analyses. A common heterogeneity parameter τ^2 was assumed across all comparisons using a random effects model within a Bayesian statistical model. Effect sizes were presented along with 95% credibility intervals (CrIs). When combining the results of direct and indirect comparisons, the extent to which these results are inconsistent (in disagreement) with each other was examined. In a network of treatments, different direct comparisons form evidence cycles, also called loops, within which inconsistency is evaluated (20). In addition, Bayesian network meta-analysis provides a ranking probability curve of each treatment (rankogram) by calculating the probability of each arm to achieve the best rank among all. A simple numerical summary

to supplement the graphical display of cumulative ranking is to estimate the surface under the cumulative ranking (SUCRA) line for each treatment; SUCRA would be one when a treatment is certain to be the best and zero when a treatment is certain to be the worst (21).

Direct comparisons and risk of bias assessment were calculated by Review Manager (RevMan), Version 5.1 (The Nordic Cochrane Centre: The Cochrane Collaboration, Copenhagen, Norway). Bayesian network meta-analyses and the node-splitting method were calculated by WinBUGS version 1.4 (MRC Biostatistics Unit, Cambridge, UK). Odds ratio, heterogeneity, and inconsistency were calculated, and diagrams were made by R version 2.13.2 (R Project for Statistical Computing, Vienna, Austria). The reporting of this meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (22).

Results

Overview of Literature Search and Study Characteristics

An electronic database search identified 1047 articles. Of these, 19 potentially eligible articles were evaluated in more detail, and 10 studies were found that met the eligibility criteria for this study (Figure 1 and Table 1). A total of 2247 patients in seven different treatment arms were assessed: CT alone; CT with tzmb, lpnb, or pzmb; tzmb and pzmb; CT with tzmb and lpnb; and CT with tzmb and pzmb. The Neosphere (23), NeoALTTO (24), and CHER-LOB (25) studies incorporated a treatment arm of dual anti-HER2 agents. Anti-HER2 agents were administered concomitantly with CT in all studies except for the NeoALTTO study, in which anti-HER2 agent alone was given for the first six weeks (24). The majority of neoadjuvant CT regimens that were chosen comprised anthracyclines and taxanes. Across the 10 studies, hormone-receptor (HR)–positive tumors accounted for 34–61%. The other risks of bias for each of the included studies were assessed in Supplementary Table 1 (available online).

Results of Direct Comparisons

From the eligible studies, 10 direct comparisons were made (Figure 2).

CT vs CT + tzmb (26–30)
CT + lpnb vs CT + tzmb (24,25,31,32)
CT + pzmb vs CT + tzmb (23)
Tzmb + pzmb vs CT + tzmb (23)
CT + tzmb + lpnb vs CT + tzmb (24,25)
CT + tzmb + pzmb vs CT + tzmb (23)
CT + tzmb + lpnb vs CT + lpnb (24,25)
Tzmb + pzmb vs CT + pzmb (23)
CT + tzmb + pzmb vs CT + pzmb (23)
CT + tzmb + pzmb vs tzmb + pzmb (23)

Among the 10 studies, five comparisons included pzmb and were based on one study (23).

The number of patients who achieved pCR was reported in 10 studies. The number of patients who completed the treatment as planned was reported in six studies (23–26,29,32). Diarrhea was reported in eight studies (23–25,28–32), in which seven of these studies (23–25,29–32) reported grade 3 and 4 events based on NCI-CTC. Neutropenia was reported in eight studies (23–26,28–30,32), in which six of these studies (23–25,29,30,32) reported grade 3 and 4 events. Cardiac events were reported in eight studies (23–29,32). Skin disorder was reported in six studies (23–25,28,30,32), in which five of these studies (23–25,30,32) reported grade 3 and 4. Figure 2 demonstrates the network diagram of eligible comparisons for pCR. The most commonly studied head-to-head comparison was CT vs CT + tzmb. The treatment effect of direct comparisons in forest plots is shown in Supplementary Figure 1, A-D (available online).

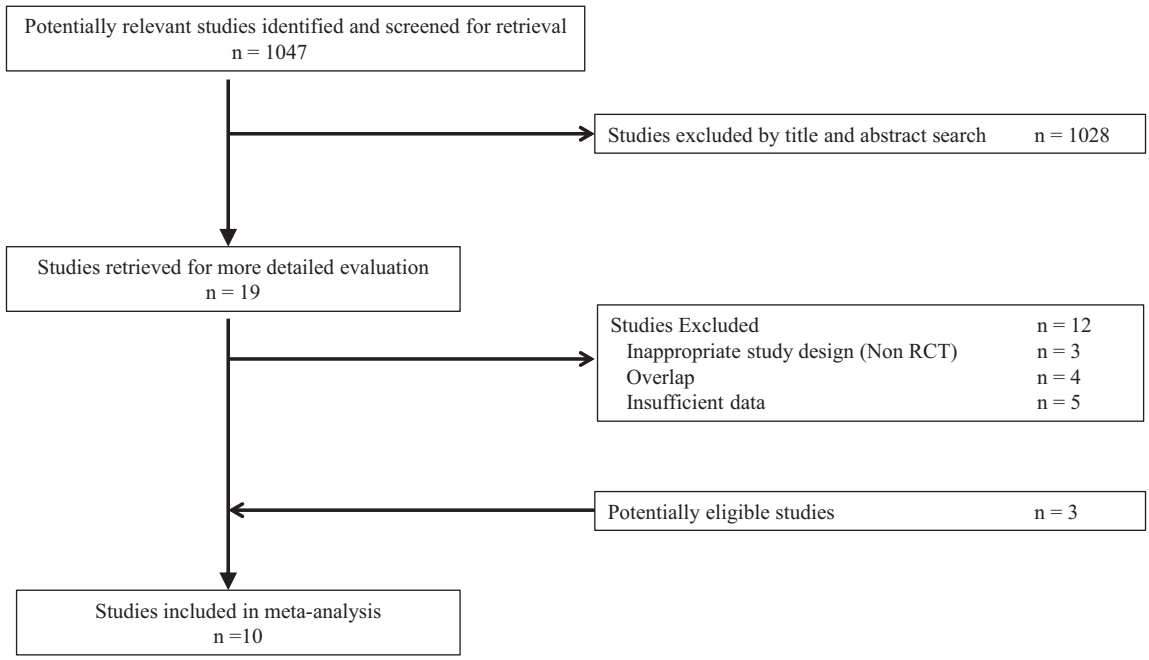

Figure 1. CONSORT diagram of study selection. RCT = randomized controlled trial.

Table 1. Characteristics of eligible studies*

Study	No. of patients	Clinical stage	Neoadjuvant chemotherapy	Neoadjuvant anti-HER2 agent	Arms	HR positive (%)	Duration (wks)	Adjuvant chemotherapy
Buzdar (26)	64	II-IIIA	Paclitaxel→FEC	Tzmb	45	25 (56)	24	None
				-	19	11 (58)		
NOAH (29)	235	T3N1 T4, any T N2-3	AP→paclitaxel→CMF	Tzmb	117	40 (35)	30	Tzmb
				-	118	40 (35)		
Pierga (30)	120	II-III	EC→docetaxel	Tzmb	62	34 (55)	12	Tzmb± fluorouracil + vinorelbine
				-	58	37 (63)		
Neosphere (23)	417	T2-4	Docetaxel	Tzmb	107	50 (47)	12	Tzmb + FEC
			Docetaxel	Tzmb + pzmb	107	50 (47)		Tzmb + FEC
			-	Tzmb + pzmb	107	51 (48)		Tzmb + docetaxel→FEC
			Docetaxel	Pzmb	96	46 (48)		Tzmb + FEC
NeoALTTO (24)	455	T2-4	Paclitaxel	Tzmb	149	75 (50)	18	Tzmb + FEC
				Lpnb	154	80 (52)		Lpnb + FEC
				Tzmb + lpnb	152	77 (51)		Tzmb + lpnb + FEC
GeparQuinto (32)	615	T1 pNSLN+, T2 cN+, T3-4, HR negative	EC→docetaxel	Tzmb	307	170 (55)	24	Tzmb
				Lpnb	308	171 (56)		
CHER-LOB (25)	121	II-IIIA	Paclitaxel→FEC	Tzmb	36	21 (58)	26	Tzmb
				Lpnb	39	24 (62)	26	
				Tzmb + lpnb	46	28 (61)	26	
H2269s (27)	29	T2-4	Docetaxel + carboplatin	Tzmb	15	NR	NR	Docetaxel + carboplatin + tzmb
				-	14	NR		
ABCSG-24 (28)	89	T1-4	Epirubicin + docetaxel + capecitabine	Tzmb	42	17 (41)	18	NR
				-	47	18 (38)		
GEICAM 2006–14 (31)	102	T2-4	EC→docetaxel	Tzmb	50	NR	24	NR

* AP = doxorubicin-paclitaxel; CMF = cyclophosphamide-methotrexate-fluorouracil; EC = epirubicin-cyclophosphamide; FEC = fluorouracil-epirubicin-cyclophosphamide; HR = hormone receptor; lpnb = lapatinib; NR = not reported; pzmb = pertuzumab; tzmb = trastuzumab.

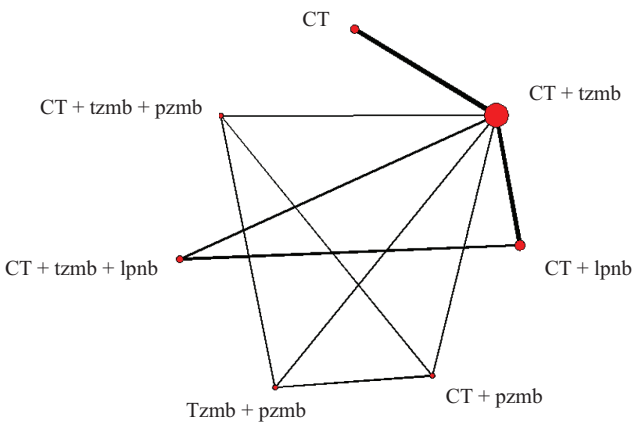

Figure 2. Network diagram of studies comparing pathological complete response (pCR) of different neoadjuvant therapies for human epidermal growth factor receptor-2-positive breast cancer. Each link represents at least 1 study and the widths of each link are proportional to the number of studies comparing the particular arms. The size of each node is proportional to the total sample size. CT = chemotherapy; lpnb = lapatinib; pzmb = pertuzumab; tzmb = trastuzumab.

Odds ratio and heterogeneity by I^2 statistics for all direct comparisons are listed in Table 2. The result showed a statistically significantly higher incidence of pCR in treatment arms of dual anti-HER2 agents with CT than in other arms. Although no statistically significant difference was found among treatment arms of a single anti-HER2 agent with CT, CT + lpnb was associated with inferior efficacy compared with CT + tzmb. Lpnb-containing treatment arms showed statistically significantly less treatment completion with more incidence of diarrhea and skin disorder compared with CT + tzmb. Tzmb + pzmb had statistically significantly less incidence of neutropenia compared with CT-containing arms. The incidence of cardiac events did not show any statistically significant difference among all the treatment arms. Across all the studies, seven patients were reported to have symptomatic congestive heart failure, although no cardiac death was reported in the eligible studies. An estimate consistent with large heterogeneity (I^2 > 50%) was seen in seven comparisons, while no large heterogeneity was seen in comparisons concerning pCR.

Bayesian Network Meta-Analysis

From the eligible studies, 21 indirect comparisons were made. Results of all possible comparisons were expressed with odds ratio and credibility interval calculated by Bayesian network meta-analysis (Table 3). Twelve statistically significant differences were found in pCR, two in treatment completion, 10 in diarrhea, six in neutropenia, four in skin disorder, and none in cardiac events. These results demonstrated that dual anti-HER2 agents with CT had a statistically significantly higher incidence of pCR than CT + tzmb (CT + tzmb + pzmb vs CT + tzmb, OR = 2.29, 95% credibility interval = 1.02 to 5.02, P = .02), whereas CT and CT + lpnb had a statistically significantly lower incidence of pCR compared with CT + tzmb. This finding strengthened the results of the direct comparisons. In particular, CT + tzmb + pzmb did not show any

Table 2. The odds ratios and heterogeneity for direct comparisons*

Outcome	No. of studies	Events	Total	Events	Total	OR (95% CI)	*P*	I^2 (%)
		CT		CT + tzmb				
pCR	5	53	256	111	281	0.43 (0.29 to 0.63)	<.001	0
Completion	2	123	137	156	162	0.40 (0.15 to 1.08)	.07	-
Diarrhea	3	5	218	4	219	1.11 (0.08 to 15.59)	.94	64
Neutropenia	4	56	237	61	242	0.70 (0.21 to 2.38)	.57	70
Cardiac events	4	30	190	31	191	0.75 (0.43 to 1.29)	.30	0
Skin disorder	2	1	105	4	104	0.25 (0.03 to 2.35	.23	-
		CT + lpnb		CT + tzmb				
pCR	4	145	548	210	628	0.69 (0.48 to 1.00)	.05	36
Completion	3	337	500	439	492	0.20 (0.09 to 0.47)	<.001	65
Diarrhea	4	93	552	13	542	7.87 (4.09 to 15.16)	<.001	8
Neutropenia	3	260	500	255	493	1.56 (0.47 to 5.13)	.47	86
Cardiac events	3	2	500	7	492	0.33 (0.08 to 1.40)	.13	0
Skin disorder	3	38	498	8	492	4.45 (1.68 to 11.76)	.003	29
		CT + pzmb		CT + tzmb				
pCR	1	17	96	23	107	0.79 (0.39 to 1.58)	.50	-
Completion	1	90	96	102	107	0.74 (0.22 to 2.49)	.62	-
Diarrhea	1	4	94	4	107	1.14 (0.28 to 4.71)	.85	-
Neutropenia	1	52	94	61	107	0.93 (0.53 to 1.63)	.81	-
Cardiac events	1	1	94	1	107	1.14 (0.07 to 18.48)	.93	-
Skin disorder	1	2	94	2	107	1.14 (0.16 to 8.26)	.90	-
		Tzmb + pzmb		CT + tzmb				
pCR	1	12	107	23	107	0.46 (0.22 to 0.98)	.05	-
Completion	1	93	107	102	107	0.33 (0.11 to 0.94)	.04	-
Diarrhea	1	0	108	4	107	0.11 (0.01 to 1.99)	.13	-
Neutropenia	1	1	108	61	107	0.01 (0.00 to 0.05)	<.001	-
Cardiac events	1	1	108	1	107	0.99 (0.06 to 16.05)	.99	-
Skin disorder	1	0	108	2	107	0.19 (0.01 to 4.10)	.29	-
		CT + tzmb + lpnb		CT + tzmb				
pCR	2	89	190	49	181	2.38 (1.54 to 3.68)	<.001	0
Completion	2	133	197	175	184	0.11 (0.05 to 0.22)	<.001	0
Diarrhea	2	48	197	4	185	14.35 (5.05 to 40.77)	<.001	0
Neutropenia	2	32	197	18	185	1.86 (0.64 to 5.34)	.25	53
Cardiac events	2	3	197	3	185	0.98 (0.20 to 4.73)	.98	0
Skin disorder	2	15	197	6	185	2.40 (0.91 to 6.35)	.08	0
		CT + tzmb + pzmb		CT + tzmb				
pCR	1	42	107	23	107	2.36 (1.29 to 4.31)	.005	-
Completion	1	102	107	102	107	1.00 (0.28 to 3.56)	1.00	-
Diarrhea	1	6	107	4	107	1.53 (0.42 to 5.58)	.52	-
Neutropenia	1	48	107	61	107	0.61 (0.36 to 1.05)	.08	-
Cardiac events	1	3	107	1	107	3.06 (0.31 to 29.87)	.34	-
Skin disorder	1	2	107	2	107	1.00 (0.14 to 7.23)	1.00	-
		CT + tzmb + lpnb		CT + lpnb				
pCR	2	89	190	40	188	3.24 (2.06 to 5.09)	<.001	0
Completion	2	132	192	133	197	1.16 (0.44 to 3.05)	.77	68
Diarrhea	2	48	197	50	192	0.89 (0.56 to 1.42)	.63	0
Neutropenia	2	32	197	38	192	0.77 (0.32 to 1.85)	.55	59
Cardiac events	2	3	197	1	192	3.08 (0.32 to 29.95)	.33	-
Skin disorder	2	15	197	16	192	0.88 (0.42 to 1.84)	.74	0
		Tzmb + pzmb		CT + pzmb				
pCR	1	12	107	17	96	0.59 (0.26 to 1.30)	.19	-
Completion	1	93	107	90	96	0.44 (0.16 to 1.20)	.11	-
Diarrhea	1	0	108	4	94	0.09 (0.00 to 1.74)	.11	-
Neutropenia	1	1	108	52	94	0.01 (0.00 to 0.06)	<.001	-
Cardiac events	1	1	108	1	94	0.87 (0.05 to 14.09)	.92	-
Skin disorder	1	0	108	2	94	0.17 (0.01 to 3.60)	.26	-
		CT + tzmb + pzmb		CT + pzmb				
pCR	1	42	107	17	96	3.00 (1.56 to 5.76)	<.001	-
Completion	1	102	107	90	96	1.36 (0.40 to 4.61)	.49	-
Diarrhea	1	6	107	4	94	1.34 (0.37 to 4.89)	.66	-
Neutropenia	1	48	107	52	94	0.66 (0.38 to 1.15)	.14	-
Cardiac events	1	3	107	1	94	2.68 (0.27 to 26.24)	.40	-
Skin disorder	1	2	107	2	94	0.88 (0.12 to 6.35)	.90	-

(Table continues)

Table 2 (Continued).

Outcome	No. of studies	Events	Total	Events	Total	OR (95% CI)	*P*	I^2 (%)
		CT + tzmb + pzmb		Tzmb + pzmb				
pCR	1	42	107	12	107	5.12 (2.50 to 10.46)	<.001	-
Completion	1	102	107	93	107	3.07 (1.06 to 8.86)	.04	-
Diarrhea	1	6	107	0	108	13.90 (0.77 to 249.83)	.07	-
Neutropenia	1	48	107	1	108	87.05 (11.72 to 646.85)	<.001	-
Cardiac events	1	3	107	1	108	3.09 (0.32 to 30.15)	.33	-
Skin disorder	1	2	107	0	108	5.14 (0.24 to 108.38)	.29	-

* CI = confidence interval; CT = chemotherapy; lpnb = lapatinib; OR = odds ratio; pCR = pathological complete response; pzmb = pertuzumab; tzmb = trastuzumab.

† The reference of OR is treatment arm in the right column.

‡ The OR was utilized for pooling effect sizes using the DerSimonian-Laird random effects model. I^2 quantifies the effect of heterogeneity in the studies' results with values above 50% indicative of large between-study heterogeneity, values of 25–50% indicative of modest heterogeneity, and values below 25% indicative of low heterogeneity. All statistical tests were two-sided.

§ I^2 was not calculated in comparisons that included the pzmb arm, because the comparisons were based on a single study.

statistically significant difference in pCR compared to CT + tzmb + lpnb. Again, lpnb-containing treatment arms showed statistically significantly less treatment completion and more diarrhea and skin disorder compared with CT + tzmb.

Analysis of inconsistency between direct and indirect comparisons indicated that a statistically significant inconsistency was identified in pCR, treatment completion, diarrhea, and neutropenia, but not in cardiac events and skin disorder. However, clinical variables that may affect these inconsistencies could not be identified in this study (Supplementary Figure 2, available online).

Ranking of Treatment Arms

Values of SUCRA (Figure 3) indicated that CT + tzmb + pzmb had the highest probability of being the best treatment arm for pCR (SUCRA = 0.93), followed by CT + tzmb + lpnb (SUCRA = 0.90), and CT + tzmb (SUCRA = 0.62). In contrast, CT alone had the lowest probability. CT + tzmb had the best result for treatment completion and the second best for diarrhea. Lpnb-containing arms had a low probability of being the best in terms of treatment completion, diarrhea, neutropenia, and skin disorder. The probability of each treatment achieving the largest number of patients with pCR is shown in Figure 4. This analysis indicated that CT + tzmb + pzmb was most probable to be the rank 1 (57.5%), CT +tzmb + lpnb to be the rank 2 (54.4%), CT + tzmb to be the rank 3 (71.1%), CT + pzmb to be the rank 4 (44.4%), CT + lpnb to be the rank 5 (46.6%), tzmb + pzmb to be the rank 6 (37.3%), and CT to be the rank 7 (63.6%).

Discussion

The concept of dual targeting therapy of HER2-positive breast cancer was introduced based on preclinical studies that showed primary and acquired resistance to anti-HER2 agents, their nonoverlapping mechanisms of action, and their synergistic interaction (33,34). Our meta-analysis also showed that patients in the dual targeting therapy arms, CT + tzmb + lpnb and CT + tzmb + pzmb, achieved statistically significantly more pCR than other treatment arms from the best available evidence.

This promising result of dual targeting therapy will lead us to the argument about whether the dual targeting therapy should be used in a neoadjuvant setting, adjuvant setting, or metastatic setting to have the best outcome as a whole. More insight was gained on how to predict long-term outcome by assessing the tumor response to neoadjuvant therapy. In HER2-positive and triple-negative breast cancer, pCR is more highly predictive of DFS within every established receptor subset than overall, demonstrating that the extent of outcome advantage conferred by pCR is specific to tumor biology (35). Survival analysis of the NOAH study showed a strong correlation between pCR and improved event-free survival (36). Meanwhile, a recent pooled analysis of the German neoadjuvant studies showed a statistically significant difference in DFS between pCR and no pCR among patients with HER2-positive/HR-negative tumors (37), indicating a hypothesis that neoadjuvant dual HER2 blockade is expected to improve DFS in this subset. In contrast, pCR was not associated with a statistically significantly better DFS compared with no pCR among patients with HER2-positive/HR-positive tumors. This conflicting result indicates that data regarding pCR should be interpreted with caution, especially in HER2-positive/HR-positive tumors, unless other data sets provide substantial evidence.

Although the pCRs in two different dual targeting therapies, CT + tzmb + lpnb and CT + tzmb + pzmb, were indistinguishable when compared indirectly in this study, treatment completion and safety were inferior in the CT + tzmb + lpnb group. Since lpnb-containing arms presented the disadvantage of less treatment completion, more diarrhea and skin disorder, patients treated with CT + tzmb + pzmb are expected to benefit from continued treatment and safety. The incidence of cardiac events did not increase in patients treated with dual targeting therapies. In regards to safety, CT + tzmb had the best result for treatment completion and the second best for diarrhea from our SUCRA analysis. Therefore, CT + tzmb therapy may remain as one of the options of neoadjuvant therapy for HER2-positive breast cancer, particularly considering the rising cost of targeted therapies and limited medical resources. A unique treatment arm without a chemotherapy partner, tzmb + pzmb, demonstrated remarkable safety in our study. However,

Table 3. The odds ratio and 95% credibility intervals calculated by Bayesian network meta-analysis*

Comparison		pCR	Completion	Diarrhea	Neutropenia	Cardiac events	Skin disorder
1	CT vs CT + tzmb	2.35 (1.46 to 3.76)	0.62 (0.16 to 2.21)	1.40 (0.56 to 3.64)	1.19 (0.54 to 2.45)	1.53 (0.34 to 6.93)	2.80 (0.84 to 10.14)
2	CT vs CT + lpnb	1.31 (0.70 to 2.45)	0.51 (0.11 to 2.08)	5.12 (1.15 to 22.92)	2.05 (0.56 to 7.94)	0.31 (0.05 to 1.56)	6.33 (1.11 to 34.23)
3	CT vs CT + pzmb	1.78 (0.66 to 4.64)	2.00 (0.30 to 13.44)	0.72 (0.10 to 5.13)	1.47 (0.26 to 8.85)	0.78 (0.05 to 9.56)	1.45 (0.14 to 13.93)
4	CT vs Tzmb + pzmb	1.03 (0.36 to 2.80)	0.87 (0.14 to 5.39)	0.07 (0.00 to 0.84)	0.01 (0.00 to 0.13)	0.66 (0.04 to 8.07)	0.20 (0.01 to 3.51)
5	CT vs CT + tzmb + lpnb	4.87 (2.36 to 10.12)	0.48 (0.10 to 2.24)	5.15 (1.09 to 25.03)	1.91 (0.45 to 8.62)	0.81 (0.15 to 4.12)	4.49 (0.71 to 26.90)
6	CT vs CT + tzmb + pzmb	5.39 (2.15 to 13.25)	2.73 (0.40 to 19.67)	0.97 (0.14 to 6.61)	0.97 (0.18 to 5.80)	2.63 (0.31 to 22.42)	1.28 (0.12 to 12.73)
7	CT + tzmb vs CT + lpnb	0.56 (0.37 to 0.84)	0.18 (0.07 to 0.38)	8.29 (3.76 to 19.43)	1.46 (0.56 to 3.87)	0.26 (0.05 to 1.15)	4.14 (1.61 to 10.50)
8	CT + tzmb vs CT + pzmb	0.76 (0.31 to 1.77)	0.71 (0.14 to 3.45)	1.17 (0.24 to 5.89)	1.05 (0.23 to 5.05)	0.65 (0.04 to 7.74)	0.95 (0.13 to 6.55)
9	CT + tzmb vs Tzmb + pzmb	0.44 (0.17 to 1.06)	0.31 (0.07 to 1.33)	0.11 (0.00 to 1.12)	0.01 (0.00 to 0.08)	0.56 (0.03 to 6.62)	0.13 (0.00 to 1.80)
10	CT + tzmb vs CT + tzmb + lpnb	2.08 (1.18 to 3.56)	0.17 (0.06 to 0.45)	8.33 (3.37 to 23.01)	1.36 (0.43 to 4.41)	0.68 (0.15 to 3.02)	2.94 (0.94 to 8.71)
11	CT + tzmb vs CT + tzmb + pzmb	2.29 (1.02 to 5.02)	0.98 (0.19 to 5.05)	1.56 (0.34 to 7.35)	0.69 (0.15 to 3.31)	2.21 (0.28 to 18.39)	0.84 (0.11 to 5.85)
12	CT + lpnb vs CT + pzmb	1.35 (0.50 to 3.45)	3.94 (0.70 to 25.08)	0.14 (0.02 to 0.87)	0.72 (0.12 to 4.53)	2.53 (0.11 to 53.57)	0.23 (0.03 to 1.96)
13	CT + lpnb vs tzmb + pzmb	0.78 (0.28 to 2.06)	1.71 (0.33 to 10.05)	0.01 (0.00 to 0.16)	0.01 (0.00 to 0.07)	2.15 (0.08 to 42.65)	0.03 (0.00 to 0.53)
14	CT + lpnb vs CT + tzmb + lpnb	3.71 (2.11 to 6.44)	0.95 (0.39 to 2.52)	1.01 (0.45 to 2.34)	0.93 (0.29 to 2.97)	2.64 (0.39 to 18.38)	0.71 (0.26 to 1.85)
15	CT + lpnb vs CT + tzmb + pzmb	4.10 (1.66 to 9.81)	5.38 (0.92 to 36.23)	0.19 (0.03 to 1.08)	0.48 (0.08 to 2.98)	8.58 (0.60 to 119.94)	0.20 (0.02 to 1.76)
16	CT + pzmb vs Tzmb + pzmb	0.58 (0.22 to 1.50)	0.43 (0.09 to 1.93)	0.09 (0.00 to 1.04)	0.01 (0.00 to 0.08)	0.85 (0.03 to 22.74)	0.14 (0.00 to 2.41)
17	CT + pzmb vs CT + tzmb + lpnb	2.74 (1.00 to 7.82)	0.24 (0.04 to 1.54)	7.11 (1.10 to 45.92)	1.30 (0.19 to 9.05)	1.05 (0.06 to 24.39)	3.09 (0.33 to 29.02)
18	CT + pzmb vs CT + tzmb + pzmb	3.03 (1.29 to 7.04)	1.37 (0.26 to 7.33)	1.34 (0.28 to 6.54)	0.66 (0.13 to 3.27)	3.39 (0.30 to 57.69)	0.88 (0.10 to 7.92)
19	Tzmb + pzmb vs CT + tzmb + lpnb	4.74 (1.66 to 13.89)	0.56 (0.09 to 3.26)	78.34 (6.17 to 1931.40)	148.12 (12.91 to 2223.86)	1.23 (0.07 to 30.51)	22.33 (1.26 to 893.37)
20	Tzmb + pzmb vs CT + tzmb + pzmb	5.24 (2.18 to 12.72)	3.16 (0.68 to 15.24)	14.72 (1.27 to 362.49)	75.64 (8.44 to 950.51)	3.98 (0.36 to 68.85)	6.35 (0.37 to 236.99)
21	CT + tzmb + lpnb vs CT + tzmb + pzmb	1.11 (0.42 to 2.86)	5.67 (0.87 to 40.33)	0.19 (0.03 to 1.16)	0.51 (0.08 to 3.55)	3.24 (0.26 to 43.51)	0.28 (0.03 to 2.73)

* CT = chemotherapy; lpnb = lapatinib; OR = odds ratio; pzmb = pertuzumab; pCR = pathological complete response; tzmb = trastuzumab.

† The reference of OR is treatment arm in the left.

‡ The model applied to analyze the data is a Bayesian consistency model as described in reference 12. All statistical tests were two-sided.

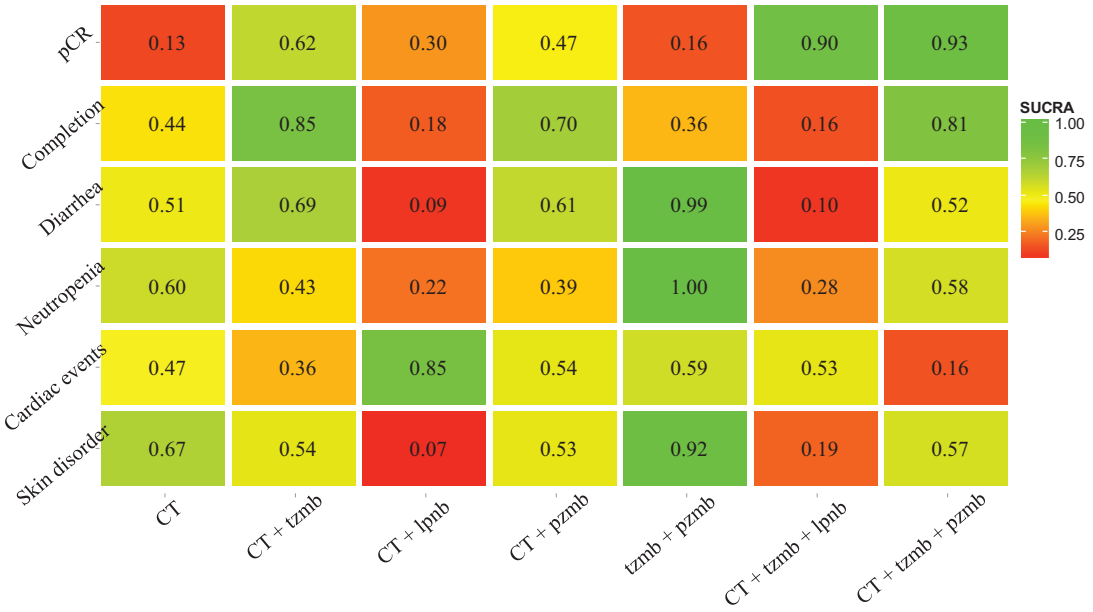

Figure 3. Heat map graph of overall efficacy according to surface under the cumulative ranking probability curve (SUCRA). Comparative strengths and limitations of each treatment arm. The **green color** indicates higher SUCRA values with greater probability to be the best treatment arm (more pathological complete response [pCR], treatment completion, and fewer adverse events), and the red color indicates lower SUCRA values with lower probability to be the best treatment arm (less pCR, treatment completion, and more adverse events). The SUCRA values are shown in each box. Chemotherapy (CT) + trastuzumab (tzmb) + lapatinib (lpnb) and CT + tzmb + pertuzumab (pzmb) are the most effective treatment arms. CT + tzmb had the best result for treatment completion and the second best for diarrhea. Lpnb-containing treatment arms have lower SUCRA values for treatment completion, diarrhea, neutropenia, and skin disorder than other treatment arms, whereas tzmb + pzmb has high SUCRA values for diarrhea, neutropenia, and skin disorder. All statistical tests were two-sided.

Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7
CT			0.1	2.1	7.2	27.0	63.6
CT + tzmb	0.1	3.0	71.1	23.4	2.4	0.1	
CT + lpnb		0.1	0.8	21.6	46.6	27.3	3.7
CT + pzmb	0.3	2.9	20.9	44.4	20.6	8.3	2.6
Tzmb + pzmb		0.3	1.8	7.5	23.0	37.3	30.1
CT + tzmb + lpnb	42.0	54.4	2.9	0.5	0.1		
CT + tzmb + pzmb	57.5	39.3	2.4	0.6	0.2		

Figure 4. Ranking for pathological complete response (pCR). Each value represents the probability of each treatment to be a specific rank. The **blue balloon area** is proportional to the probability. For example, the probability of chemotherapy (CT) + trastuzumab (tzmb) + pertuzumab (pzmb) to have the largest number of patients with pCR among all treatments is 57.5%, and the probability of CT to have the smallest number of patients with pCR is 63.6%. All statistical tests were two-sided. lpnb = lapatinib.

tzmb + pzmb is not recommended as neoadjuvant therapy because pCR in the tzmb + pzmb arm was statistically significantly inferior compared with CT + tzmb.

This study provides insight into the best HER2-targeted therapies for HER2-positive breast cancer; however, it does have some limitations. First, the number of studies and the number of patients included are relatively small. In particular, the informative value of the direct comparisons of the pzmb-containing arms was limited by the low number of events in small study populations. For some treatment comparisons in the examined network, no direct evidence was available, and thus evaluation of inconsistency (ie, the extent of disagreement between direct and indirect evidence) was impossible. Second, given the retrospective nature of the meta-analysis, publication bias and selective reporting biases cannot be excluded. Although such biases may affect sporadic comparisons, they are unlikely to refute the overall result. Third, the patient populations vary across studies, which may cause the heterogeneity of our analysis. Finally, an important consideration is that this study only analyzes pCR and treatment completion as an efficacy, and future study needs separate confirmation of the surrogacy relation of pCR with survival data.

In conclusion, our study, with randomized data regarding three different anti-HER2 agents (tzmb, lpnb, and pzmb), provides evidence that neoadjuvant dual targeting using anti-HER2 agents with CT shows a statistically significantly larger number of patients with pCR than CT alone, single targeting with CT, and dual targeting without CT for HER2-positive breast cancer.

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Funding

This work was supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan Grants-in-Aid for Scientific Research (Grant NOs. #25293292, #25461997, and #25861163).

Notes

The study sponsors had no role in the design of the study, the collection, analysis, or interpretation of the data, the writing of the manuscript, nor the decision to submit the manuscript for publication. A. Nagayama owns stock options of Chugai, Inc. A. Nagayama's immediate family member has a leadership position with Chugai, Inc. and Roche, Inc. Y. Kitagawa received research grants and lecture fees from Chugai, Inc. T. Hayashida received lecture fees from Chugai, Inc. H. Jinno received research grants and lecture fees from Chugai, Inc. and GSK, Inc. We thank Toshimi Takano, MD, in Toranomon Hospital, for critical reading.

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