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Review Article

ErbB inhibitors as neoadjuvant therapy for triple-positive breast cancer: a network meta-analysis

Danxiang Chen*, Lingli Jin*, Yiying Xu, Adheesh Bhandari, Ouchen Wang

*Department of Breast Surgery, The First Affiliated Hospital of Wenzhou Medical University, Nan Bai Xiang Street, Wenzhou 325006, Zhejiang, People's Republic of China. *Equal contributors.*

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Abstract: Background: Evidence on the effectiveness of ErbB inhibitor interventions for women with triple-positive breast cancer (TPBC) is scarce. Exposure to hormone receptors was reported to eclipse targeted intervention effectiveness. Here, we aimed to explore the optimum targeted regimen for TPBC. Methods: We conducted a thorough search of the literature focusing on neoadjuvant targeted therapy with both hormone receptor-positive and HER2 (ErbB2)-positive patients and performed a network meta-analysis comparing the regimens using a random-effects model. The rate of pathological complete response (pCR) (ypT0/is) was the primary outcome. The odds ratio (OR) with 95% confidence interval (CI) was used to assess the association among twelve regimens. Results: Thirteen studies meeting the inclusion criteria were included. Significantly more TPBC patients receiving ado-trastuzumab emtansine plus lapatinib experienced pCR events than other patients. In the high-performance ranking of the twelve regimens, ado-trastuzumab emtansine plus lapatinib (TDM-1+L) ranked top, followed by ado-trastuzumab emtansine (TDM-1), trastuzumab plus carboplatin, taxanes and pertuzumab (TCHP), trastuzumab plus docetaxel and lapatinib (THL), trastuzumab, taxanes and pertuzumab (THP), ado-trastuzumab emtansine plus pertuzumab (TDM1+P), trastuzumab plus taxanes (TH), trastuzumab plus taxanes and neratinib, taxanes plus pertuzumab (HP), taxanes and neratinib (HN), trastuzumab plus lapatinib (TL), trastuzumab plus pertuzumab (TP) in sequence. Conclusion: Double-targeted therapy in chemotherapy-based regimens was associated with better pCR than single-targeted therapy, and TDM-1+L stood out. For either single-targeted or double-targeted therapies, regimens free of chemotherapy were always worse than those with targeted therapy. Our data support guidelines that recommend combinations of chemotherapies plus targeted therapies in the neoadjuvant setting for early TPBC.

Keywords: Breast neoplasms, molecular targeted therapy, neoadjuvant therapy, network meta-analysis

Background

Breast cancer is currently promoted to the position that causes female cancer-specific death [1]. Approximately 15-25% of invasive breast cancer is characterized by overexpression of human ErbB2 [2], whose high invasiveness, in turn, brings a bleak prognosis [3, 4]. Food and Drug Administration (FDA) has already authorized 1-year trastuzumab added to chemotherapy as a standard regimen. However, the picture is now rather complicated by the rich options of anti-ErbB2 agents in the neoadjuvant context. The past decades have seen a flurry of targeted therapeutic drugs, comprising humanized monoclonal antibodies, antibody-drug conjugates, and tyrosine kinase inhibitors [5-7]. The questions surrounding HER2-positive breast cancer patients' treatment as well as the potential direction towards the development of a surrogate agent's alternative to trastuzumab are overwhelmingly discussed among many studies. Nevertheless, these studies did not perform a systematic subgroup analysis with a focus on triple-positive breast cancer (TPBC) to observe the curative effect of anti-ErbB2 agents. Given these problems, a network meta-analysis [8] is needed to assess direct and indirect comparisons of anti-ErbB2 agents to emerge on the pharmaceutical market. Accordingly, we included randomized controlled trials that reported pCR results of the TPBC subgroup during the last decade. Our study aims to rank neoadjuvant targeted agents available based on the relative efficiency of TPBC.

Materials and methods

Search strategy

Our network meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. PubMed, Embase, Cochrane Library, and Web of Science were searched to identify the published literature before Sep 1, 2020. Then, our analysis was performed using the following MeSH words: (mammary OR breast) AND (cancer OR malignancy OR tumour OR carcinoma) AND (neoadjuvant chemotherapy) AND (HER2-positive) AND (pCR OR complete pathological response). Furthermore, relevant publications were manually screened through the reference lists for more complete inclusion.

Selection criteria

Inclusion and exclusion standards were predefined as follows: randomized controlled clinical trials involving the efficacy of neoadjuvant targeted treatment for early breast cancer (EBC) with hormone receptor positivity (HR+, i.e., ER+ and/or PgR+) and HER2 (ErbB2) positive; exclusion criteria include but are not limited to 1) animal studies, editorial reviews, reviews, or case reports; 2) without raw statistics; 3) single arm or dose exploration trials; and 4) ongoing trials that have not yet reached their endpoint. In addition, a complete pathological response was deemed a primary outcome.

Data extraction

The narrative characteristics employing narrative tables were necessary in light of dissimilarity in trial designs and potential sources of bias. Thus, the characteristics and endpoint data of each trial were extracted separately by two reviewers; the other two resolved the dissimilarities and reached a consensus. Recorded information was summarized as follows: the first author, publication year, registry country, trial phase, number of research centres, sample size, interventions. Endpoint data were extracted as the ratio of pCR individuals to the total HR-positive and HER2-positive numbers.

Outcome definition

Because this meta-analysis emphasized the comparison of HER2-targeted therapies, the imparity between chemotherapy and endocrine regimens was not taken into consideration. Thus, the addition of a single drug or combination targeted regimens to any standard chemotherapy and endocrine therapy could be considered a new scheme, which was reflected on the network diagram in the form of blue nodes. Each arm in a multiarm study was supposed to be a scheme, and the sample size could be combined if the content of the arm was consistent regardless of delivery order and period. Pathological complete response was deemed a primary outcome, namely, ypT0/is (defined as mere carcinoma in situ or absence of infiltrating breast cancer focus). If pCR was not reported, tPCR (ypT0/is ypN0) was extracted as endpoint data instead. If only the percentage of results was reported, the sample size multiplied by the corresponding proportion was the final event number.

Statistical analysis

The nodes in the network diagram represent the treatment schemes, and black lines lacing together indicate the direct or indirect comparison within two regimens. In addition, the size of nodes and width of lines are both positively correlated with the number of RCTs for comparison. Eleven nodes, namely, (1) TH, (2) THL, [9] THN, (4) THP, (5) TL, (6) TN, (7) TP, (8) HP, (9) TCHP, (10) TDM-1 and (11) TDM-1+L, constitute the network system as follows, in which T represents trastuzumab, H represents taxanes (paclitaxel or docetaxel), N represents neratinib, L represents lapatinib, P represents pertuzumab, and C represents carboplatin. Dichotomous data here meant to be pCR, and non-pCR percentages were analysed using Mantel-Haenszel (MH) methods to calculate the OR, which had to be calculated from the included studies or was publicly available. The method, based on minimal assumptions, provides estimators of the degree of association and the null hypothesis of no association. As mentioned above, systematic differences existed among all 13 trials, and thus heterogeneity testing by measuring an indicator of inconsistency degree (I^2) came into routine work. This percentage of heterogeneity was generally set to the boundary of 50%. STATA was used for analysis (STATA version 10, Stata Corp, College Station, TX, USA).

Results

Overview of literature search

The literature retrieval yielded 978 studies limited to clinical trials from PubMed, Embase,

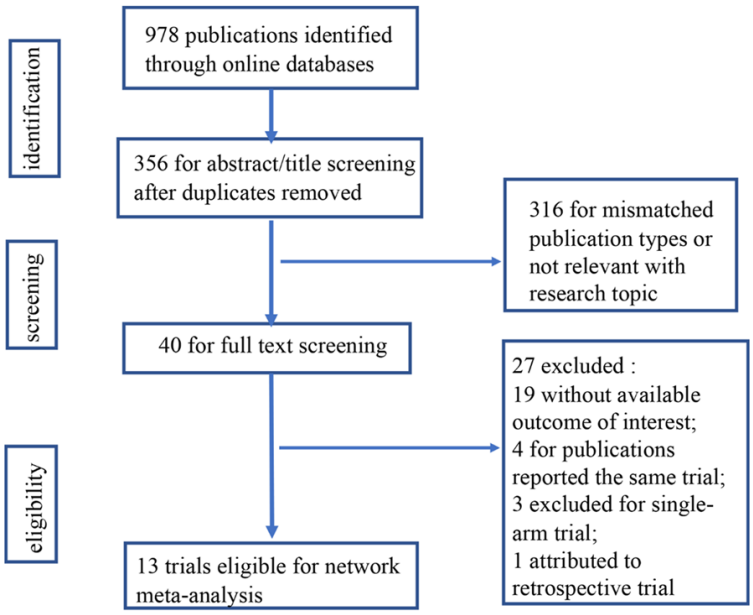

Figure 1. Flow diagram for the inclusion of studies.

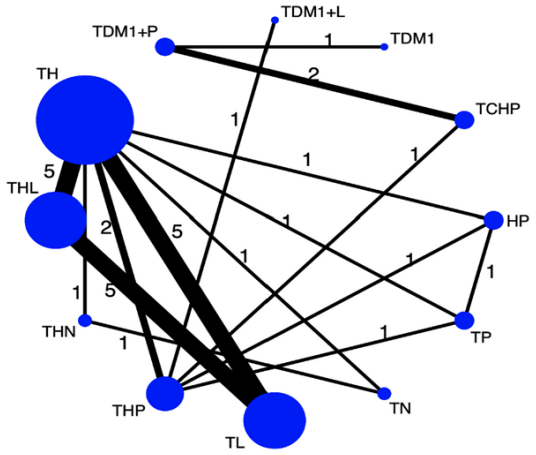

Figure 2. Network diagram of thirteen eligible regimens for pCR. The blue nodes represent the specified targeted regimen, and the node size is proportional to the event numbers of the corresponding regimen. The width of the line is proportional to the number of studies between the two compared regimens.

Cochrane Library, Web of Science and Clinical Trials.gov, and the screening of the titles and abstracts revealed that 316 of these articles did not match the eligibility criteria. Twenty-seven of 40 works of literature with full text were excluded for the following reasons: 19 did not report the outcome of interest (pCR or tPCR), four were duplicates, and the rest were considered single-arm trials, with three retrospective trials for one (**Figure 1**). As a consequence, a total of 13 trials [10-22] were eligible for our network meta-analysis (**Figure 2**).

Characteristics of eligible trials

The full network meta-analysis among 12 treatment algorithms with a sample size of 1837 patients comprised six two-arm trials, six three-arm trials and one unique four-arm trial. Five studies compared the efficacy of monotargeted to dual-targeted therapy with lapatinib in the trastuzumab-based regimen. In addition, two studies compared trastuzumab to trastuzumab plus pertuzumab, and the other two studies compared trastuzumab plus pertuzumab to TDM-1 plus pertuzumab in a straightway manner. The remaining comparisons included TDM1 plus pertuzumab versus TDM-1, TDM1 plus lapatinib versus trastuzumab plus pertuzumab, trastuzumab plus pertuzumab with or without carboplatin, pertuzumab with or without trastuzumab, trastuzumab plus pertuzumab with or without taxanes, trastuzumab plus taxanes versus trastuzumab plus neratinib, trastuzumab versus pertuzumab both in combination with taxanes, trastuzumab plus taxanes versus trastuzumab plus pertuzumab, and pertuzumab plus taxanes with or without trastuzumab. In addition, 7 of 13 studies reported pCR data, and 9 of 13 reported tPCR, where three studies presented both. In consideration of nearly similar incidences of pCR and tPCR, pCR is intended to be the final report outcome. **Table 1** summarizes the main characteristics of the eligible studies, and the qualification assessment is displayed in **Figure 2**.

Quality assessment

The large number of trials went through the risk of bias evaluation assessed with the Cochrane risk of bias tool. All of the trials were reported as having a low risk of reporting bias and attribution bias (100%). Additionally, 69.2% of trials loosely performed the blinding method, and

Table 1. Characteristics of the included randomized controlled trials

Study	ID	Publication	Phase	Stage	Multi-centric	N	Industry-sponsored	Follow-up (Y)
CALGB 40601	NCT00770809	Carey 2015	III	II-III	43	173	National Cancer Institute	5
EORTC 10054	NCT00450892	Bonnefoi 2014	IIb	IIA-IIIC	14	64	GlaxoSmithKline/EORTC	5.5
NSABP B41	NCT00486668	Robidoux 2013	III	II-III	40	329	NSABP Foundation, Inc GlaxoSmithKline	5
NSABP FB-7	NCT01008150	Jacobs 2019	II	IIB-IIIC	42	79	NSABP Foundation, Inc Puma Biotechnology, Inc	5
CHER-LOB	NA	Guarneri 2012	IIb	II to IIIA	NA	73	GlaxoSmithKline	NA
NeoALTTO	NCT00553358	Baselga 2012	III	NA	23	232	Novartis Pharmaceuticals Breast International Group; SOLTI Breast Cancer Research Group	2.4
PEONY	NCT02586025	Zhimin Shao 2019	III	III	4	173	Hoffmann-La Roche	1.5
NEOSPHERE	NCT00545688	Gianni 2012	II	II-III	16	197	Hoffmann-La Roche	8
BP22572	NCT00934856	Martin 2016	Ib	IIA-IIIC	5	39	Hoffmann-La Roche	4.25
KRISTINE	NCT02131064	Hurvitz 2017	phase III	II-IIIC	21	259	Hoffmann-La Roche	1.5
Neospeaks	UMIN000014649	Masuda 2019	phase II	I-III	17	89	NA	NA
TRYPHAENA	NCT00976989	Schneeweiss 2013	phase II	NA	44	114	Hoffmann-La Roche	1.5
Teal	NCT02073487	Patel 2019	phase II	II-III	3	16	Celgene Corporation Novartis	5

Abbreviations: AC, allocation concealment; AS, allocation sequence; C, control arm; IO, incomplete outcome; N, number of patients; NA, not available; SR, selective report; Y, years.

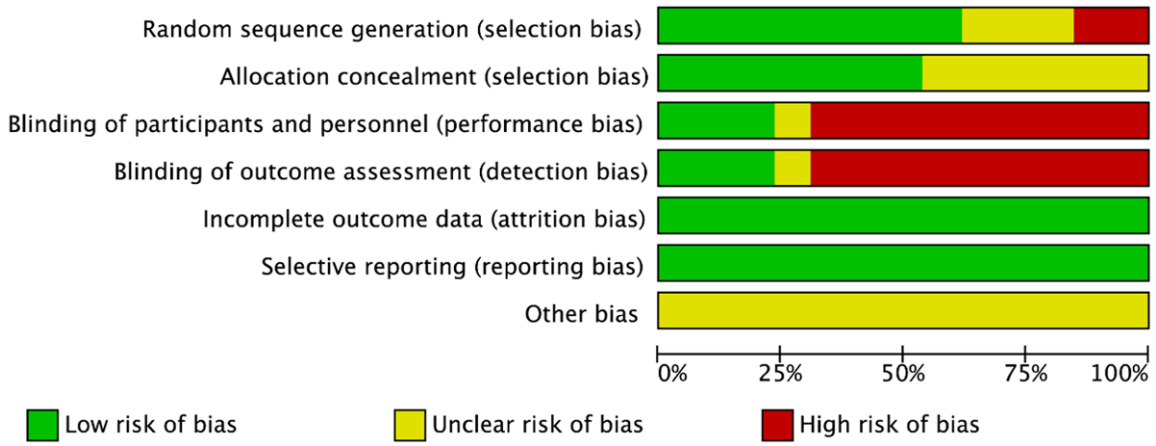

Figure 3. Quality assessment diagram.

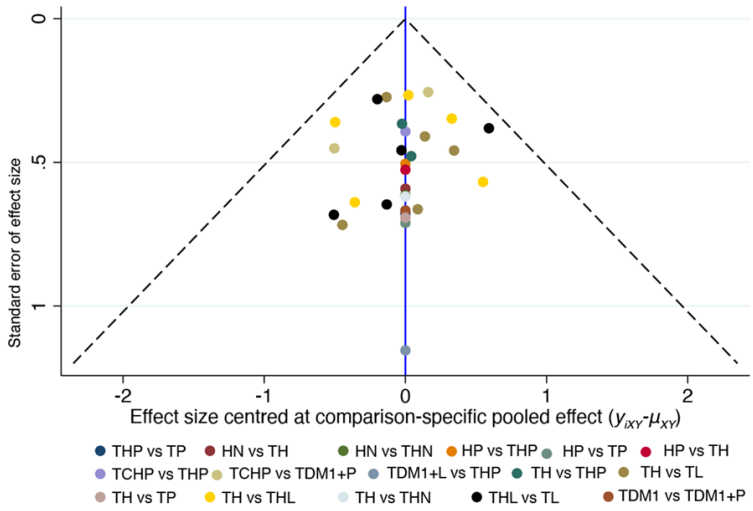

Figure 4. Funnel plot of publication bias.

only three trials achieved double blinding. Selection bias was reported as 15.4% high risk. However, the generation of randomization (23.1%), concealment of allocation (46.2%), and blinding of both participants and outcome assessment (7.7%) were reported unclearly. The quality assessment is shown in **Figure 3**, and publication bias is shown in **Figure 4**.

Bayesian network meta-analysis of direct comparison

Based on the overarching network diagram, lapatinib in combination with trastuzumab and taxanes can be directly compared with many trastuzumab-based regimens, which include single-target therapies and double-target therapies. indirect comparison of the THL regimen using the Bucher method could be conducted with most interventions in this network. Single trastuzumab had a worse pCR than the combination with lapatinib (OR = 0.68; 97.5% CI: 0.45-1.00) in Carey 2015, Bonnefoi 2014, Robidoux 2013, Guarneri 2012, Baselga 2012 [10, 11, 13, 14, 20], but it remained unclear whether it reached statistical significance. Head-to-head comparisons between TH and the other three double-targeted regimens (THL, THN, THP) were available. In the double-blind, placebo-controlled, phase 3 Peony trial, the tPCR rate in the ER- and/or PR-positive population was 33.3% in the pertuzumab arm and 25% in the placebo arm, showing a nonsignificant difference in favour of the addition of pertuzumab, with a difference of 8.3% (95% CI, -6.9% to 23.5%). It is worth mentioning that the Peony trial was dedicated to the Asian population and compatible with previous pertuzumab trials, which further confirmed the efficacy of pertuzumab across races. In another randomized, open-label phase 2 NeoSphere trial, complete pathological responses were reached in 10 of 50 women (20%) following trastuzumab and chemotherapy rid of pertuzumab compared with 13 of 50 (26%) with the addition of pertuzumab. Both trials showed a consistent

trend of therapeutic benefits with the addition of pertuzumab to trastuzumab and docetaxel in the neoadjuvant setting.

By comparison, 8 of 27 women (29.6%) given trastuzumab plus taxanes had a complete pathological response, as did 7 of 23 (30.4%) women treated with the addition of neratinib. FB-7 showed the difference in pCR rates between single-agent neratinib and trastuzumab in both HER2+ and HR- patients and the triple-positive subgroup.

To our amazement, single-target therapy with chemotherapy had a better pCR than double-target therapy without chemotherapy. Thus, concomitant or sequential chemotherapy is expected to show an additional impact in TPBC. These comparisons were partitioned into four categories: trastuzumab plus lapatinib versus trastuzumab plus taxanes; trastuzumab plus pertuzumab versus trastuzumab plus taxanes; trastuzumab plus pertuzumab versus pertuzumab plus taxanes; and trastuzumab and pertuzumab plus chemotherapy (carboplatin and taxanes) versus TDM-1 plus pertuzumab.

The pairwise meta-analysis for comparison of TL and TH was performed in five studies. The results showed that there was a nonsignificant trend towards better pCR in HR+ Her2+ patients treated with TH than in those treated with TL (OR = 0.76; 95% CI = 0.53-1.10, P = 0.139). Pathological complete response rates for the HR+ Her2+ population indicated nonsignificant favour of TCHP in comparison to TDM1+P in the Neospeaks and Kristine trials (OR = 1.22; 95% CI = 0.64-2.18).

Significantly, TPBC patients receiving the double-targeted regimen experienced fewer pCR events than those in the combined arm with the double-targeted regimen plus chemotherapy (OR = 0.53; 95% CI = 0.37-0.78, P = 0.001), as did those receiving the single-targeted regimen plus chemotherapy (OR = 0.71; 95% CI = 0.51-0.99, P = 0.045). Only if chemotherapy was included in the treatment scheme could we conclude that the double-target regimen outbalanced the single-target regimen.

TDM-1 has been proven to work better in terms of TPBC combined with lapatinib or alone. Nevertheless, the TDM-1 plus pertuzumab regimen may be incompatible with the other TDM-1-based treatment regimens in the Kristine and Neospeaks trials. The phase 3 Kristine trial and phase 2 Neospeaks trial both compare TDM-1 plus pertuzumab to docetaxel, carboplatin, and trastuzumab plus pertuzumab but acquire the opposite consequences. The triple-arm Neospeaks trial favouring TDM-1 plus pertuzumab roughly assigned participants (1:1:2) to receive TCbHP (Group A), TCbHP followed by TDM-1 plus P (Group B) and TDM-1 plus P (Group C). For direct comparison, Group B was excluded when incorporating the ER-positive subgroup into the meta-analysis; thus, pCR rates after four cycles of T-DM1+P (Group C; 50.8%) were better than those of the standard TCbHP regimen (Group A; 43.3%), while the two comparative groups reached equivalent pCR (57%) irrespective of HR status. In contrast, the larger Kristine trial with a sample size of 277 analysing TCbHP obtained a more satisfactory response. We found that TDM-1 and pertuzumab were advantageous in the case of more advanced clinical settings, such as higher stage, more lymph node involvement, and higher Ki67 index, when taking a broad view of the Kristine trial. Baseline characteristics of the Kristine trial [15] included 17% of participants with stage III disease, while the Neospeaks trial [18] concentrated on a lower stage (70.6% T2; 63.2% N0); this may account for the tendency towards disparity in the targeted scheme of the two trials. Forest plots of pairwise meta-analyses for the complete pathological response (pCR) are shown in **Figure 5**.

Indirect comparison

After the pros and cons analysis of double-targeted therapy, single-targeted therapy and addition of chemotherapy by direct comparison evidence, we indirectly compared different targeted agents based on the same regimens using the Bucher method.

Two anti-ErbB2 agents (lapatinib and pertuzumab), but not neratinib, significantly improved pCR rates compared with placebo when added to the TH regimen, with ORs ranging from 1.47 (for lapatinib: 95% CI [1.00-2.22]) to 1.43 (for pertuzumab: 95% CI [0.72-2.78]) (**Figure 6**). In addition to trastuzumab-based regimens, indirect comparison of TDM1-based targeted regimens also demonstrated that TDM1 plus lapatinib was superior to TDM1 plus pertuzumab (OR = 11.71; 95% CI = 0.98-164.92), which provided further proof that lapatinib may perform

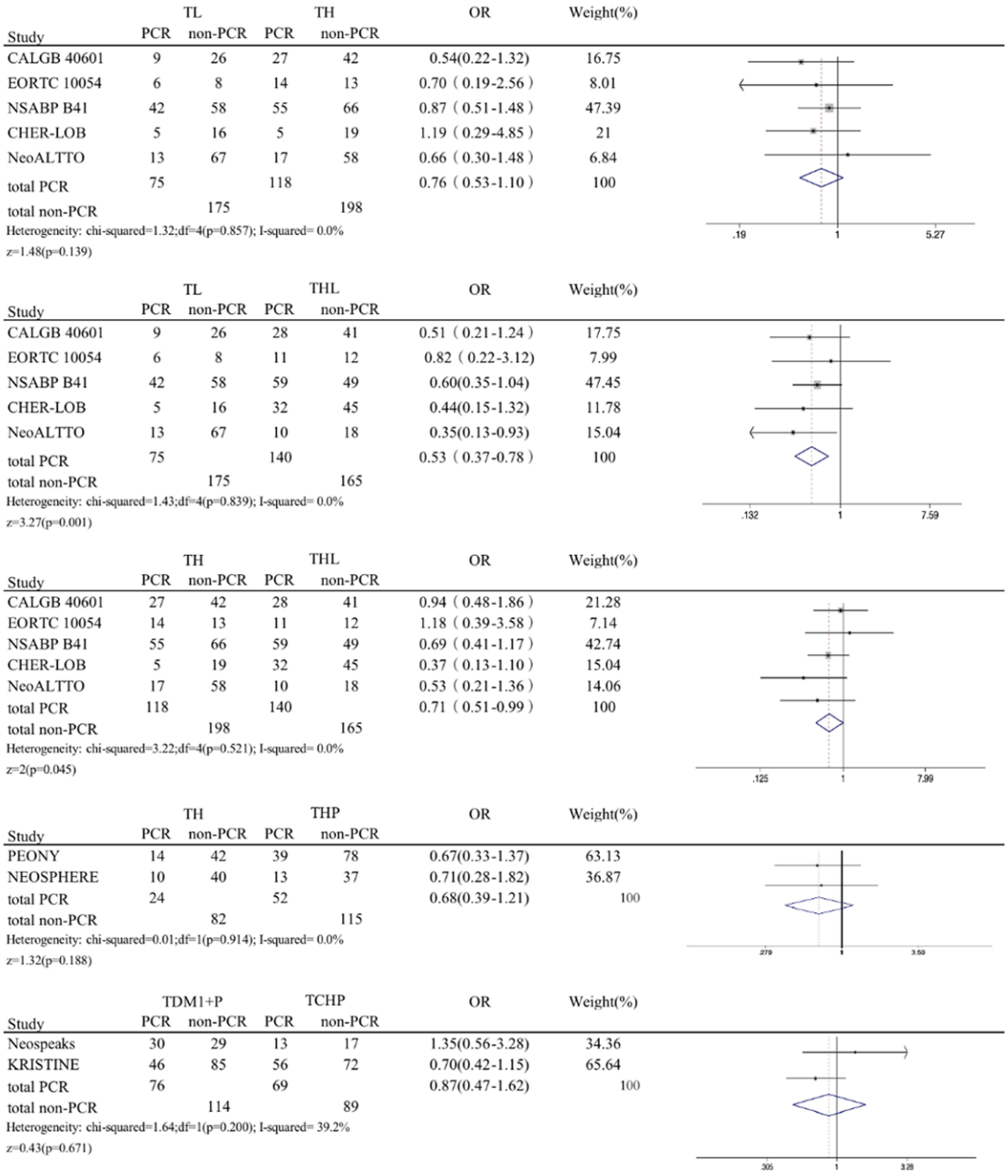

Figure 5. Forest plots of pairwise meta-analysis for pCR. (i) TL vs. TH; (ii) TL vs. THL; (iii) TH vs. THL; (iv) TH vs. THP; (v) TDM1+P vs. TCHP. Abbreviations: TCHP, trastuzumab plus carboplatin, taxanes and pertuzumab; TDM1+P, ado-trastuzumab emtansine plus pertuzumab; TH, trastuzumab plus taxanes; THL, trastuzumab plus taxanes and lapatinib; THP, trastuzumab plus taxanes and pertuzumab; TL, trastuzumab plus lapatinib.

better than pertuzumab in combination with trastuzumab or TDM-1 (**Figure 7**).

Discussion

International guidelines recommended that administration of dual-targeted therapies with or without chemotherapy in HER2-positive breast cancer was superior to monotargeted therapy in the context of the neoadjuvant setting. However, there is a lack of evidence to date is available from head-to-head randomized controlled trials comparing the curative effect of neoadjuvant regimens in the TPBC

	HN	HP	TCHP	TDM1	TDM1+L	TDM1+P	TH	THL	THN	THP	TL	TP
HN		0.96 (0.19, 6.26)	0.50 (0.10, 3.31)	0.35 (0.04, 4.91)	0.06 (0.00, 0.73)	0.60 (0.11, 4.11)	0.84 (0.21, 3.36)	0.56 (0.16, 2.38)	0.78 (0.25, 3.21)	0.56 (0.15, 2.64)	1.16 (0.31, 4.96)	3.68 (0.70, 26.07)
HP	0.46 (0.13, 2.21)		0.46 (0.13, 2.21)	0.34 (0.04, 3.38)	0.05 (0.00, 0.58)	0.62 (0.13, 3.44)	0.80 (0.27, 3.62)	0.52 (0.17, 2.62)	0.88 (0.13, 4.71)	0.58 (0.19, 1.98)	1.04 (0.35, 5.08)	4.30 (0.88, 17.93)
TCHP	0.73 (0.14, 3.04)	1.59 (0.30, 8.37)		0.73 (0.14, 3.04)	0.10 (0.01, 1.09)	1.22 (0.64, 2.18)	1.68 (0.54, 4.61)	1.15 (0.33, 3.50)	1.79 (0.24, 9.20)	1.16 (0.46, 2.64)	2.26 (0.68, 6.76)	7.56 (1.40, 44.58)
TDM1	1.51 (0.43, 7.92)	2.35 (0.33, 16.77)	1.52 (0.21, 11.66)		0.15 (0.01, 2.06)	1.51 (0.43, 7.92)	2.35 (0.33, 16.77)	1.52 (0.21, 11.66)	2.30 (0.18, 23.32)	1.61 (0.29, 10.12)	2.75 (0.43, 22.86)	12.01 (1.27, 101.12)
TDM1+L	11.71 (0.98, 164.92)	16.21 (1.59, 228.09)	10.89 (1.01, 150.02)	15.31 (1.13, 259.80)	10.87 (1.30, 133.35)	22.02 (1.70, 329.98)	78.07 (5.91, 1134.23)					
TDM1+P	1.36 (0.41, 4.70)	1.53 (0.19, 8.95)	0.92 (0.26, 3.42)	1.01 (0.24, 3.68)	0.91 (0.34, 2.88)	1.75 (0.53, 6.75)	6.47 (1.11, 35.87)					
TH	0.68 (0.45, 1.00)	1.52 (0.35, 5.64)	0.70 (0.36, 1.38)	1.35 (0.89, 2.11)	4.44 (1.23, 25.43)							
THL	1.01 (0.49, 2.20)	2.02 (1.33, 3.12)	6.70 (1.73, 34.61)									
THN	0.72 (0.16, 3.56)	1.35 (0.35, 5.99)	4.97 (0.76, 34.22)									
THP	2.03 (0.91, 4.35)	6.66 (1.76, 32.65)										
TL	3.31 (0.82, 16.02)											
TP												

Figure 6. The league table of direct and indirect comparisons. An OR > 1 is in support of the treatments in the column, while an OR < 1 favours the treatments in the row.

A

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9	Rank 10	Rank 11	Rank 12
HN	0	0.05	0.08	0.05	0.05	0.05	0.08	0.11	0.1	0.13	0.26	0.04
HP	0	0.05	0.03	0.03	0.06	0.06	0.08	0.09	0.16	0.21	0.2	0.02
TCHP	0	0.2	0.22	0.19	0.11	0.1	0.06	0.05	0.04	0.02	0.01	0
TDM1	0.11	0.42	0.07	0.07	0.04	0.04	0.07	0.06	0.03	0.03	0.04	0.01
TDM1+L	0.86	0.05	0.05	0.02	0.01	0	0	0	0	0	0	0
TDM1+P	0	0.03	0.14	0.19	0.12	0.15	0.09	0.08	0.07	0.08	0.04	0.01
TH	0	0	0.01	0.02	0.11	0.1	0.18	0.27	0.2	0.11	0.01	0
THL	0.01	0.08	0.15	0.19	0.2	0.18	0.12	0.05	0.02	0	0	0
THN	0.01	0.08	0.07	0.06	0.09	0.07	0.09	0.09	0.14	0.16	0.11	0.04
THP	0	0.04	0.17	0.17	0.21	0.22	0.1	0.05	0.02	0.01	0	0
TL	0	0	0	0	0.01	0.03	0.13	0.14	0.2	0.22	0.25	0.02
TP	0	0	0	0	0	0	0	0.01	0.01	0.03	0.08	0.86

B

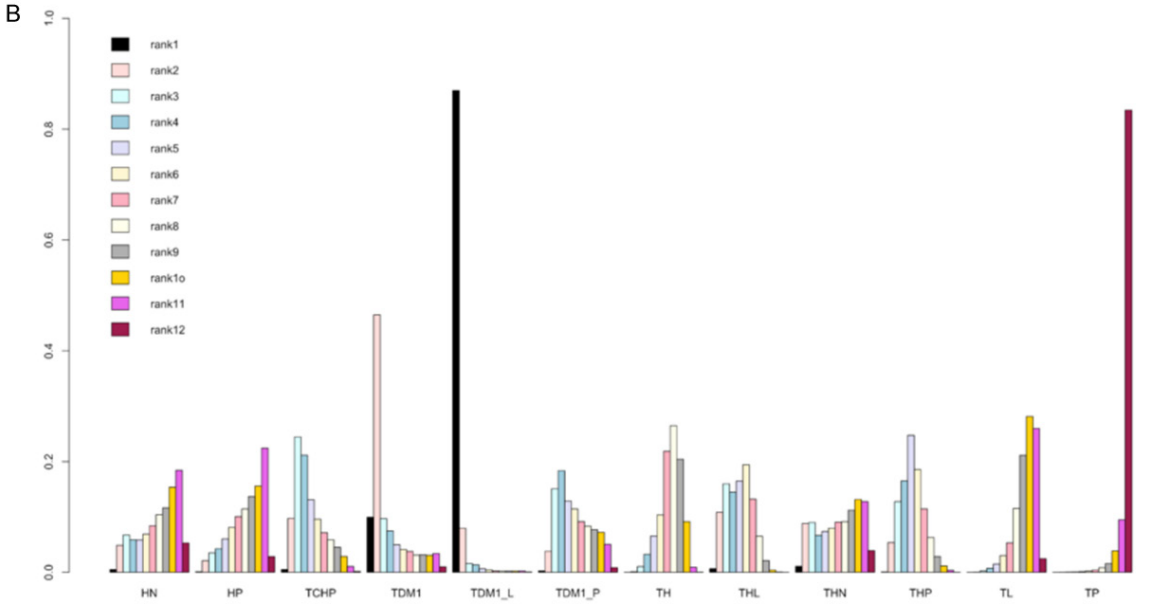

Figure 7. Heatmap and histogram of the rank probability for pCR. The order of the rank reflects the pros and cons of the efficacy. Rank 1 represents the best treatment, and rank 12 represents the worst.

subset. From anti-ErbB2 treatment in a variety of clinical trials, TPBC was more inclined to be a her2-dominated subtype because of the definite benefit in the her2-positive population irre-

spective of the hormone receptor status [23-25].

Our network meta-analysis enabled the clinically relevant exploration of neoadjuvant tissue for TPBC. Owing to the preciseness and practical-minded nature of evidence-based medicine, several novel observations from the network meta-analysis are expected to influence clinical trial designs in the future. The findings of this large network meta-analysis suggested that TPBC benefited more from TDM-1+L therapy than any other in terms of pCR, taking no account of endocrine therapy and chemotherapy. In addition, the final result demonstrated that double-targeted therapies perform better than monotherapy, and lapatinib performed relatively well among these collocation agents. However, double-targeted therapies without chemotherapy even became inferior to single-targeted therapies with chemotherapy, which indicated that the precision of targeted therapy and extensive cytotoxicity of chemotherapy were both indispensable.

Approximately 8-10% of breast cancer is TPBC, defined by the molecular peculiarity of hormone receptor- and Her2-positive breast cancer [26]. Past studies described copositive BC as unfortunately susceptible to late relapses, which presented an urgent demand to reduce the relapse risk in the neoadjuvant stage.

In the post-trastuzumab era, the her2 receptor acted more like a functional therapeutic target rather than an adverse factor. A better prognosis in terms of DFS and OS was associated with TPBC than the Her2-positive or HR-positive subtype, which overturned the conventional concept that TPBC predicted worse outcomes [27].

Albeit with increasingly targeted strategies to block Her2 signalling, drug resistance develops in the TPBC subset due to genetic or epigenetic alterations in response to the interaction of Her2 and ERα. These facts reflected that the routine regimen for Her2+ BC was not applicable for TPBC, which aroused the exploration of a dual blockage of both the ER and HER signalling pathways.

In general, the intensive regimens performed better than the de-escalated regimens. Based on these data, the upfront use of chemotherapy should be appropriately sustained in neoadjuvant treatment. Studies proved a distinct gene expression modality between Her-positive, ER-negative and TPBC patients, which contributed to the disparity of their outcome. Membrane IGF1R protein, Her3, cytoplasmic PTEN, and serum AREG expression were higher in TPBC than in Her2-positive, ER-negative patients [28]. Lyu et al. found that IGF-1R-initiated Src activation commonly rendering trastuzumab resistance in copositive patients had little impact on lapatinib sensitivity [26], in accordance with our result supporting the significance of lapatinib.

Neratinib is an irreversible pan-HER tyrosine kinase inhibitor, whose benefit in terms of risk reduction must be interpreted in the context of other HER-targeted treatments. Luftner et al. further validated its function against resistance towards other targeted agents in the adjuvant stage [29]. Thus, our orientation towards immediate profit, regardless of long-term outcome, could in part explain the order priority. Although this is a reasonable mechanism based on our data, others cannot be ruled out.

The NA-PHER2 trial verified that TPBC patients could be exempt from chemotherapy with the treatment of trastuzumab, pertuzumab, palbociclib and fulvestrant [30]. The efficacy of targeted agents undoubtedly has been potentiated in combination with diverse hormone therapies. However, few trials could enable objective reflection on the influence of hormone therapy given the paucity of the endocrine therapy cycle. Additionally, another limitation lies in our neglect of comparing the adverse effects and cost-effectiveness, which account for much of the quality of life. Even though intensive and advanced chemotherapy yields a higher likelihood of pCR, de-escalation of general toxicity in the absence of chemotherapy in the neoadjuvant phase may suffice in collaboration with sequential adjuvant strategies [31].

Meta-analysis enables the systematic analysis of specific clinically relevant issues. However, alternative trials incorporate assumptions that could be hard to evaluate in the real world on account of the limited combinatorial regimens.

Conclusion

In conclusion, our analysis supports targeted therapy combined with chemotherapy as the

preferred regimen in the neoadjuvant setting of TPBC patients.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ouchen Wang, Department of Breast Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China. Tel: +86-577-55578527; E-mail: woc863@hotmail.com

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