Efficacy and safety of neoadjuvant therapy for HER2-positive early breast cancer: a network meta-analysis

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Abstract

Aims: Currently, there are many approaches available for neoadjuvant therapy for human epidermal growth factor receptor 2 (HER2)-positive breast cancer that improve therapeutic efficacy but are also controversial. We conducted a two-step Bayesian network meta-analysis (NMA) to compare odds ratios (ORs) for pathologic complete response (PCR) and safety endpoints.

Methods: The Cochrane Central Register of Controlled Trials, PubMed, Embase, and online abstracts from the American Society of Clinical Oncology and San Antonio Breast Cancer Symposium were searched comprehensively and systematically. Phase II/III randomised clinical trials for targeted therapy in at least one arm were included.

Results: A total of 9779 published manuscripts were identified, and 36 studies including 10,379 patients were finally included in our analysis. The NMA of PCR showed that dual-target therapy is better than single-target therapy and combination chemotherapy is better than monochemotherapy. However, anthracycline did not bring extra benefits, whether combined with dual-target therapy or single-target therapy. On the other hand, the addition of endocrine therapy in the HER2-positive, hormone receptor (HR)-positive subgroup might have additional beneficial effects but without significant statistical difference. By performing a conjoint analysis of the PCR rate and safety endpoints, we found that 'trastuzumab plus pertuzumab' and 'T-DM1 containing regimens' were well balanced in terms of efficacy and toxicity in all target regimens.

Conclusion: In summary, trastuzumab plus pertuzumab-based dual-target therapy with combination chemotherapy regimens showed the highest efficacy of all optional regimens. They also achieved the best balance between efficacy and toxicity. As our study showed that anthracycline could be replaced by carboplatin, we strongly recommended TCbHP as the preferred choice for neoadjuvant treatment of HER2-positive breast cancer. We also look forward to the potential value of T-DM1 in improving outcomes, which needs further study in future trials.

Keywords: breast cancer, chemotherapy, HER2-positive, neoadjuvant, network meta-analysis, target therapy

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Introduction

Human epidermal growth factor receptor 2-positive (HER2-positive) breast cancer, which accounts for 25–30% of all breast cancers, was once considered an aggressive, dangerous, or even lethal subtype based on the characteristics of its biological behaviour.[1,2] However, the situation has now changed. With one-year adjuvant

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trastuzumab therapy combined with standard adjuvant chemotherapy, nearly 70% of early stage HER2-positive breast cancer patients participating in the HERA clinical trial lived 10 years longer, without invasive disease.[3] Furthermore, HER2-positive breast cancer patients achieved a significantly longer disease-free survival under dual anti-HER2 blockade, which adds pertuzumab to trastuzumab, according to the results of the APHINITY clinical trial.[4]

Neoadjuvant therapy has recently been greatly revolutionised.[5] According to some neoadjuvant clinical trials, adding trastuzumab to conventional chemotherapies can nearly double the pathologic complete response (PCR) rate, up to 30–40%, as compared with monochemotherapies.[6,7] Furthermore, the PCR rate was also found to be doubled in some dual-target arms.[8–11] Given the high PCR rate obtained by targeted therapies, which also means a higher survival rate in HER2-positive breast cancer, neoadjuvant therapies have been extensively used in most HER2-positive early breast cancer patients, including operable cases.[5,10,12–14] Recently, the results of the KATHERINE trial indicate that neoadjuvant therapies can not only identify patients who show the best response to targeted therapies, but also improve the prognosis of those who show poor initial sensitivity to preoperative treatments by using postoperative enhanced therapy.[15] Unequivocally, the aim of neoadjuvant therapy is not only to increase the probabilities of surgical resection or breast conservation, but also to improve overall survival through individual therapeutic regimens, including optimised preoperative therapy, accurate efficacy evaluation, and reasonable postoperative disease management.

As the list of new drugs and promising therapeutic regimens has grown in recent years, the growing debate regarding neoadjuvant therapy for HER2-positive patients has also widened. Among the various anti-HER2 drugs, which should be the priority? If we aim to enhance targeted therapies, could the combination chemotherapy be de-escalated? Is monochemotherapy adequate as a favourable partner to dual-target therapy? May anthracyclines be discontinued? Does intensive targeted therapy benefit patients with HER2-positive and hormone receptor-positive (HR+) as much as patients with HER2-positive but HR-negative (HR–) breast cancer? Between better outcomes and fewer toxicities, which is more important? Overall, it is important to conduct a complete analysis of all relevant clinical studies and offer a useful reference for clinical practice. Although there have been some meta-analyses undertaken, including some network analyses trying to compare different targeted therapies, none of them have focused on the intensity of the combination chemotherapy, not to mention the selection of different drugs.[16–19] Therefore, the questions mentioned above remain unresolved. Since pair-wise comparison is not available, we conducted a network meta-analysis (NMA) using up-to-date data to provide a comprehensive overview of neoadjuvant regimens for HER2-positive breast cancer.

Material and methods

Identification of studies

Electronic databases, including the Cochrane Central Register of Controlled Trials, PubMed, and Embase, were searched comprehensively and systematically. All online abstracts from two important international meetings, the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium, were also carefully reviewed individually. The following search string was used: "(neoadjuvant OR preoperative) AND (treatment OR therapy OR chemotherapy OR target therapy) AND (breast OR mammary) AND (cancer OR carcinoma OR malignant OR neoplasm OR tumour) AND (HER-2 OR HER2 OR HER2/neu OR ERBB2 OR human epidermal growth factor receptor 2) AND (positive OR +)" (Supplemental File 1). Furthermore, references of the selected studies were reviewed to find other relevant trials. Only publications in English were selected. The most recent research was published in November 2020.

Selection criteria

The pre-specified inclusion and exclusion criteria were as follows: (i) phase II or III randomised controlled trials that focused on neoadjuvant therapy for HER2-positive breast cancer, (ii) trials involved two or more treatment arms, (iii) the publication provided PCR rates for the experimental and control arms, and (iv) targeted therapy was administered to at least one arm. Case reports, systemic reviews, retrospective studies, single-arm studies, and exploratory studies were excluded. If multiple publications were derived from the same clinical study, only the latest result was included. Posters that were presented more

than 5 years ago without formal publications were also excluded. Two reviewers independently reviewed all the studies. If they disagreed on whether a study should be included or not, a consensus was reached after discussion with a third reviewer.

Data extraction

All data from the included studies were independently extracted by two investigators. The following information was collected: title, trial name, first author's name, publication date, country, patient characteristics (including the number of patients enrolled, tumour stage, HR status), details of intervention (including drug, dose, cycle, and duration), and outcomes (PCR and side effects).

Definition of outcomes

PCR was defined as the absence of residual invasive disease in both breast and axilla by pathological examination, according to the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual* eighth edition. However, some articles published before the consensus on the definition of PCR provided inaccurate data. These data were also retained and noted in the characteristics of the inclusive trials (Supplemental File 2). Anaemia, neutropenia, thrombocytopenia, vomiting/nausea, diarrhoea, stomatitis, mucositis, skin and subcutaneous tissue disorders, sensory neuropathy, hepatic toxicity, and cardiac disorder were considered the most critical side effects of chemotherapy and targeted therapy.

Study design

The study was carried out in three steps. Firstly, all treatment arms were divided into several experimental arms according to the prescribed drugs. The details of all arms are summarised in Supplemental File 3. Since most of the patients withdrew from the trials due to intolerable toxicities, dropout rates were used as surrogate quantitative indicators for adverse events.

Secondly, arms receiving the same therapy strategy were gathered into one group, such as the dual-target therapy group or single-target therapy group, the combination chemotherapy group, or monochemotherapy group, by adopting the prespecified criteria to include the treatment arms as the groups shown in Supplemental File 3 (Groups 1–8, Supplemental File 3). Four groups with combined chemotherapy and targeted therapy and endocrine therapy were added to the NMA in the HER2-positve and HR-positive subgroups (Groups 9–12, Supplemental File 3).

Thirdly, direct comparisons were performed to evaluate the efficacy of the PCR between single-target therapy and dual-target therapy, combination chemotherapy and single-agent chemotherapy, and anthracycline-containing and non-anthracycline therapy.

Statistical analysis

In order to integrate direct and indirect comparisons of various neoadjuvant therapies for HER2-positive breast cancer, we conducted Bayesian NMA using Markov chain Monte Carlo methods in WinBUGS (version 1.4.3).[20] The PCR data and adverse events were extracted from all studies included. These data were pooled in a separate NMA, and analysed in two steps: the first was to estimate the efficacy and safety outcome in experimental arms, and the second was to obtain the efficacy results in different strategy groups. Since both the PCR and dropout events were categorical variables, the results of the NMA were presented as odds ratios (OR) or 95% confidence intervals (CI), and the statistical significance was defined at a two-sided threshold of $p < 0.05$. Three Markov chains were run for 50,000 iterations simultaneously with different initial values. The ranking of all regimens was based on the surface under the cumulative ranking curve (SUCRA).[21] The SUCRA values ranged from 0% to 100%. A higher SUCRA value was associated with a higher PCR rate and a lower dropout rate. Subsequently, we combined efficacy and safety analyses by setting the maximum SUCRA value at 50 for efficacy (PCR) and 50 for safety (dropout rate) for each arm. A comparison of PCR rates between HR-positive and HR-negative subgroups was made using the *t*-test. A random-effects model was used to calculate each outcome due to the heterogeneity in different clinical trials. The risk of bias for each eligible study was assessed using the Cochrane Collaboration's Risk of Bias tool in Review Manager (version 5.3). We conducted pair-wise meta-analyses to generate all direct evidence. Heterogeneity was calculated using the Mantel–Haenszel Chi-squared-based test and the I^2 test. A fixed-effects model was used to calculate the outcomes of direct comparisons.

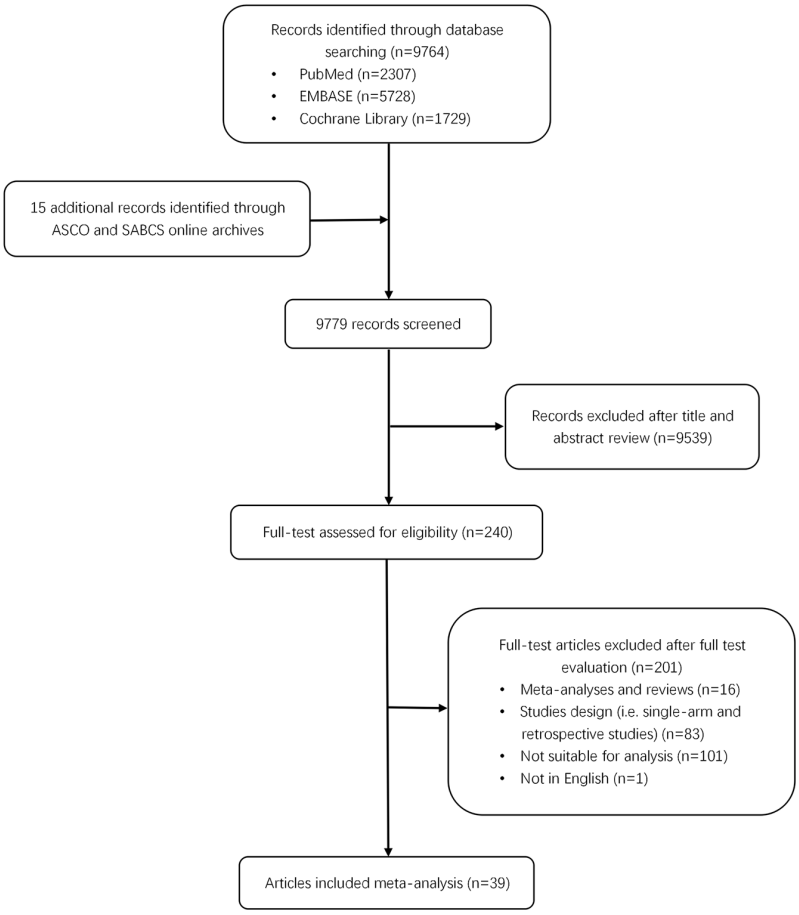

Figure 1. Flowchart outlining the process of selecting studies to be included in the meta-analysis.

Ethics approval and consent

Since the data used in this study came from previously published material, ethics approval and informed consent were not required.

Results

Study selection

A total of 9764 potentially relevant manuscripts and 15 additional abstracts were identified by the initial search. Among them, 9539 manuscripts were excluded after reviewing the titles and abstracts. A full-text review was performed for the remaining 240 articles, 201 of which were discarded for nonconformity with the prespecified inclusion and exclusion criteria. Finally, 39 articles from 36 trials were considered eligible for the NMA. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart outlining the study selection procedure is shown in Figure 1. The corresponding PRISMA checklist is provided in Supplemental File 4.

Characteristics of studies

Finally, our study included 36 clinical trials published between 2007 and 2020, involving 89 treatment arms, focusing on neoadjuvant therapy for HER2-positive breast cancer, and involving a total of 10,379 patients (Supplemental File 2).[6,8,9,11,22–56] Some of the studies compared chemotherapy with targeted therapy, and others compared dual-target therapy with single-target therapy. Five trials evaluated the efficacy of T-DM1 in neoadjuvant therapy, and another five focused on trastuzumab biosimilars.

All included trials reported data regarding overall PCR rates and side effects. Among them, 19 reported on PCR rates in HR-positive and HR-negative subgroups.

Bias assessment

The overall risk of bias was low in all included trials (the chart of bias assessment is shown in Supplemental File 5). As most of the trials (29/36) adopted open-label designs, performance bias that did not affect the outcomes might exist. Seven out of 36 trials did not analyse the outcomes in the intent-to-treat population, which might have led to attrition bias to a small extent. Nineteen out of 36 trials described the method of randomisation, and only one had a high bias risk. Another trial showed a high risk of bias for allocation concealment. None of these trials showed a high risk of detection or reporting bias. However, there were other biases in seven trials, mainly caused by high dropout rates. There was no obvious publication bias (Supplemental File 6).

PCR and side effects network

The NMA of the PCRs and dropout rates in the experimental arms and strategy groups are described in Figure 2.

PCRs of experimental arms. All of these experimental arms were ranked by the NMA of the PCRs (Figure 3, Table 1, Supplemental File 7). The regimens containing combination chemotherapy associated with trastuzumab and pertuzumab probably

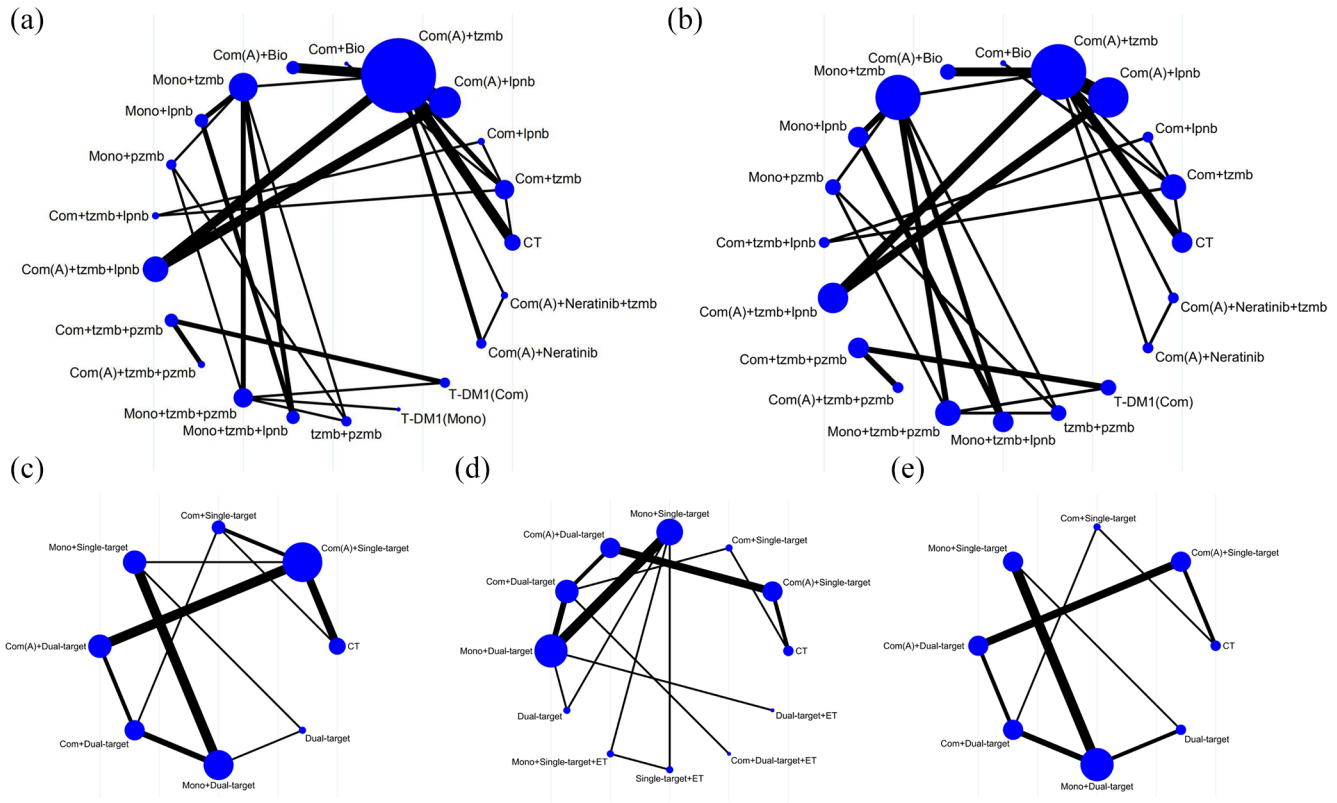

Figure 2. Network diagrams of PCRs and dropout rates in eligible experimental arms and eligible strategy groups. (a) PCR. (b) Dropout rate. (c) PCRs of overall populations in eight groups. (d) PCRs of HER2-positive and HR-positive population in 12 groups. (e) PCRs of HER2-positive and HR-negative populations in eight groups.
Direct comparisons are shown in black lines. The width of the lines reflects the number of trials that directly compare each pair of experimental arms. Meanwhile, the size of every point represents the number of patients included in each experimental arm.
HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PCR, pathologic complete response.
Experimental arms: CT, chemotherapy alone; Com(A)+tzmb, combination chemotherapy (with anthracycline) + trastuzumab; Com+tzmb, combination chemotherapy (without anthracycline) + trastuzumab; Com(A)+lpnb, combination chemotherapy (with anthracycline) + lapatinib; Com+lpnb, combination chemotherapy (without anthracycline) + lapatinib; Com(A)+Neratinib, combination chemotherapy (with anthracycline) + neratinib; Mono+tzmb, mono chemotherapy + trastuzumab; Mono+lpnb, mono chemotherapy + lapatinib; Mono+pzmb, mono chemotherapy + pertuzumab; Com(A)+tzmb+lpnb, combination chemotherapy (with anthracycline) + trastuzumab + lapatinib; Com+tzmb+lpnb, combination chemotherapy (without anthracycline) + trastuzumab + lapatinib; Com(A)+Neratinib+tzmb, combination chemotherapy (with anthracycline) + trastuzumab + neratinib; Com(A)+tzmb+pzmb, combination chemotherapy (with anthracycline) + trastuzumab + pertuzumab; Com+tzmb+pzmb, combination chemotherapy (without anthracycline) + trastuzumab + pertuzumab; Mono+tzmb+lpnb, mono chemotherapy + trastuzumab +lapatinib; Mono+tzmb+pzmb, mono chemotherapy + trastuzumab + pertuzumab; tzmb+pzmb, trastuzumab + pertuzumab; T-DM1(mono), T-DM1 alone; T-DM1(com), T-DM1 + other target therapy and/or chemotherapy; Com(A)+bio, combination chemotherapy (with anthracycline) + trasutuzumab biosimilar; Com+bio, combination chemotherapy (without anthracycline) + trasutuzumab biosimilar.
Strategies groups: Com(A) + Dual-target, combination chemotherapy (with anthracycline) + dual-target therapy; Com+Dual-target, combination chemotherapy (without anthracycline) + dual-target therapy; Mono + Dual-target, mono chemotherapy + dual-target therapy; Com(A) + Single-target, combination chemotherapy (with anthracycline) + Single-target therapy; Com + Single-target, combination chemotherapy (without anthracycline) + single-agent target therapy; Mono + Single-target, single-drug chemotherapy + single-target therapy; Dual-target, target therapy alone (including dual-target therapy alone); CT, chemotherapy alone; Com + Dual-target + ET, combination chemotherapy + dual-target therapy + endocrine therapy; Mono + Single-target + ET, single-drug chemotherapy + single-target therapy + endocrine therapy; Dual-target + ET, dual-target therapy + endocrine therapy; Single-target + ET, single-target therapy + endocrine therapy.

show the best PCRs, with 89.8% and 84.9% posterior probabilities of being the best, followed by T-DM1(com) with a 81.9% posterior probability. Based on the rank order, trastuzumab+pertuzumab ranked higher than trastuzumab+TKI (lapatinib or neratinib); as an irreversible TKI, neratinib ranked higher than lapatinib; T-DM1 might be better than trastuzumab plus paclitaxel; and trastuzumab biosimilars were equivalent to trastuzumab.

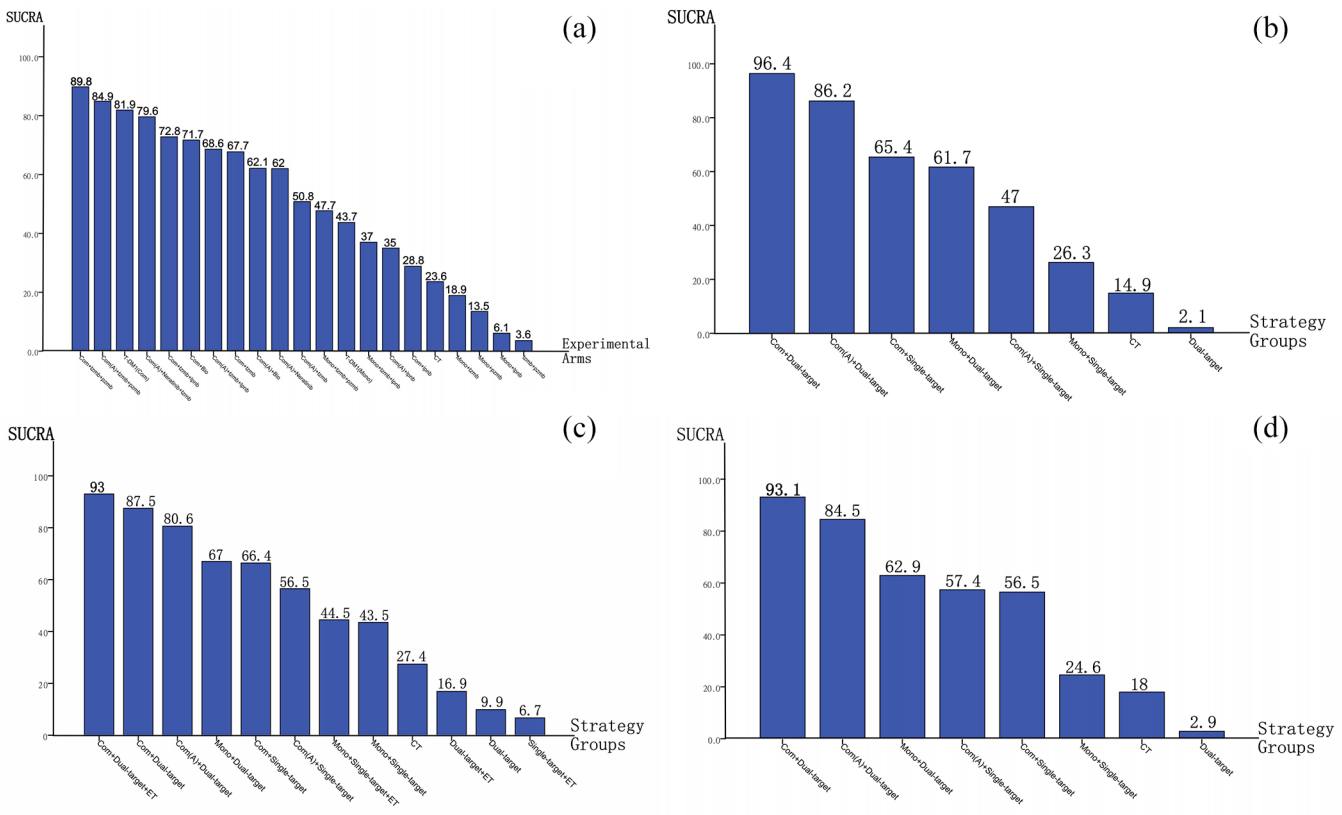

Figure 3. PCR rates ranking for experimental arms and strategy groups. (a) PCR rate ranking for experimental arms. (b) PCR rate ranking for strategy groups. (c) PCR rate ranking for HR-positive and HER2-positive subgroups. (d) PCR rate ranking for HR-negative and HER2-positive subgroups.
See Figure 2 footnotes.

PCRs of different strategy groups in the general population, HR-positive patients, and HR-negative patients. Finally, 24 out of 36 studies were included in this analysis. The results of SUCRA and cross-comparison in the eight strategy groups are shown in Figure 3 (see also Supplemental File 8) and Table 1, respectively. Combination chemotherapies combined with dual-target therapy (one using anthracycline and the other using carboplatin) were ranked as the top two by the SUCRA analysis (Figure 3). Dual-target therapy alone without chemotherapy and chemotherapy alone without targeted therapy were both associated with the worst outcomes. Dual-target therapy was significantly better than single-target therapy [Com(A)+Dual-target *versus* Com(A)+Single-target, $p < 0.05$]. Combination chemotherapy was significantly better than single-agent chemotherapy (Com+Dual-target *versus* Mono+Dual-target, $p < 0.05$). Another comparison between the regimens with and without anthracycline indicated that adding anthracycline to chemotherapy might not improve the outcome [Com+Single-target *versus* Com(A)+Single-target OR: 1.293 (95% CI: 0.859–1.864), Com+Dual-target *versus* Com(A)+Dual-target OR: 1.169 (95% CI: 0.813–1.621)].

The PCR rate in the HR-positive patients was significantly lower than that in the HR-negative patients by paired *t*-test ($t = -10.256$, $p < 0.0001$). For the HR-positive subgroup, when compared with the traditional neoadjuvant treatments combining chemotherapy and targeted therapy without endocrine therapy, those regimens containing endocrine therapy were ranked higher by the SUCRA analysis but did not show a significant benefit by cross-comparison Table 2).

PCRs of direct comparisons. Eleven studies directly compared single-target therapy with dual-target therapy, four studies directly compared combination chemotherapy with single-agent chemotherapy, and four studies directly

Table 1. Cross-comparison odds ratios (ORs) and their respective 95% confidence intervals (CIs) for pathologic complete response (PCR) among different experimental arms and strategy groups.*.

CT										CT								Cross-comparison odds ratios (ORs) and their respective 95% CIs for PCR among different strategy groups.
3.115 (1.906, 4.837)	Com+ tzmb									2.353 (1.608, 3.349)	Com(A)+ Single-target							
1.326 (0.3246, 3.729)	0.4251 (0.1172, 1.119)	Com+ lpnb								2.996 (1.943, 4.366)	1.293 (0.859, 1.864)	Com+ Single-target						
1.5 (0.878, 2.448)	0.4986 (0.2722, 0.8475)	1.633 (0.3735, 4.705)	Com(A)+ lpnb							1.399 (0.713, 2.49)	0.5957 (0.3433, 0.9773)	0.4759 (0.2466, 0.839)	Mono+ Single-target					
2.284 (1.497, 3.386)	0.7593 (0.4578, 1.189)	2.49 (0.5929, 6.943)	1.561 (1.125, 2.112)	Com(A) +tzmb						4.038 (2.51, 6.325)	1.717 (1.277, 2.28)	1.375 (0.8515, 2.099)	3.049 (1.779, 4.9)	Com(A) +Dual-target				
3.752 (1.496, 7.886)	1.205 (0.5677, 2.246)	3.979 (0.831, 11.93)	2.628 (0.9618, 5.719)	1.684 (0.6638, 3.535)	Com+ Bio					4.679 (2.739, 7.609)	1.994 (1.307, 2.899)	1.588 (0.9497, 2.501)	3.473 (2.237, 5.143)	1.169 (0.8131, 1.621)	Com +Dual-target			
2.763 (1.65, 4.389)	0.9188 (0.512, 1.52)	3.013 (0.6968, 8.523)	1.889 (1.213, 2.77)	1.21 (0.9111, 1.56)	0.8625 (0.3242, 1.876)	Com(A) +Bio				2.956 (1.574, 5.138)	1.26 (0.7439, 2.001)	1.006 (0.5344, 1.738)	2.14 (1.638, 2.745)	0.7398 (0.4462, 1.142)	0.6354 (0.4368, 0.8871)	Mono +Dual-target		
0.9197 (0.2106, 2.581)	0.3066 (0.06555, 0.8668)	1.008 (0.1194, 3.674)	0.6304 (0.1492, 1.719)	0.404 (0.09878, 1.068)	0.2868 (0.04887, 0.915)	0.34 (0.08042, 0.9175)	Mono +tzmb			0.6676 (0.2317, 1.473)	0.2843 (0.1066, 0.5964)	0.2268 (0.08037, 0.5007)	0.4805 (0.2089, 0.9149)	0.1668 (0.06321, 0.3485)	0.1436 (0.05761, 0.2871)	0.2267 (0.09787, 0.4387)	Dual-target	
0.5231 (0.1056, 1.577)	0.1746 (0.03333, 0.5281)	0.5724 (0.06192, 2.185)	0.3587 (0.07377, 1.054)	0.2299 (0.04911, 0.6534)	0.1634 (0.02507, 0.5543)	0.1935 (0.04034, 0.5611)	0.5699 (0.3303, 0.9178)	Mono+ lpnb										
0.7616 (0.1313, 2.487)	0.2539 (0.04128, 0.8227)	0.8337 (0.07876, 3.358)	0.5224 (0.09174, 1.63)	0.3347 (0.06168, 1.019)	0.2383 (0.03155, 0.8624)	0.2817 (0.05041, 0.8749)	0.8287 (0.3508, 1.638)	1.553 (0.5491, 3.453)	Mono+ pzmb									
4.267 (1.268, 10.87)	1.369 (0.4677, 3.208)	3.878 (1.224, 9.627)	2.974 (0.8429, 7.711)	1.908 (0.5646, 4.8)	1.288 (0.3286, 3.578)	1.606 (0.4595, 4.123)	6.928 (1.018, 25.3)	12.98 (1.718, 49.59)	9.708 (1.106, 39.02)	Com+ tzmb +lpnb								
3.181 (1.761, 5.425)	1.058 (0.5476, 1.864)	3.462 (0.7708, 9.975)	2.15 (1.422, 3.131)	1.393 (0.9326, 2.016)	0.9929 (0.3549, 2.254)	1.172 (0.7168, 1.841)	5.034 (1.201, 14.38)	9.425 (1.967, 28.89)	7.058 (1.266, 23.45)	0.9829 (0.2665, 2.581)	Com(A) +tzmb +lpnb							
23.3 (0.9918, 122)	7.74 (0.3212, 40.88)	25.68 (0.6909, 146)	15.84 (0.6961, 81.78)	10.2 (0.4592, 52.67)	7.326 (0.2572, 40.17)	8.558 (0.3769, 44.44)	27.39 (1.893, 129.1)	51.88 (3.195, 247)	37.86 (2.234, 188.9)	7.19 (0.2242, 40.83)	7.623 (0.325, 39.34)	Com +tzmb +pzmb						

(Continued)

Table 1. (Continued)

21.04 (0.8462, 111.1)	6.983 (0.2729, 37.05)	23.18 (0.5929, 132)	14.3 (0.5887, 73.15)	9.201 (0.3894, 47.51)	6.609 (0.2231, 35.83)	7.72 (0.3206, 40.51)	24.71 (1.571, 118.8)	46.75 (2.675, 226.9)	34.16 (1.89, 171.6)	6.477 (0.1909, 36.59)	6.88 (0.2778, 35.47)	0.9087 (0.5624, 1.375)	Com(A) +tzmb +pzmb							
2.226 (0.4574, 6.756)	0.7411 (0.1452, 2.272)	2.424 (0.2606, 9.304)	1.522 (0.3216, 4.482)	0.9755 (0.215, 2.786)	0.6944 (0.1071, 2.365)	0.8213 (0.1744, 2.381)	2.424 (1.433, 3.873)	4.546 (2.105, 8.704)	3.292 (1.461, 6.637)	0.6868 (0.08701, 2.504)	0.7279 (0.1503, 2.166)	0.2901 (0.01906, 1.174)	0.3348 (0.02078, 1.397)	Mono +tzmb +pzmb						
1.677 (0.3412, 4.966)	0.5596 (0.108, 1.668)	1.838 (0.1989, 6.989)	1.15 (0.2427, 3.333)	0.7372 (0.1612, 2.072)	0.524 (0.08096, 1.747)	0.6207 (0.1309, 1.783)	1.827 (1.12, 2.816)	3.334 (1.942, 5.367)	2.565 (0.9485, 5.755)	0.5183 (0.06647, 1.848)	0.5498 (0.1126, 1.613)	0.2341 (0.01306, 0.9937)	0.2703 (0.01429, 1.192)	0.8038 (0.3844, 1.486)	Mono +tzmb +lpnb					
0.4477 (0.07573, 1.491)	0.1493 (0.02396, 0.4969)	0.4902 (0.04419, 2.03)	0.3059 (0.05219, 0.9726)	0.1961 (0.03468, 0.6152)	0.1398 (0.0181, 0.5091)	0.1652 (0.02816, 0.5294)	0.4878 (0.1966, 0.9972)	0.915 (0.3099, 2.097)	0.6497 (0.2335, 1.45)	0.1387 (0.01465, 0.5438)	0.1461 (0.02451, 0.4702)	0.06012 (0.003083, 0.2594)	0.0694 (0.003397, 0.31)	0.2071 (0.08534, 0.4163)	0.2818 (0.09779, 0.6331)	tzmb +pzmb				
2.137 (0.3461, 7.15)	0.7111 (0.1104, 2.412)	2.321 (0.2085, 9.68)	1.459 (0.2414, 4.753)	0.9344 (0.1613, 2.975)	0.6668 (0.0844, 2.473)	0.7873 (0.132, 2.558)	2.324 (0.8978, 5.005)	4.359 (1.413, 10.46)	3.16 (0.9934, 7.792)	0.6593 (0.06808, 2.59)	0.6977 (0.1127, 2.29)	0.2785 (0.01552, 1.216)	0.3214 (0.0169, 1.472)	0.9589 (0.4424, 1.827)	1.343 (0.4486, 3.164)	5.45 (1.657, 13.63)	T-DM1 (Mono)			
17.98 (0.8325, 93.07)	5.976 (0.2658, 31.08)	19.82 (0.5755, 109.5)	12.24 (0.5873, 61.47)	7.878 (0.3874, 39.44)	5.658 (0.2158, 30.66)	6.613 (0.3182, 33.37)	21.1 (1.618, 96.72)	39.93 (2.736, 185.9)	29.09 (1.891, 140.9)	5.52 (0.1862, 30.64)	5.894 (0.2727, 29.47)	0.8137 (0.505, 1.273)	0.9428 (0.48, 1.74)	8.783 (0.727, 39.13)	12.29 (0.8525, 57.09)	51 (3.251, 242.3)	10.4 (0.6979, 48.14)	T-DM1 (Com)		
3.007 (1.188, 6.426)	1.002 (0.3727, 2.215)	3.296 (0.5891, 10.6)	2.058 (0.8428, 4.249)	1.318 (0.5872, 2.585)	0.9399 (0.2563, 2.445)	1.109 (0.4722, 2.277)	4.768 (0.8978, 15.48)	8.914 (1.508, 29.98)	6.684 (0.9892, 23.98)	0.9333 (0.2017, 2.774)	0.9836 (0.3896, 2.074)	0.6186 (0.0216, 3.009)	0.7157 (0.02424, 3.617)	2.095 (0.3536, 7.169)	2.749 (0.48, 9.316)	11.57 (1.655, 42.91)	2.489 (0.3362, 9.221)	0.7616 (0.02876, 3.681)	Com(A) +Neratinib	
5.068 (1.624, 12.44)	1.69 (0.5113, 4.213)	5.596 (0.85, 19.27)	3.469 (1.155, 8.251)	2.221 (0.7904, 5.04)	1.59 (0.3623, 4.632)	1.871 (0.636, 4.403)	8.024 (1.351, 27.75)	15.03 (2.266, 53.85)	11.21 (1.473, 42.77)	1.574 (0.2909, 5.043)	1.657 (0.5325, 3.985)	1.017 (0.0329, 5.143)	1.18 (0.03649, 6.036)	3.516 (0.5295, 12.64)	4.632 (0.7125, 16.7)	19.38 (2.496, 74.46)	4.182 (0.5136, 16.32)	1.249 (0.04357, 6.163)	1.81 (0.6453, 4.102)	Com(A)+ Neratinib +tzmb

Cross-comparison odds ratios (ORs) and their respective 95% CIs for PCR among different experimental arms.

*Pooled estimates for each outcome of all strategy groups. The OR with 95%CI for the comparison of the treatment in the row heading being compared to the column heading was presented in the corresponding square. ORs with Bayesian *p*-value less than 0.05 are in yellow.

Experimental arms: Com(A)+tzmb, combination chemotherapy (with anthracycline) + trastuzumab; Com+tzmb, combination chemotherapy (without anthracycline) + trastuzumab; Com(A)+lpnb, combination chemotherapy (with anthracycline) + lapatinib; Com+lpnb, combination chemotherapy (without anthracycline) + lapatinib; Com(A)+Neratinib, combination chemotherapy (with anthracycline) + neratinib; Mono+tzmb, mono chemotherapy + trastuzumab; Mono+lpnb, mono chemotherapy + lapatinib; Mono+pzmb, mono chemotherapy + pertuzumab; Com(A)+tzmb+lpnb, combination chemotherapy (with anthracycline) + trastuzumab + lapatinib; Com+tzmb+lpnb, combination chemotherapy (without anthracycline) + trastuzumab + lapatinib; Com(A)+Neratinib+tzmb, combination chemotherapy (with anthracycline) + trastuzumab + neratinib; Com(A)+tzmb+pzmb, combination chemotherapy (with anthracycline) + trastuzumab + pertuzumab; Com+tzmb+pzmb, combination chemotherapy (without anthracycline) + trastuzumab + pertuzumab; Mono+tzmb+lpnb, mono chemotherapy + trastuzumab +lapatinib; Mono+tzmb+pzmb, mono chemotherapy + trastuzumab + pertuzumab; tzmb+pzmb, trastuzumab + pertuzumab; T-DM1(mono), T-DM1 alone; T-DM1(com), T-DM1 + other target therapy and/or chemotherapy; Com(A)+bio, combination chemotherapy (with anthracycline) + trasutuzumab biosimilar; Com+bio, combination chemotherapy (without anthracycline) + trasutuzumab biosimilar.

Strategies groups: Com(A)+Dual-target, combination chemotherapy (with anthracycline) + dual-target therapy; Com+Dual-target, combination chemotherapy (without anthracycline) + dual-target therapy; Mono+Dual-target, mono chemotherapy + dual-target therapy; Com(A)+Single-target, combination chemotherapy (with anthracycline) + Single-target therapy; Com+Single-target, combination chemotherapy (without anthracycline) + single-agent target therapy; Mono+Single-target, single-drug chemotherapy + single-target therapy; Dual-target, target therapy alone (including dual-target therapy alone); CT, chemotherapy alone.

Table 2. Cross-comparison odds ratios (ORs) and their respective 95% confidence intervals (CIs) for pathologic complete response (PCR) in HR-positive and HR-negative subgroups.*

	PCR for HR-negative breast cancer											
PCR for HR-positive breast cancer	CT	3.913 (1.237, 9.805)	3.402 (1.454, 6.826)	1.568 (0.3046, 4.909)	6.6 (1.943, 16.68)	7.994 (2.27, 20.6)	4.763 (1.016, 14.35)	0.681 (0.1092, 2.285)	NA	NA	NA	NA
	2.492 (0.9824, 5.276)	Com(A)+ Single-target	1.079 (0.298, 2.75)	0.4265 (0.107, 1.185)	1.733 (0.9321, 2.874)	2.19 (0.8259, 4.709)	1.297 (0.365, 3.41)	0.1854 (0.03822, 0.5572)	NA	NA	NA	NA
	2.903 (1.282, 5.594)	1.34 (0.4591, 3.019)	Com+ Single-target	0.4899 (0.1, 1.499)	2.118 (0.593, 5.447)	2.502 (0.7507, 6.221)	1.49 (0.335, 4.365)	0.2125 (0.03597, 0.6963)	NA	NA	NA	NA
	1.949 (0.5194, 4.977)	0.8164 (0.2792, 1.888)	0.7175 (0.2041, 1.859)	Mono+ Single-target	5.537 (1.484, 14.13)	6.176 (2.352, 12.53)	3.207 (2.019, 4.834)	0.4495 (0.1884, 0.8834)	NA	NA	NA	NA
	3.952 (1.444, 8.481)	1.614 (0.985, 2.522)	1.477 (0.5263, 3.376)	2.374 (0.935, 5.07)	Com(A)+ Dual-target	1.276 (0.5824, 2.438)	0.7571 (0.2459, 1.857)	0.1083 (0.02488, 0.3071)	NA	NA	NA	NA
	4.547 (1.616, 10.02)	1.905 (0.9153, 3.626)	1.67 1 (0.6257, 3.701)	2.613 (1.291, 4.891)	1.187 (0.6742, 2.003)	Com+ Dual-target	0.5908 (0.2817, 1.137)	0.08421 (0.02696, 0.2011)	NA	NA	NA	NA
	3.14 (0.9139, 7.604)	1.318 (0.494, 2.881)	1.154 (0.3575, 2.793)	1.679 (1.1, 2.413)	0.8208 (0.3513, 1.62)	0.692 (0.3772, 1.119)	Mono+ Dual-target	0.1425 (0.06328, 0.2716)	NA	NA	NA	NA
	0.6024 (0.06141, 2.201)	0.2525 (0.03058, 0.8564)	0.2224 (0.02409, 0.8208)	0.3147 (0.05313, 0.9012)	0.1578 (0.02002, 0.5122)	0.1328 (0.0191, 0.4078)	0.1922 (0.03157, 0.5579)	Dual-target	NA	NA	NA	NA
	2.068 (0.4143, 6.118)	0.8671 (0.2174, 2.401)	0.7645 (0.1631, 2.301)	1.061 (0.477, 2.088)	0.54 (0.1506, 1.401)	0.4542 (0.1468, 1.056)	0.6586 (0.2641, 1.4)	5.751 (0.9008, 22.15)	Mono+ Single-target+ET	NA	NA	NA
	0.496 (0.09493, 1.49)	0.2091 (0.04846, 0.5862)	0.1831 (0.03692, 0.563)	0.2558 (0.1029, 0.5277)	0.1298 (0.03346, 0.3439)	0.1094 (0.03244, 0.2642)	0.1587 (0.05751, 0.3509)	1.386 (0.2014, 5.463)	0.2586 (0.105, 0.5298)	Single-target+ET	NA	NA
	5.921 (1.534, 15.61)	2.482 (0.8387, 5.905)	2.178 (0.609, 5.811)	3.414 (1.183, 8.034)	1.546 (0.585, 3.44)	1.299 (0.6089, 2.437)	2.034 (0.7856, 4.555)	17.99 (2.544, 69.73)	3.734 (0.929, 10.35)	15.96 (3.759, 46.55)	Com+ Dual-target+ET	NA
	0.8034 (0.1632, 2.325)	0.3375 (0.08408, 0.9076)	0.2966 (0.06374, 0.8707)	0.4307 (0.1541, 0.9568)	0.2106 (0.05739, 0.5445)	0.1773 (0.05636, 0.4111)	0.2568 (0.1023, 0.5336)	2.277 (0.3231, 8.828)	0.4686 (0.1212, 1.245)	2.005 (0.4831, 5.624)	0.1553 (0.03756, 0.417)	Dual-target +ET

*Pooled estimates for each outcome of all strategy groups. The OR with 95%CI for the comparison of the treatment in the row heading being compared to the column heading was presented in the corresponding square. ORs with Bayesian *p*-value less than 0.05 are in yellow.
Com+Dual-target+ET, combination chemotherapy + dual-target therapy + endocrine therapy; Mono+Single-target+ET, single-drug chemotherapy + single-target therapy + endocrine therapy; Dual-target+ET, dual-target therapy + endocrine therapy; Single-target+ET, single-target therapy + endocrine therapy; others were presented in Table 1 footnotes.

compared anthracycline-containing regimens with non-anthracycline regimens. After pooling analysis, dual-target therapy was significantly better than single-target therapy; combination chemotherapy was significantly better than single-agent chemotherapy; no significant difference was found between anthracycline-containing and non-anthracycline regimens. These results are shown in Figure 4.

Safety. According to the trial design, patient characteristics, and purposes, the side effects in different studies were also reported. Therefore, we could not make an effective closed-loop assessment of every safety issue by NMA; dropout events were used as surrogate outcome indicators, which might well reflect the tolerance of different regimens. The analysis was carried out in 20 arms (Figure 2, Supplemental File 9). As

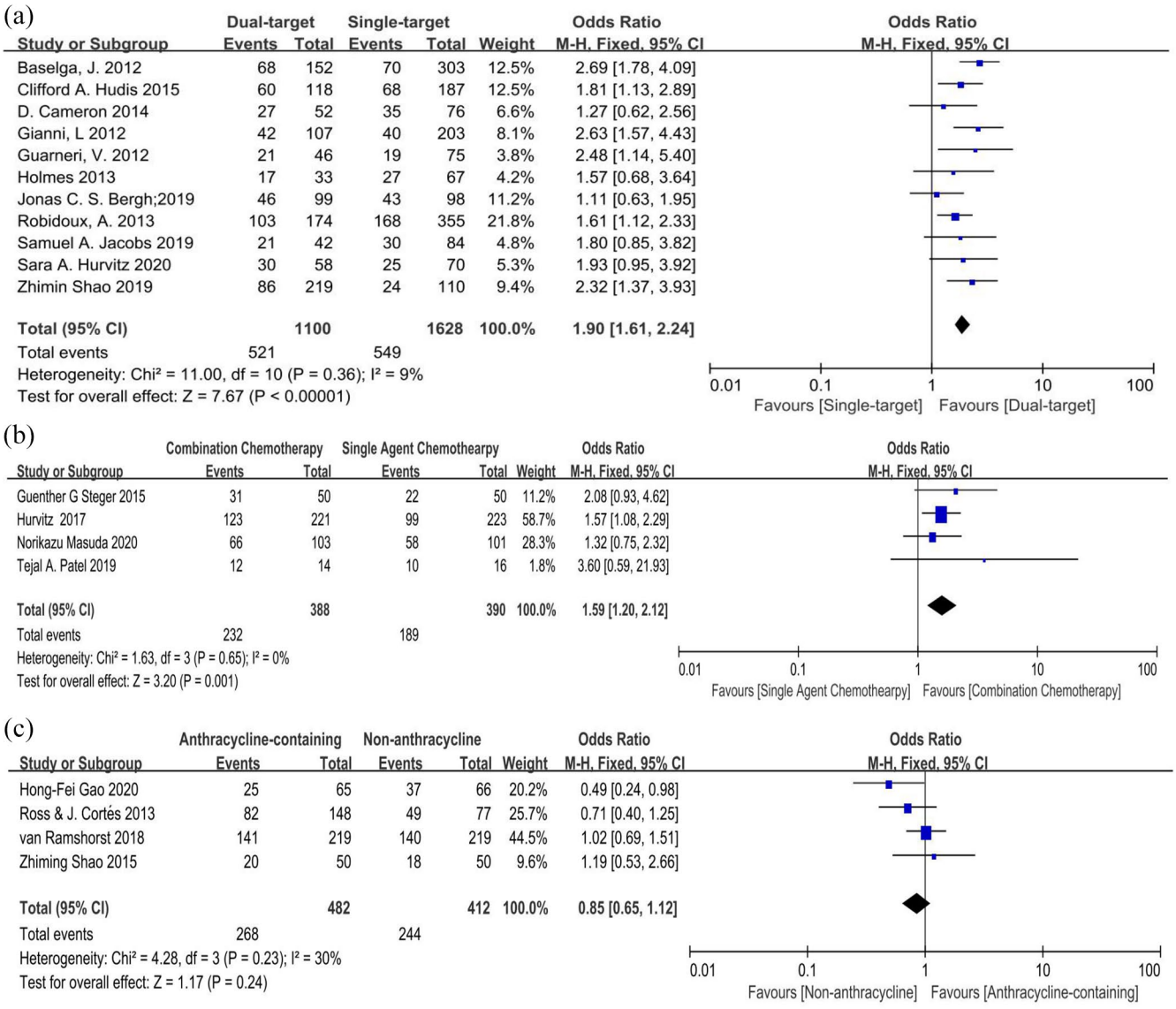

Figure 4. Direct comparison of PCRs. (a) Dual-target therapy *versus* single-target therapy. (b) Combination chemotherapy *versus* single-drug chemotherapy. (c) Anthracycline-containing *versus* non-anthracycline-containing.
See Figure 2 footnotes.

shown in the SUCRA analysis, combination chemotherapy was associated with a higher dropout rate than monotherapy, especially when using anthracycline. In contrast, dual-target therapy did not lead to a higher withdrawal rate than single-target therapy. It should be pointed out that the clinical value of some drugs, such as neratinib, was counteracted by significant dropout rates. To weigh the pros and cons more objectively, we combined PCR outcomes with adverse events to comprehensively evaluate the clinical value of each experimental arm. Trastuzumab plus pertuzumab, whether combined with combination chemotherapy or monochemotherapy, excellently balanced efficacy and side effects. T-DM1-containing regimens also showed high clinical value in reducing toxicity while improving the curative effects (Figure 5).

The main toxicities are shown in Supplemental File 10. Compared with monochemotherapy, combination chemotherapy was associated with a higher incidence of haematotoxicity. Nevertheless, febrile neutropenia, which negatively affects the quality of life, did not frequently occur. Anthracycline, usually considered a hyperemetic

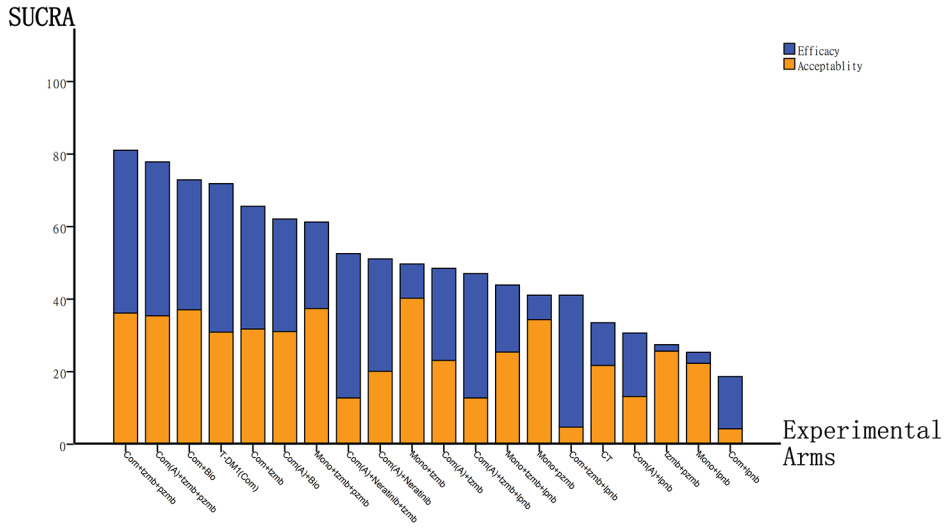

Figure 5. Experimental arms ordered by their overall probability as the best treatment in terms of both efficacy and dropout rate.
The cumulative percentages after normalisation (0–100) are shown in the key. Every regimen was scored up to a maximum of 50 points for efficacy and 50 points for acceptability (overall maximum score 100) using data from the SUCRAs.
See Figure 2 footnotes.

drug that is associated with a high incidence of vomiting or nausea, slightly increased the incidence of cardiac disorders. Both lapatinib and neratinib lead to a high incidence of diarrhoea, especially neratinib, which caused diarrhoea in more than 30% of patients. Additionally, TKI aggravated the liver burden apart from chemotherapy-induced liver dysfunction, which also deserves attention. It must be noted that more potent treatments always result in more toxicities. However, most of these side effects were properly controlled without affecting tolerance.

Discussion

With the increasing number of anti-HER2 drugs now available, it is vital that a comprehensive assessment is performed.

Similar to other studies, our study also demonstrated that dual-target therapy-based regimens are superior to single-target therapy-based regimens.[16,57–60] However, the question still remains that which is the best choice among all the dual-target therapies. According to our results, we suggest that the dual anti-HER2 blockade that combines trastuzumab and pertuzumab is better than the combination of trastuzumab and TKIs. This result is consistent with previously published findings[17] and means that targeting the extracellular domains of the HER-2 receptor can better block the activation of the pathway. Meanwhile, antibody-dependent cellular cytotoxicity activity induced by FcγRIII binding could also enhance efficacy. Nevertheless, we should pay attention to a neratinib-containing regimen, which showed higher efficacy than a lapatinib-containing regimen by SUCRA analysis. As an irreversible inhibitor of EGFR, HER2, and HER4 RTKs, neratinib has been shown to be more effective than the reversible tyrosine kinase inhibitor lapatinib in *in vivo* and *in vitro* studies.[34,61] NASBP FB-7 showed numerical improvement in the PCR rate in the treatment arm using trastuzumab plus neratinib compared with the control arm using trastuzumab or neratinib alone.[48] Its clinical value was also proven in other studies where neratinib improved both PCR and disease-free survival (DFS).[34,62] Nevertheless, the high incidence of diarrhoea may restrict its clinical use. Tucatinib and pyrotinib, the other irreversible inhibitors, have shown good performance and better safety in metastatic breast cancer.[63–65] Considering that the planned evaluation in the post-neoadjuvant chemotherapy setting of tucatinib is in progress (HER2CLIMB-04), it may become the post-neoadjuvant therapy of choice in the future. As demonstrated in our study, T-DM1-containing regimens also show great efficacy, especially when combined with

other targeted drugs or chemotherapies.[51,54] Compared with the traditional targeted therapy, the use of antibody drug conjugate (ADC) to increase the drug concentration in tumour cells may further enhance efficacy. However, we also noticed that 'KAITLIN', a phase III study directly comparing T-DM1 plus pertuzumab with taxane plus trastuzumab and pertuzumab after anthracycline as adjuvant therapy, did not meet its co-primary end point that T-DM1 is better than the control.[66] Therefore, more evidence is still needed to support the priority use of T-DM1 in the neoadjuvant setting. Currently, for patients who cannot accept a combination chemo/dual anti-HER2 targeting regimen, T-DM1 is recommended because of its lower toxicity.

Whether the intensity of chemotherapy can be reduced in dual-target regimens is currently a clinical concern. When more powerful targeted drugs are available, chemotherapy will no longer be considered as important as before. The KRISTIN trial compared TCbHP with T-DM1+P, a combination chemotherapy *versus* a DM1 monochemotherapy, with the same dual-target treatment. They found that TCbHP had a higher PCR rate but also caused more adverse events than T-DM1+P.[38–40] In our study, we designed two combination chemotherapy + dual-target therapy arms [Com+Dual-target and Com(A)+Dual-target], and both showed a better outcome than the monochemotherapy+Dual-target therapy arm. Although the side effects of combination chemotherapy were greater than those of monochemotherapy, they were still properly controlled. Therefore, we suggest that chemotherapy is still important in the era in which dual-target therapy is gaining popularity. Combination chemotherapy combined with dual-target therapy might be the optimal treatment strategy in the neoadjuvant treatment of HER2-positive breast cancer.

Another question arose that is related to the use of anthracycline. It is known that the combination of pertuzumab with trastuzumab can enhance the inhibition of HER2 signalling, which may increase the risk of cardiac heart failure. Therefore, adding anthracycline to pertuzumab and trastuzumab will increase concerns about the risk of heart failure. In our study, we found that anthracycline treatment did not affect outcomes. This result agreed with the TRYPHAENA trial and the TRAIN2 trial, which directly compared an anthracycline-containing regimen with a non-anthracycline-containing regimen.[28,45,67] Anthracycline did not contribute to better outcomes but increased side effects when compared with the non-anthracycline regimen. Among nearly all trials combining carboplatin with taxane in the non-anthracycline combination chemotherapy regimens, carboplatin was a good alternative for anthracycline.

Single-target regimens are still the only choice in some regions due to the lack of access to dual-target drugs. Strengthening the intensity of chemotherapy is particularly important in this case. Combination chemotherapy can result in significantly better results than monotherapy when combined with single-target therapy. This means that chemotherapy may make up for the deficiency of targeted therapy to some degree. Surprisingly, unlike previous studies, we did not find better outcomes for using anthracycline in single-target therapy regimens.[68,69] This might be explained by the following reason. In our study, we divided combination chemotherapy and monochemotherapy into different arms. Since anthracycline is generally used as a medicine in combination chemotherapy, we only compared the efficacy of anthracycline in combination chemotherapy arms. However, in previous studies, anthracycline groups were compared with non-anthracycline groups, including combination chemotherapy and monochemotherapy. Obviously, mixing combination chemotherapy and monochemotherapy in one group could impair the efficacy of the non-anthracycline group and lead to an erroneous conclusion. Hence, adding anthracycline to chemotherapy might not significantly improve the outcome in a single-target therapy-based regimen, which was also demonstrated in BCIRG006.[70]

HR-positive (oestrogen and/or progestogen receptor-positive) and HER2-positive breast cancer is a subtype of HER2-positive breast cancer. The PCR rate is significantly lower in HR-positive subgroups than that in HR-negative subgroups, as indicated by our study and most of the studies previously published.[26,71] ER receptor and HER2 receptor co-expression can activate each other and amplify the cell growth-promoting effects.[72] Crosstalk between the ER pathway and the HER2 pathway enhances the resistance to anti-HER2 treatment and anti-ER treatment, which may lower the outcome in HR-positive and HER2-positive breast cancer.[73] Dual blockade of the ER and HER2 pathways by

the concomitant use of endocrine therapy and targeted therapy may overcome resistance. As expected, the group that received endocrine therapy ranked first in the NMA of the HR-positive subgroup. This arm came from NSABP B-52 trial. Endocrine therapy was added to TCbHP, resulting in an increase in the PCR rate of 5.2%.[43] Although no statistically significant benefit was observed, there were no additional toxicities. Therefore, it is reasonable to add endocrine therapy to neoadjuvant therapy for some HR-positive and HER2-positive breast cancer patients. However, this suggestion needs further investigation.

Our study included the largest number of clinical studies involving a sufficient sample size when compared with other meta-analyses previously published. Using NMA, various regimens were ranked quantitatively and intuitively. Subgroup analyses were performed with respect to HR status. Combining efficacy and safety events may help us to comprehensively evaluate each regimen. However, it should be pointed out there are some potential limitations in this NMA. To close the loop of the NMA, we excluded some single-arm studies. In addition, all the calculations were based on published results and not individual data. The final limitation is the inherent defects of NMA itself, which cannot be avoided.

Conclusion

In summary, trastuzumab plus pertuzumab-based dual-target therapy with combination chemotherapy regimens showed the highest efficacy in all optional regimens (they were ranked first and second by the SUCRA analysis). They also achieved the best balance between efficacy and toxicity. As our study showed that anthracycline could be replaced by carboplatin, we strongly recommended TCbHP as the preferred choice for neoadjuvant treatment of HER2-positive breast cancer. We also look forward to the potential value of T-DM1 in improving outcomes, which needs further study in future trials.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

References

1. Slamon DJ, Clark GM, Wong SG, *et al*. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987; 235: 177–182.
2. Slamon DJ, Leyland-Jones B, Shak S, *et al*. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; 344: 783–792.
3. Cameron D, Piccart-Gebhart MJ, Gelber RD, *et al*. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017; 389: 1195–1205.
4. von Minckwitz G, Procter M, de Azambuja E, *et al*. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med* 2017; 377: 122–131.
5. Gradishar WJ, Anderson BO, Abraham J, *et al*. Breast cancer, version 3.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2020; 18: 452–478.
6. Gianni L, Eiermann W, Semiglazov V, *et al*. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet* 2010; 375: 377–384.
7. Untch M, Rezai M, Loibl S, *et al*. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. *J Clin Oncol* 2010; 28: 2024–2031.
8. Gianni L, Pienkowski T, Im YH, *et al*. Efficacy and safety of neoadjuvant pertuzumab and

trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; 13: 25–32.

9. Robidoux A, Tang G, Rastogi P, *et al*. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013; 14: 1183–1192.
10. de Azambuja E, Holmes AP, Piccart-Gebhart M, *et al*. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol* 2014; 15: 1137–1146.
11. Shao Z, Pang D, Yang H, *et al*. Efficacy, safety, and tolerability of pertuzumab, trastuzumab, and docetaxel for patients with early or locally advanced ERBB2-positive breast cancer in Asia: the PEONY phase 3 randomized clinical trial. *JAMA Oncol* 2020; 6: e193692.
12. Gianni L, Eiermann W, Semiglazov V, *et al*. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet Oncol* 2014; 15: 640–647.
13. Gianni L, Pienkowski T, Im YH, *et al*. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol* 2016; 17: 791–800.
14. Cortazar P, Zhang L, Untch M, *et al*. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014; 384: 164–172.
15. von Minckwitz G, Huang CS, Mano MS, *et al*. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med* 2019; 380: 617–628.
16. Debiasi M, Polanczyk CA, Ziegelmann P, *et al*. Efficacy of anti-HER2 agents in combination with adjuvant or neoadjuvant chemotherapy for early and locally advanced HER2-positive breast cancer patients: a network meta-analysis. *Front Oncol* 2018; 8: 156.
17. Wu D, Chen T, Jiang H, *et al*. Comparative efficacy and tolerability of neoadjuvant immunotherapy regimens for patients with HER2-positive breast cancer: a network meta-analysis. *J Oncol* 2019; 2019: 3406972.
18. Clavarezza M, Puntoni M, Gennari A, *et al*. Dual block with lapatinib and trastuzumab versus single-agent trastuzumab combined with chemotherapy as neoadjuvant treatment of HER2-positive breast cancer: a meta-analysis of randomized trials. *Clin Cancer Res* 2016; 22: 4594–4603.
19. Ma W, Zhao F, Zhou C, *et al*. Targeted neoadjuvant therapy in the HER-2-positive breast cancer patients: a systematic review and meta-analysis. *Onco Targets Ther* 2019; 12: 379–390.
20. Lunn DJ, Thomas A, Best N, *et al*. WinBUGS - a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput* 2000; 10: 325–337.
21. Salanti G, Ades AE and Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; 64: 163–171.
22. Buzdar AU, Valero V, Ibrahim NK, *et al*. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. *Clin Cancer Res* 2007; 13: 228–233.
23. Pierga JY, Delaloge S, Espie M, *et al*. A multicenter randomized phase II study of sequential epirubicin/cyclophosphamide followed by docetaxel with or without celecoxib or trastuzumab according to HER2 status, as primary chemotherapy for localized invasive breast cancer patients. *Breast Cancer Res Treat* 2010; 122: 429–437.
24. Untch M, Loibl S, Bischoff J, *et al*. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. *Lancet Oncol* 2012; 13: 135–144.
25. Guarneri V, Frassoldati A, Bottini A, *et al*. Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHER-LOB study. *J Clin Oncol* 2012; 30: 1989–1995.
26. Baselga J, Bradbury I, Eidtmann H, *et al*. Lapatinib with trastuzumab for HER2-positive

early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet* 2012; 379: 633–640.

27. Holmes FA, Espina V, Liotta LA, *et al.* Pathologic complete response after preoperative anti-HER2 therapy correlates with alterations in PTEN, FOXO, phosphorylated Stat5, and autophagy protein signaling. *BMC Res Notes* 2013; 6: 507.
28. Schneeweiss A, Chia S, Hickish T, *et al.* Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol* 2013; 24: 2278–2284.
29. Steger GG, Greil R, Lang A, *et al.* Epirubicin and docetaxel with or without capecitabine as neoadjuvant treatment for early breast cancer: final results of a randomized phase III study (ABCSG-24). *Ann Oncol* 2014; 25: 366–371.
30. Alba E, Albanell J, de la Haba J, *et al.* Trastuzumab or lapatinib with standard chemotherapy for HER2-positive breast cancer: results from the GEICAM/2006-14 trial. *Br J Cancer* 2014; 110: 1139–1147.
31. Bonnefoi H, Jacot W, Saghatchian M, *et al.* Neoadjuvant treatment with docetaxel plus lapatinib, trastuzumab, or both followed by an anthracycline-based chemotherapy in HER2-positive breast cancer: results of the randomised phase II EORTC 10054 study. *Ann Oncol* 2015; 26: 325–332.
32. Huang L, Chen S, Yang W, *et al.* Efficacy and safety analysis of trastuzumab and paclitaxel based regimen plus carboplatin or epirubicin as neoadjuvant therapy for clinical stage II-III, HER2-positive breast cancer patients: a phase 2, open-label, multicenter, randomized trial. *Oncotarget* 2015; 6: 18683–18692.
33. Steger G, Greil R, Hubalek M, *et al.* Abstract P3-11-06: Bevacizumab in combination with docetaxel+trastuzumab +/- non-pegylated liposomal doxorubicin: final results of ABCSG-32, a prospective, randomized phase II-study. *Cancer Res* 2015; 75: P3–11.
34. Park JW, Liu MC, Yee D, *et al.* Adaptive randomization of neratinib in early breast cancer. *N Engl J Med* 2016; 375: 11–22.
35. Carey LA, Berry DA, Cirrincione CT, *et al.* Molecular heterogeneity and response to neoadjuvant human epidermal growth factor receptor 2 targeting in CALGB 40601, a randomized phase III trial of paclitaxel plus trastuzumab with or without lapatinib. *J Clin Oncol* 2016; 34: 542–549.
36. Wang RX, Chen S, Jin X, *et al.* Weekly paclitaxel plus carboplatin with or without trastuzumab as neoadjuvant chemotherapy for HER2-positive breast cancer: loss of HER2 amplification and its impact on response and prognosis. *Breast Cancer Res Treat* 2017; 161: 259–267.
37. Stebbing J, Baranau Y, Baryash V, *et al.* CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial. *Lancet Oncol* 2017; 18: 917–928.
38. Hurvitz SA, Martin M, Symmans WF, *et al.* Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2018; 19: 115–126.
39. Hurvitz SA, Martin M, Jung KH, *et al.* Neoadjuvant trastuzumab (H), pertuzumab (P), and chemotherapy versus trastuzumab emtansine (T-DM1) and P in human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC): final outcome results from the phase III KRISTINE study. *J Clin Oncol* 2019; 37: 500.
40. Hurvitz SA, Martin M, Jung KH, *et al.* Neoadjuvant trastuzumab emtansine and pertuzumab in human epidermal growth factor receptor 2-positive breast cancer: three-year outcomes from the phase III KRISTINE study. *J Clin Oncol* 2019; 37: 2206–2216.
41. Nitz UA, Gluz O, Christgen M, *et al.* De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR- phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel. *Ann Oncol* 2017; 28: 2768–2772.
42. Harbeck N, Gluz O, Christgen M, *et al.* De-escalation strategies in human epidermal growth factor receptor 2 (HER2)-positive early Breast Cancer (BC): final analysis of the West German Study Group adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early BC HER2- and hormone receptor-positive phase II randomized trial-efficacy, safety, and predictive markers for 12 weeks of neoadjuvant trastuzumab emtansine with or without Endocrine Therapy (ET) versus trastuzumab plus ET. *J Clin Oncol* 2017; 35: 3046–3054.

43. Rimawi M, Cecchini RS, Rastogi P, *et al.* Abstract S3-06: A phase III trial evaluating pCR in patients with HR+, HER2-positive breast cancer treated with neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) +/- estrogen deprivation: NRG Oncology/NSABP B-52. *Cancer Res* 2017; 77: S3-06.

44. von Minckwitz G, Colleoni M, Kolberg HC, *et al.* Efficacy and safety of ABP 980 compared with reference trastuzumab in women with HER2-positive early breast cancer (LILAC study): a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2018; 19: 987–998.

45. van Ramshorst MS, van der Voort A, van Werkhoven ED, *et al.* Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2018; 19: 1630–1640.

46. Pivot X, Bondarenko I, Nowecki Z, *et al.* Phase III, randomized, double-blind study comparing the efficacy, safety, and immunogenicity of SB3 (trastuzumab biosimilar) and reference trastuzumab in patients treated with neoadjuvant therapy for human epidermal growth factor receptor 2-positive early breast cancer. *J Clin Oncol* 2018; 36: 968–974.

47. Lammers PE, Dank M, Masetti R, *et al.* Neoadjuvant PF-05280014 (a potential trastuzumab biosimilar) versus trastuzumab for operable HER2+ breast cancer. *Br J Cancer* 2018; 119: 266–273.

48. Jacobs SA, Robidoux A, Abraham J, *et al.* NSABP FB-7: A phase II randomized neoadjuvant trial with paclitaxel + trastuzumab and/or neratinib followed by chemotherapy and postoperative trastuzumab in HER2(+) breast cancer. *Breast Cancer Res* 2019; 21: 133.

49. Sun X, Wang XE, Zhang ZP, *et al.* Neoadjuvant therapy and sentinel lymph node biopsy in HER2-positive breast cancer patients: results from the PEONY trial. *Breast Cancer Res Treat* 2020; 180: 423–428.

50. Bergh JCS, Andersson A, Bjohle J, *et al.* Docetaxel, trastuzumab, pertuzumab versus trastuzumab emtansine as neoadjuvant treatment of HER2-positive breast cancer: results from the Swedish PREDIX HER2 trial identifying a new potential de-escalation standard? *J Clin Oncol* 2019; 37(Suppl. 15): 501.

51. Patel TA, Ensor JE, Creamer SL, *et al.* A randomized, controlled phase II trial of neoadjuvant ado-trastuzumab emtansine, lapatinib, and nab-paclitaxel versus trastuzumab, pertuzumab, and paclitaxel in HER2-positive breast cancer (TEAL study). *Breast Cancer Res* 2019; 21: 100.

52. Gluz O, Nitz U, Christgen M, *et al.* De-escalated chemotherapy versus endocrine therapy plus pertuzumab+ trastuzumab for HR+/HER2+ early breast cancer (BC): first efficacy results from the neoadjuvant WSG-TP-II study. *J Clin Oncol* 2020; 38: 515.

53. Gao H-F, Wu Z, Lin Y, *et al.* Neoadjuvant TCH (docetaxel/darboplatin/trastuzumab) versus EC-TH (epirubicin/cyclophosphamide followed by docetaxel/trastuzumab) in patients with HER2-positive breast cancer (neoCARH): a randomised, open-label, multicenter, phase II trial. *J Clin Oncol* 2020; 38: 585.

54. Masuda N, Ohtani S, Takano T, *et al.* A randomized, 3-arm, neoadjuvant, phase 2 study comparing docetaxel + carboplatin + trastuzumab + pertuzumab (TCbHP), TCbHP followed by trastuzumab emtansine and pertuzumab (T-DM1+P), and T-DM1+P in HER2-positive primary breast cancer. *Breast Cancer Res Treat* 2020; 180: 135–146.

55. Xavier P, Hii CSJ, Mclendon K, *et al.* 166MO a phase III trial to compare the efficacy, safety, pharmacokinetics and immunogenicity of HD201 to trastuzumab in HER2+ early breast cancer patients (TROIKA). *Ann Oncol* 2020; 31: S307.

56. Hurvitz SA, Caswell-Jin JL, McNamara KL, *et al.* Pathologic and molecular responses to neoadjuvant trastuzumab and/or lapatinib from a phase II randomized trial in HER2-positive breast cancer (TRIO-US B07). *Nat Commun* 2020; 11: 5824.

57. Nakashoji A, Hayashida T, Yokoe T, *et al.* The updated network meta-analysis of neoadjuvant therapy for HER2-positive breast cancer. *Cancer Treat Rev* 2018; 62: 9–17.

58. Chen S, Liang Y, Feng Z, *et al.* Efficacy and safety of HER2 inhibitors in combination with or without pertuzumab for HER2-positive breast cancer: a systematic review and meta-analysis. *BMC Cancer* 2019; 19: 973.

59. Yu L, Fu F, Li J, *et al.* Dual HER2 blockade versus a single agent in trastuzumab-containing regimens for HER2-positive early breast cancer: a systematic review and meta-analysis of randomized controlled trials. *J Oncol* 2020; 2020: 5169278.

60. Schettini F, Pascual T, Conte B, *et al.* HER2-enriched subtype and pathological complete response in HER2-positive breast cancer: a systematic review and meta-analysis. *Cancer Treat Rev* 2020; 84: 101965.

61. Awada A, Dirix L, Manso Sanchez L, *et al.* Safety and efficacy of neratinib (HKI-272) plus vinorelbine in the treatment of patients with ErbB2-positive metastatic breast cancer pretreated with anti-HER2 therapy. *Ann Oncol* 2013; 24: 109–116.
62. Martin M, Holmes FA, Ejlertsen B, *et al.* Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; 18: 1688–1700.
63. Ma F, Li Q, Chen S, *et al.* Phase I study and biomarker analysis of pyrotinib, a novel irreversible Pan-ErbB receptor tyrosine kinase inhibitor, in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol* 2017; 35: 3105–3112.
64. Ma F, Ouyang Q, Li W, *et al.* Pyrotinib or lapatinib combined with capecitabine in HER2-positive metastatic breast cancer with prior taxanes, anthracyclines, and/or trastuzumab: a randomized, phase II study. *J Clin Oncol* 2019; 37: 2610–2619.
65. Murthy RK, Loi S, Okines A, *et al.* Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med* 2020; 382: 597–609.
66. Harbeck N, Im S-A, Barrios CH, *et al.* Primary analysis of KAITLIN: a phase III study of trastuzumab emtansine (T-DM1) + pertuzumab versus trastuzumab + pertuzumab + taxane, after anthracyclines as adjuvant therapy for high-risk HER2-positive early breast cancer (EBC). *J Clin Oncol* 2020; 38(Suppl. 15): 500.
67. van der Voort A, Ramshorst M, van Werkhoven E, *et al.* Three-year follow-up of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2-blockade for HER2-positive breast cancer (TRAIN-2): a randomized phase III trial. *J Clin Oncol* 2020; 38: 501.
68. Wu Y-T, Xu Z, Arshad B, *et al.* Significantly higher pathologic complete response (pCR) after the concurrent use of trastuzumab and anthracycline-based neoadjuvant chemotherapy for HER2-positive breast cancer: evidence from a meta-analysis of randomized controlled trials. *J Cancer* 2018; 9: 3168–3176.
69. Wu YT, Xu Z, Zhang K, *et al.* Efficacy and cardiac safety of the concurrent use of trastuzumab and anthracycline-based neoadjuvant chemotherapy for HER2-positive breast cancer: a systematic review and meta-analysis. *Ther Clin Risk Manag* 2018; 14: 1789–1797.
70. Slamon D, Eiermann W, Robert N, *et al.* Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; 365: 1273–1283.
71. Guarneri V, Frassoldati A, Piacentini F, *et al.* Preoperative chemotherapy plus lapatinib or trastuzumab or both in HER2-positive operable breast cancer (CHERLOB trial). *Clin Breast Cancer* 2008; 8: 192–194.
72. Razandi M, Pedram A, Park ST, *et al.* Proximal events in signaling by plasma membrane estrogen receptors. *J Biol Chem* 2003; 278: 2701–2712.
73. Shou J, Massarweh S, Osborne CK, *et al.* Mechanisms of tamoxifen resistance: increased estrogen receptor-HER2/neu cross-talk in ER/HER2-positive breast cancer. *J Natl Cancer Inst* 2004; 96: 926–935.