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# The updated network meta-analysis of neoadjuvant therapy for HER2-positive breast cancer

Ayako Nakashoji [a], Tetsu Hayashida [a,*], Takamichi Yokoe [a], Hinako Maeda [a], Tomoka Toyota [a], Masayuki Kikuchi [a], Rurina Watanuki [a], Aiko Nagayama [a], Tomoko Seki [a], Maiko Takahashi [a], Takayuki Abe [b], Yuko Kitagawa [a]

[a] Department of Surgery, Keio University School of Medicine, Shinanomachi 35, Shinjuku-ku, 160-8582 Tokyo, Japan
[b] Department of Preventive Medicine and Public Health, Keio University School of Medicine, Shinanomachi 35, Shinjuku-ku, 160-8582 Tokyo, Japan

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ABSTRACT

*Background:* We previously described a systematic assessment of the neoadjuvant therapies for human epidermal growth factor receptor-2 (HER2) positive breast cancer, using network meta-analysis. Accumulation of new clinical data has compelled us to update the analysis.
*Methods:* Randomized trials comparing different anti-HER2 regimens in the neoadjuvant setting were included, and odds ratio for pathologic complete response (pCR) in seven treatment arms were assessed by pooling effect sizes. Direct and indirect comparisons using a Bayesian statistical model were performed. All statistical tests were two-sided.
*Results:* A database search identified 993 articles with 13 studies meeting the eligibility criteria, including three new studies with lapatinib (lpnb). In an indirect comparison, dual anti-HER2 agents with CT achieved a better pCR rate than other arms. The credibility intervals of CT + tzmb + lpnb arm were largely reduced compared to our former report, which we added sufficient clinical evidence by this update. Values of surface under the cumulative ranking (SUCRA) suggested that CT + tzmb + pzmb had the highest probability of being the best treatment arm for pCR, widening the difference between the top two dual-HER2 blockade arms compared to our former report. The overall consistency with our first report enhanced the credibility of the results.
*Conclusion:* Network meta-analysis using new clinical data firmly establish that combining two anti-HER2 agents with CT is most effective against HER2-positive breast cancer in the neoadjuvant setting. New pzmb related trials are required to fully determine the best neoadjuvant dual-HER2 blockade regimen.



## Introduction

The characterization of the human epidermal growth factor receptor 2 (HER2), as a proto-oncogene, a poor prognostic marker, and finally as a therapeutic target has dramatically changed the categorization, risk assessment, and treatment of breast cancer. Overexpression or amplification of HER2 occurs in approximately 20% of human breast cancers, and trastuzumab (tzmb), an anti-HER2 agent, has demonstrated clinically significant efficacy against HER2-positive breast cancer [1].

As neoadjuvant systemic therapies are now routinely delivered in primary operable breast cancer [2], it is becoming increasingly popular to use neoadjuvant chemotherapy including anti-HER2 agents in patients with operable HER2-positive breast cancers. National Comprehensive Cancer Network (NCCN) Guidelines Version 2. 2017 recommend treating HER2-positive patients with systemic therapy incorporating tzmb for at least 9 weeks in the neoadjuvant setting. They also add that pertuzumab (pzmb) containing regimen may be administered preoperatively to patients with ≥ T2 or ≥ N1, HER2-positive early-stage breast cancer [3].

Increasing options for HER2-targeted agents prompts us to define the best neoadjuvant therapy for HER2-positive breast cancer. The agents include tyrosine kinase inhibitor lapatinib (lpnb) or monoclonal antibody pzmb, antibody-drug conjugate trastuzumab-DM1 (T-DM1), and neratinib, an HER2, HER4, and EGFR tyrosine kinase inhibitor. Lpnb is a small molecule tyrosine kinase inhibitor of the HER1 and HER2 receptors that suppresses the downstream signaling involving MAPK/Erk1/2 and P13K/Akt pathways [4]. Pzmb is a humanized monoclonal antibody that inhi-

* Corresponding author.
*E-mail address:* tetsu@keio.jp (T. Hayashida).

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bits dimerization of HER2 with other HER receptors [5]. Based on the results of the CLEOPATRA trial, the combination of tzmb and pzmb with taxane has become a new first-line standard treatment for HER2-positive advanced breast cancer patients with good performance status [6].

Although trials have been conducted to compare various treatment regimens, it remains difficult to integrate information on their relative efficacies since each trial has compared only a few treatments at one time. In 2014, we reported the results of a systematic assessment of the efficacy and safety of neoadjuvant therapies for HER2-positive breast cancer, using a network meta-analysis based on the Bayesian model, conducting direct and indirect comparisons from multiple randomized clinical trials [7]. After collecting information from a network of trials, the network meta-analysis combines both the direct and indirect evidence for the relative effectiveness of treatments and ranks them thereafter [8–10]. By indirect comparison, we can compare treatment arms which are not directly compared in clinical trials. As the complexity of the analysis supporting the clinical guidelines increase, it helps to make sound clinical decisions [11].

In our previous study, we reported that the patients receiving dual-HER2 blockade treatments presented significantly better pathologic complete response (pCR) rates than those in other treatment arms, and recommended the combination of two anti-HER2 agents with chemotherapy (CT) to be the most effective treatment modality in the neoadjuvant setting for HER2-positive breast cancer [7]. Though there was no significant difference between the two dual targeting treatment arms of CT + tzmb + lpnb and CT + t zmb + pzmb, the latter was slightly more likely to be the best treatment arm in terms of pCR considering the values of ranking probability curve.

As mentioned before, NCCN Guidelines now recommend using two anti-HER2 antibodies preoperatively in selected HER2-positive breast cancer patients. Dual-HER2 blockade in a neoadjuvant setting is, therefore, getting to be more popular than it was at the time of our previous report [12]. Since our primary report, several important network meta-analysis were reported in the area of breast cancer therapy [13–15]. However, whether if dual neoadjuvant anti-HER2 antibody inhibition produce clinically significant improvements has still remained in controversy [2].

Five years after our first article search, we decided to update our analysis based on the new clinical evidence available and further verify the effectiveness of dual-HER2 blockade. We also aimed to determine if more clinical studies of neoadjuvant HER2-positive breast cancer are required, and if so, which treatment regimens require additional studies the most.

## Methods

### *Search strategy*

Searches were performed using MEDLINE and the Cochrane Central Register of Controlled Trials without any year and language restrictions, using the following keywords: Breast neoplasms AND Neoadjuvant therapy AND Antibodies, Monoclonal OR Receptor, erbB-2. The last search was updated in November 2016. In addition, the reference lists of all studies fulfilling the eligibility criteria were examined for other relevant articles missed by the electronic searches.

### *Selection criteria*

Eligibility and exclusion criteria were prespecified. All randomized trials that compared at least two arms of different treatment regimens involving CT and/or anti-HER2 agents in HER2-positive breast cancer patients in the neoadjuvant settings were considered. All cytotoxic CT regimens were considered eligible for the meta-analysis. If multiple publications of the same trial were retrieved or if there was a case mixed between publications, only the most recent and informative publication was included. Using the Cochrane Collaboration risk of bias tool [16], two independent reviewers (AN and TH) assessed all studies for appropriateness of allocation, blinding, management of incomplete outcome data and the completeness of reporting of outcomes.

### *Data extraction*

Data were extracted independently by two authors (AN and TH) according to a prespecified protocol, and a consensus was reached on all items. From each eligible trial, the first author, year of publication, journal, country of origin as noted in their affiliations, sample size, age, estrogen receptor/progesterone receptor status, node positivity, CT regimens, and anti-HER2 agent(s) dose/duration were recorded. Primary and secondary outcome measures were also recorded.

### *Definition of outcomes*

The primary outcome in this study was the number of patients who achieved pCR, which was defined as the absence of invasive residual cancer in the breast tissue and nodes (ypT0/is ypN0); non-invasive breast residuals were allowed. Other definitions of pCR were substituted if not reported. Secondary outcomes were the number of patients who completed the treatment as planned and the number of patients who had grade 3 or 4 adverse events, including diarrhea, neutropenia, and skin disorders. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) version 4.0. If adverse events were not graded as per the NCI-CTC, the corresponding numbers of the adverse events were used. Cardiac events, including asymptomatic events, such as less than 50% left ventricular ejection fraction or a drop of at least 10% from baseline, and symptomatic events, such as congestive heart failure or cardiac deaths were reported separately. However, outcomes, such as overall survival (OS) and disease-free survival (DFS), were not analyzed because of insufficient data.

### *Statistical methods*

We basically followed the methods described previously [7]. Briefly, we utilized the odds ratio (OR) for pooling effects size because all outcomes were binary variables and followed binomial distributions. For pairwise meta-analysis (i.e., direct comparisons), we used the random-effects model of DerSimonian–Laird [17], which takes heterogeneity between studies into account. We reported the results with 95% confidence intervals (CIs) and with a two-sided $P < 0.05$ as statistically significant. To assess heterogeneity, we calculated the Cochrane Q statistics and $I^2$ statistics.

For multiple treatment comparisons, we conducted a network meta-analysis within a Bayesian framework. We used a hierarchical Bayesian model, which utilizes information from direct and indirect comparisons, for synthesizing the OR for each pair of multiple treatments. The analysis model used was the multivariate random-effects Bayesian consistency model of Caldwell [9]. We reported the outcomes with 95% credibility intervals (CrIs). To assess any inconsistency (i.e., disagreement between the direct and indirect comparisons), we applied the inconsistency model of Ian White using estimable coefficients in design-by-treatment terms [18,19]. We used the Wald-like test to evaluate inconsistencies in the whole study. Furthermore, we evaluated the ranking probability curve for each treatment by plotting the probability