Original Article



# Efficacy and safety of neoadjuvant pertuzumab plus trastuzumab in combination with chemotherapy regimen in Chinese patients with HER2-positive early breast cancer: a real-world retrospective multi-center cohort study

**Meirong Zhou[1], Shouman Wang[2], Nengbin Wan[3], Songlin Yuan[4], Xiongqiang Hu[5], Wei Zhou[6], Bohua Qing[7], Mingwen Liu[8], Weihua Sun[9], Peizhi Fan[10], Jianguo Wang[11], Hong Cao[12], Haifan Xu[13], Bin Dai[14], Peizhi Tang[15], Liyuan Qian[16], Xi Zhao[17], Jun Xiao[18], Huaiying Zhou[19], Jinhui Hu[20], Li Ding[21], Domenico Tripodi[22], Nicholas Zdenkowski[23], Thomas J. O'Keefe[24], Alejandro Martin Sanchez[25], Li Chen[1], Ping Zhang[1], Feng Xu[1]**

[1]Department of General Surgery, Xiangya Second Hospital, Central South University, Changsha, China; [2]Department of Breast Surgery, Xiangya Hospital, Central South University, Changsha, China; [3]Department of Breast Surgery 2, Hunan Cancer Hospital, Changsha, China; [4]Department of Breast and Thyroid Surgery, The First People's Hospital of Changde City, Changde, China; [5]Surgical Oncology of Breast and Thyroid, Chenzhou No. 1 People's Hospital, Chenzhou, China; [6]Department of Breast Surgery, Xiangya Hospital Zhuzhou, Central South University, Zhuzhou, China; [7]Head and Neck Tumor Department of Mammary Gland, The Central Hospital of Yongzhou, Yongzhou, China; [8]Breast and Thyroid Surgery, The First People's Hospital of Xiangtan City, Xiangtan, China; [9]Department of Breast Surgery, Huaihua Cancer Hospital, Huaihua, China; [10]Surgical Department of Breast and Thyroid Gland, Hunan Provinscial People's Hospital, the First Affiliated Hospital of Hunan Normal University, Changsha, China; [11]Second Department of General Surgery, Xiangtan Central Hospital, Xiangtan, China; [12]Breast and Thyroid Surgery, The Second Affiliated Hospital of University of South China, Hengyang, China; [13]Breast and Thyroid Surgery, The First Affiliated Hospital of University of South China, Hengyang, China; [14]Department of Breast and Thyroid Surgery, The Central Hospital of Shaoyang, Shaoyang, China; [15]Breast and Thyroid Surgery, Xiangxi Autonomous Prefecture People's Hospital, Xiangxi Tujia and Miao Autonomous Prefecture, China; [16]Breast and Thyroid Surgery, The Third Xiangya Hospital of Central South University, Changsha, China; [17]Department of Breast Surgery, Hunan Province Directly Affiliated TCM Hospital, Changsha, China; [18]Department of Breast Surgery, Yueyang Central Hospital, Yueyang, China; [19]Oncology Department, Yongzhou Third People's Hospital, Yongzhou, China; [20]Department of Breast Surgery, The First Affiliated Hospital of Hunan University of Chinese Medicine, Changsha, China; [21]Breast and Thyroid Surgery, The First People's Hospital of Huaihua, Huaihua, China; [22]Department of Surgical, Division of Breast Surgery Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; [23]School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia; [24]Division of Breast Surgery and the Comprehensive Breast Health Center, University of California San Diego, La Jolla, CA, USA; [25]Multidisciplinary Breast Center, Fondazione Policlinico Universitario Agostino Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy

*Contributions:* (I) Conception and design: F Xu, M Zhou; (II) Administrative support: F Xu; (III) Provision of study materials or patients: S Wang, N Wan, S Yuan, X Hu, W Zhou, B Qing, M Liu, W Sun, P Fan, J Wang, H Cao, H Xu, B Dai, P Tang, L Qian, X Zhao, J Xiao, H Zhou, J Hu, L Ding, F Xu; (IV) Collection and assembly of data: F Xu, L Chen, P Zhang; (V) Data analysis and interpretation: F Xu, M Zhou, L Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Feng Xu. Department of General Surgery, Xiangya Second Hospital, Central South University, 139 Middle People Road, Changsha 410011, China. Email: 503412@csu.edu.cn.

**Background:** Pertuzumab plus trastuzumab combined with chemotherapy has become a standard neoadjuvant therapy option for patients with high-risk human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC). There is still not enough evidence for the efficacy and safety of neoadjuvant pertuzumab and trastuzumab plus chemotherapy in HER2-positive BC patients in China, both in clinical trials and real-world settings. This study aimed to assess the efficacy and safety of neoadjuvant pertuzumab plus trastuzumab in combination with chemotherapy in Chinese patients with HER2-positive BC in real-world clinical application.

**Methods:** We retrospectively collected the data from the electronic medical records of HER2-positive

© Annals of Translational Medicine. All rights reserved.

patients treated with neoadjuvant trastuzumab and pertuzumab plus chemotherapy from December 2018 to May 2021 at 21 hospitals located in Hunan Province, China, including age, American Joint Committee on Cancer (AJCC) stage, clinical tumor size, clinical lymph node status, pathological characteristics (before neoadjuvant systemic therapy), treatment approach, adverse events to neoadjuvant therapy, and achievement of pathological complete response (pCR). The primary endpoint was the total rate of pCR, and the secondary endpoints were the rate of pCR of each subgroup and the safety of dual anti-HER2 therapy.

**Results:** A total of 188 patients met the inclusion criteria and were included in the analysis. Of the 188 patients, 119 (63.3%) were diagnosed at stage II and 64 (34.0%) at stage III; 163 (86.7%) were cT2-3; 149 patients (79.3%) were ≥ cN1; 84 patients (44.7%) were hormone receptor (HR)-positive. pCR was observed in 88 of 188 patients (46.8%). The pCR rate of HR-negative patients (54.8%) was higher (P=0.014) than that of HR-positive patients (36.9%). Patients with Ki-67 <15% achieved a higher (P=0.033) pCR rate (68.2%) than those with Ki-67 ≥15% (44.0%). Anemia was the most common adverse event (63.4%), and the most common grade 3–4 adverse event was nausea and vomiting (8.5%).

**Conclusions:** Our study confirmed the benefit of neoadjuvant pertuzumab plus trastuzumab in combination with chemotherapy on pCR with a tolerable safety profile in routine clinical practice in Chinese patients with HER2-positive BC. HR-negativity and Ki-67 <15% were associated with pCR in these patients.

**Keywords:** Breast cancer (BC); neoadjuvant; trastuzumab; pertuzumab; real-world

Submitted Oct 20, 2022. Accepted for publication Dec 19, 2022.
doi: 10.21037/atm-22-6054
**View this article at:** https://dx.doi.org/10.21037/atm-22-6054

## Introduction

Breast cancer (BC) is the most common malignancy in women worldwide. It has a high degree of heterogeneity and a significant impact on women's lives and health. Overexpression of human epidermal growth factor receptor 2 (HER2) or amplification of the *erbB2* gene is present in approximately 15–25% of BCs (1,2), and is associated with a poor prognosis (3). Anti-HER2 therapy with trastuzumab has been shown to improve overall and disease-specific survival for these patients (4-6). Pertuzumab, a second-generation anti-HER2 drug, both induces antibody-mediated cytotoxicity by its binding to HER2 and also interferes with signaling by preventing its binding to partner receptors (7). The use of pertuzumab in combination with trastuzumab as dual anti-HER2 therapy in patients with HER2-positive BC has been associated with improved overall and progression-free survival, as well as increased rates of pathologic complete response (pCR), defined as the eradication of invasive disease on pathology assessment of surgical specimens after completion of neoadjuvant therapy (8-10).

The use of neoadjuvant therapy offers potential benefits both to patients with HER2-positive early breast cancer (EBC) and locally advanced breast cancer (LABC). Neoadjuvant therapy may lead to downstaging of the tumor, which may affect candidacy for breast-conserving surgery (BCS) (11-13). Neoadjuvant therapy also allows for early evaluation of tumor response, which may guide further

### Highlight box

**Key findings**

- This study confirms the benefit of neoadjuvant pertuzumab and trastuzumab plus chemotherapy on pCR with a tolerable safety profile in routine clinical practice in Chinese patients with HER2-positive breast cancer (BC). HR-negativity and Ki-67 <15% were associated with pCR in these patients.

**What is known and what is new?**

- Previous studies confirmed the efficacy and safety of neoadjuvant trastuzumab and pertuzumab plus chemotherapy for human epidermal growth factor receptor 2 (HER2)-positive BC, but there is still not enough evidence for this in Chinese patients;
- Our study presented the largest cohort real-world data on evaluating the efficacy and safety of neoadjuvant pertuzumab and trastuzumab plus chemotherapy in Chinese patients with HER2-positive early or LABC.

**What is the implication, and what should change now?**

- Neoadjuvant pertuzumab and trastuzumab plus chemotherapy is recommended for HER2-positive patients in China who need neoadjuvant therapy.

© Annals of Translational Medicine. All rights reserved.

systemic treatment plans (14).

Patients who achieve pCR after neoadjuvant therapy have a significantly improved event-free and overall survival (15,16). Thus, pCR is not only an important factor in determining the adjuvant therapy strategy but also has implications for survival. In the early 21st century, it was found that the addition of trastuzumab to standard neoadjuvant chemotherapy significantly improved the pCR rate of HER2-positive BC patients (17-19). The NeoSphere trial demonstrated that combining trastuzumab and pertuzumab with neoadjuvant chemotherapy could achieve a higher pCR rate (42%) than trastuzumab alone with neoadjuvant chemotherapy (23%) (10). The TRYPHAENA trial and BERENICE trial showed that dual HER2 blockade with trastuzumab and pertuzumab plus neoadjuvant chemotherapy achieved rates of pCR of 57–66% (20,21). Therefore, pertuzumab plus trastuzumab combined with chemotherapy has become a standard neoadjuvant therapy option for patients with HER2-positive BC.

The proportion of Asian patients in previous studies which confirmed the efficacy and safety of dual HER2 blockade with trastuzumab and pertuzumab plus neoadjuvant chemotherapy was <25% (10,20). The PEONY trial adds to the totality of the data showing the benefit and safety of neoadjuvant pertuzumab and trastuzumab with chemotherapy in HER2-positive BC of Asian patients (22), however, pertuzumab was not approved in China until December 2018 and was not officially clinical used until March 2019. So, there is still not enough evidence for the efficacy and safety of neoadjuvant pertuzumab and trastuzumab plus chemotherapy in HER2-positive BC patients in China, both in clinical trials and real-world settings. This retrospective, observational study aimed to assess the efficacy and safety of neoadjuvant pertuzumab plus trastuzumab in combination with chemotherapy regimens in Chinese patients with early-stage HER2-positive BC. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6054/rc).

## Methods

### *Patients and data collection*

This is a retrospective, observational, multi-center study conducted at certified BC centers in 21 hospitals located in Hunan, China. The data were collected retrospectively by staff trained in relevant data collection, including age, American Joint Committee on Cancer (AJCC) stage (according to AJCC staging version 8), clinical tumor size, clinical lymph node status, pathological characteristics (before neoadjuvant systemic therapy), treatment approach, adverse events (AEs) to neoadjuvant therapy, and achievement of pCR. Data were collected from the electronic medical records, and they recorded the information gathered on data forms. All forms were collected and delivered to the central investigator for quality control and re-screening to exclude cases that did not meet the inclusion criteria. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Clinical Research Ethics Board of Xiangya Second Hospital, Central South University (No. LYF2021182). In addition, all the relevant ethics committees approved the study. Written informed consent was provided by each participant for the use of their data.

Inclusion criteria included patients with early or locally advanced HER2-positive BC without distant metastases who underwent at least 4 cycles of neoadjuvant dual anti-HER2 therapy with trastuzumab and pertuzumab, completed their first cycle of neoadjuvant therapy prior to December 31, 2020, underwent surgery after their neoadjuvant therapy, had complete preoperative and postoperative pathological and clinical data, and a baseline left ventricular ejection fraction (LVEF) of at least 50% as measured by echocardiography. There were no exclusion criteria. Variables were categorized as follows: neoadjuvant chemotherapy regimen (with or without anthracyclines, with or without albumin-bound paclitaxel), neoadjuvant therapy cycles (<6 cycles, 6 cycles, or >6 cycles), clinical lymph node status (with or without metastasis assessed at baseline), clinical tumor size (≤2 cm, 2.1–5 cm, >5 cm at baseline), hormone receptor (HR) status (positive or negative at baseline). The treatment plan and dosing strategies for chemotherapy drugs of neoadjuvant therapy was determined by the attending physician based on each patient's condition and disease according to the national guideline. The trastuzumab loading dose was 8 mg/kg followed by 6 mg/kg intravenously, once every 3 weeks. The pertuzumab loading dose was 840 mg followed by 420 mg intravenously, once every 3 weeks.

### *Pathological analysis*

The status of estrogen receptor (ER), progesterone receptor (PR), HER2, and grading were directly documented from

© Annals of Translational Medicine. All rights reserved. 

the pathology reports. There was no central review of biomarkers. We defined ER and PR status as positive if ≥1% of the nuclei were stained. The HER2 status was considered positive based on an immunohistochemical (IHC) score of 3+ or 2+ with positive fluorescence in situ hybridization/competitive in situ hybridization (FISH/CISH) findings. pCR was defined as complete disappearance of residual invasive tumor by microscopic examination of the breast and axillary lymph nodes (ypT0/Tis and ypN0).

### *Study endpoints*

The primary endpoint was the total rate of pCR. The Miller-Payne grading system or the residual cancer burden (RCB) were routinely used to assess pathological responses in clinical practice (23). Grade 5 of the Miller-Payne criteria or a score of 0 on the RCB index were designated as pCR. The secondary endpoints were the rate of pCR of each subgroup and the safety of dual anti-HER2 therapy. AEs were categorized according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 5.0).

### *Statistical analysis*

Quantitative variables were described in terms of central tendency and dispersion (median and quartile difference) and qualitative variables were reported in terms of counts and percentages. The missing data were directly eliminated and not included in statistical analysis. Continuous variables were compared using the Mann-Whitney U test, whereas categorical variables were compared using the chi-squared or Fisher's exact test. Multivariate logistic regression analysis was used to evaluate the influence of parameters on pCR. Due to the small number of parameters included in this study and sufficient sample size, all variables in the univariate analysis were included in the multiple logistic regression analysis as independent variables, and then the odds ratio (OR) value and 95% confidence intervals (CIs) of each variable were calculated. All statistical analyses were carried out using the software SPSS 18.0 (IBM Corp., Chicago, IL, USA) and two-tailed P values <0.05 were considered statistically significant.

## Results

A total of 188 patients met the inclusion criteria and were included in the analysis from December 2018 to May 2021 (*Table 1*). Median age at diagnosis was 48.5 [interquartile range (IQR), 27–74] years. Of the 188 patients, 119 (63.3%) were diagnosed at stage II, 64 (34.0%) at stage III and 5 (2.7%) at stage I; 163 (86.7%) were cT2-3; 39 patients (20.7%) were cN0, and 149 patients (79.3%) were ≥ cN1. A total of 84 (44.7%) of these patients were HR positive (defined as ER or PR positive). For HER2 receptor status, 150 (79.8%) of patients had an IHC score of 3+ and the remaining 38 (20.2%) had an IHC score of 2+.

The neoadjuvant therapy regimens were carboplatin plus taxane in combination with pertuzumab and trastuzumab (TCbHP) every 3 weeks (76 patients, 40.4%), taxane in combination with trastuzumab and pertuzumab (THP) every 3 weeks (38 patients, 20.2%), a sequence of 3–4 cycles of anthracycline plus cyclophosphamide every 3 weeks followed by 3–4 cycles of taxane plus pertuzumab and trastuzumab (AC-THP) every 3 weeks (56 patients, 29.8%), and other neoadjuvant chemotherapy regimens plus dual HER2-targeted therapy (18 patients, 9.6%) (*Table 1*). Among all cases, 69 patients (36.7%) received anthracycline-based neoadjuvant chemotherapy regimen, and the other 119 patients (63.3%) received non-anthracycline regimen; 36 patients (19.1%) received albumin-bound paclitaxel as a taxane, whereas 152 patients (80.9%) received a conventional taxane regimen. The neoadjuvant treatment cycles were defined as <6 (25 patients, 13.3%), equal to 6 (98 patients, 52.1%), and greater than 6 (65 patients, 34.6%), whereas the neoadjuvant targeted therapy cycles were categorized as <6 (83 patients, 44.1%) and ≥6 (105 patients, 55.9%).

All cases underwent curative surgery 2–4 weeks after the last cycle of neoadjuvant therapy. When the lymph node status was ≥ cN1, ultrasound-guided core needle biopsy or fine needle aspiration was performed at the time of BC diagnosis. Of the 149 patients who received lymph node biopsy, 127 (85.2%) had histopathological confirmation of axillary lymph node metastasis. For curative surgery, 183 patients (97.3%) received a mastectomy, and only 5 patients (2.7%) underwent BCS (*Table 2*). During the time, the standard method of axillary surgery was axillary lymph node dissection (ALND), and only 6 patients underwent sentinel lymph node biopsy Among the cohort, 3 (1.6%) patients underwent immediate reconstruction with breast implants (2 patients, 1.1%) or autologous flap (1 patient, 0.5%) after mastectomy.

After curative surgery, pCR was achieved in 88 of 188 patients (46.8%) (*Table 1*). Univariate analysis found that the pCR rate was significantly associated with HR status (P=0.014) and Ki-67 levels (P=0.033). The pCR

© Annals of Translational Medicine. All rights reserved. 

**Table 1** Baseline characteristics (n=188) and univariate analysis of factors associated with pCR

| Parameters | Total, n (%) | pCR, n (%) | Univariate P value |
|---|---|---|---|
| Age (years), mean [range] | 48.5 [27–74] | | |
| <40 | 34 (18.1) | 12 (35.3) | 0.279 |
| 40–59 | 138 (73.4) | 67 (48.6) | |
| ≥60 | 16 (8.5) | 9 (56.3) | |
| AJCC stage | | | 0.352 |
| I | 5 (2.7) | 4 (80.0) | |
| IIa | 42 (22.3) | 20 (47.6) | |
| IIb | 77 (41.0) | 38 (49.4) | |
| III | 64 (34.0) | 26 (40.6) | |
| Clinical tumor size | | | 0.642 |
| cT1 | 25 (13.3) | 11 (44.0) | |
| cT2 | 113 (60.1) | 56 (49.6) | |
| cT3 | 50 (26.6) | 21 (42.0) | |
| Clinical lymph node status | | | 0.177 |
| cN0 | 39 (20.7) | 22 (56.4) | |
| ≥ cN1 | 149 (79.3) | 66 (44.3) | |
| HR status | | | 0.014 |
| Negative | 104 (55.3) | 57 (54.8) | |
| Positive | 84 (44.7) | 31 (36.9) | |
| HER2 receptor status | | | 0.938 |
| 2+ | 38 (20.2) | 18 (47.4) | |
| 3+ | 150 (79.8) | 70 (46.7) | |
| Ki-67 levels | | | 0.033 |
| <15% | 22 (11.7) | 15 (68.2) | |
| ≥15% | 166 (88.3) | 73 (44.0) | |
| Neoadjuvant chemotherapy | | | 0.317 |
| Anthracycline | 69 (36.7) | 29 (42.0) | |
| Non-anthracycline | 119 (63.3) | 59 (49.6) | |
| Neoadjuvant chemotherapy | | | 0.821 |
| TCbHP | 76 (40.4) | 36 (47.4) | |
| THP | 38 (20.2) | 20 (52.6) | |
| AC-THP | 56 (29.8) | 24 (42.9) | |
| Others | 18 (9.6) | 8 (44.4) | |

**Table 1** (*continued*)

© Annals of Translational Medicine. All rights reserved.

**Table 1** (*continued*)

| Parameters | Total, n (%) | pCR, n (%) | Univariate P value |
|---|---|---|---|
| Neoadjuvant cycles | | | 0.472 |
| <6 | 25 (13.3) | 11 (44.0) | |
| 6 | 98 (52.1) | 50 (51.0) | |
| >6 | 65 (34.6) | 27 (41.5) | |
| Targeted therapy cycles | | | 0.965 |
| <6 | 83 (44.1) | 39 (47.0) | |
| ≥6 | 105 (55.9) | 49 (46.7) | |
| Taxanes | | | 0.056 |
| Albumin-bound paclitaxel | 36 (19.1) | 22 (61.1) | |
| Conventional taxanes | 152 (80.9) | 66 (43.4) | |

pCR, pathological complete response; AJCC, American Joint Committee on Cancer; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TCbHP, carboplatin plus taxane in combination with pertuzumab and trastuzumab; THP, taxane in combination with trastuzumab and pertuzumab; AC-THP, a sequence of anthracycline plus cyclophosphamide followed by taxane plus pertuzumab and trastuzumab.

**Table 2** The surgical treatments of the patients

| Surgery | Patients, n (%) |
|---|---|
| Axillary lymph node biopsy on diagnosis | |
| Yes | 149 (79.3) |
| No | 39 (20.7) |
| Breast surgery | |
| Mastectomy | 183 (97.3) |
| Breast-conserving | 5 (2.7) |
| Axillary lymph node surgery | |
| Axillary lymph node dissection | 182 (96.8) |
| Sentinel lymph node biopsy | 6 (3.2) |
| Breast reconstruction | |
| Yes | 3 (1.6) |
| No | 185 (98.4) |

rate of HR-negative patients (54.8%) was higher than that of HR-positive patients (36.9%). Patients with Ki-67 <15% achieved a higher pCR rate (68.2%) than those with Ki-67 ≥15% (44.0%). There were no statistically significant differences in pCR between patients undergoing neoadjuvant chemotherapy with (42.0%) or without (49.6%) anthracycline (P=0.317), or those with (61.1%) or without (43.4%) albumin paclitaxel (P=0.056). pCR of patients treated with TcbHP, THP, AC-THP, and other regimens were 47.4%, 52.6%, 42.9%, and 44.4%, respectively, with no statistical significance among them (P=0.821). The pCR rate was higher among patients treated with 6 neoadjuvant treatment cycles (51.0%) compared with patients with >6 cycles (41.5%) and <6 cycles (44.0%), but the difference was not significant (P=0.472). pCR was not significantly associated with the clinical tumor size (P=0.642), AJCC stage (P=0.352), clinical lymph node status (P=0.177), or IHC HER2 receptor status (P=0.938). In multivariate analysis of the associations between baseline characteristics and pCR (*Table 3*), HR status was an independent predictor of pCR (OR: 0.444, 95% CI: 0.235–0.839; P=0.012) as well as the Ki-67 level (OR: 0.349, 95% CI: 0.130–0.933; P=0.036).

A total of 153 of 188 (81.4%) patients had available data on toxicities including 65 patients with TCbHP regimen, 35 with THP regimen, 37 with AC-THP regimen, and 16 with other regimens. The common AEs included anemia, nausea and vomiting, hair loss, fatigue, neutropenia, transaminitis, diarrhea, thrombocytopenia, change in cardiac function, rash, febrile neutropenia, and drug allergy, among which anemia was the most common AE (*Table 4*). Most of these toxicities were grade 1–2. The most common grade 3–4 AE was nausea and vomiting (13, 8.5%) followed by anemia (11, 7.2%). Although the pegylated recombinant human

© Annals of Translational Medicine. All rights reserved. 

**Table 3** Multivariate analysis of factors associated with pCR

| Parameters | OR | 95% CI | P value |
|---|---|---|---|
| AJCC stage | 0.690 | 0.316–1.505 | 0.351 |
| Clinical tumor size | 1.291 | 0.593–2.812 | 0.520 |
| Clinical lymph node status | 0.981 | 0.298–3.233 | 0.975 |
| Targeted therapy cycles | 0.911 | 0.237–3.507 | 0.893 |
| Neoadjuvant cycles | 0.575 | 0.246–1.343 | 0.201 |
| Anthracycline or non-anthracycline | 0.593 | 0.133–2.642 | 0.493 |
| HR status | 0.444 | 0.235–0.839 | 0.012 |
| Taxanes | 2.099 | 0.951–4.632 | 0.066 |
| Ki-67 | 0.349 | 0.130–0.933 | 0.036 |

pCR, pathological complete response; OR, odds ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; HR, hormone receptor.

**Table 4** Adverse events reported during the treatment

| Toxicity | Incidence of any grade, n (%) | Incidence of grade 3–4, n (%) |
|---|---|---|
| Anemia | 97 (63.4) | 11 (7.2) |
| Nausea and vomiting | 78 (51.0) | 13 (8.5) |
| Hair loss | 68 (44.4) | 0 (0.0) |
| Fatigue | 67 (43.8) | 0 (0.0) |
| Neutropenia | 61 (39.9) | 9 (5.9) |
| Elevated transaminase | 47 (30.7) | 6 (3.9) |
| Diarrhea | 34 (22.2) | 1 (0.7) |
| Thrombocytopenia | 34 (22.2) | 3 (2.0) |
| Decrease in cardiac function | 12 (7.8) | 0 (0.0) |
| Rash | 10 (6.5) | 0 (0.0) |
| Febrile neutropenia | 5 (3.3) | 0 (0.0) |

**Table 5** Adverse events related to anthracycline/taxane-based, single-agent taxane-based, and platinum-based chemotherapy in combination with pertuzumab and trastuzumab

| Toxicities | TCbHP (n=65), n (%) | | THP (n=35), n (%) | | AC-THP (n=37), n (%) | |
|---|---|---|---|---|---|---|
| | Any grade | Grade 3–4 | Any grade | Grade 3–4 | Any grade | Grade 3–4 |
| Neutropenia | 23 (35.4) | 2 (3.1) | 13 (37.1) | 3 (8.6) | 16 (43.2) | 3 (8.1) |
| Anemia | 50 (76.9) | 7 (10.8) | 15 (42.9) | 1 (2.9) | 19 (51.4) | 2 (5.4) |
| Thrombocytopenia | 25 (38.5) | 3 (4.6) | 2 (5.7) | 0 (0.0) | 3 (8.1) | 0 (0.0) |
| Elevated transaminase | 18 (27.7) | 3 (3.2) | 10 (28.6) | 3 (8.6) | 16 (43.2) | 0 (0.0) |
| Nausea and vomiting | 36 (55.4) | 8 (12.3) | 17 (48.6) | 2 (5.7) | 19 (51.4) | 1 (2.7) |
| Diarrhea | 14 (21.5) | 0 (0.0) | 7 (20.0) | 0 (0.0) | 11 (29.7) | 1 (2.7) |
| Febrile neutropenia | 4 (6.2) | 0 (0.0) | 1 (2.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Decrease in cardiac function | 4 (6.2) | 0 (0.0) | 2 (5.7) | 0 (0.0) | 5 (13.5) | 0 (0.0) |
| Fatigue | 27 (41.5) | 0 (0.0) | 15 (42.9) | 0 (0.0) | 21 (56.8) | 0 (0.0) |
| Hair loss | 28 (43.1) | 0 (0.0) | 12 (34.3) | 0 (0.0) | 18 (48.6) | 0 (0.0) |
| Rash | 7 (10.8) | 0 (0.0) | 2 (5.7) | 0 (0.0) | 1 (2.7) | 0 (0.0) |

TCbHP, carboplatin plus taxane in combination with pertuzumab and trastuzumab; THP, taxane in combination with trastuzumab and pertuzumab; AC-THP, a sequence of anthracycline plus cyclophosphamide followed by taxane plus pertuzumab and trastuzumab.

granulocyte colony-stimulating factor was widely used during the neoadjuvant therapy, neutropenia was observed in 61 patients (39.9%), including grade 3-4 neutropenia in 9 patients (5.9%) and febrile neutropenia in 5 patients (3.3%). A decrease in cardiac function was observed in 12 patients (7.8%). However, no case was associated with a greater than 10% decline in LVEF from baseline. No AE resulting in death was reported.

Among patients who received TcbHP, nausea and vomiting were the most common grade 3–4 AEs (8, 12.3%) followed by anemia (7, 10.8%) (*Table 5*). As the most common grade 3–4 toxicities in patients treated with THP,

© Annals of Translational Medicine. All rights reserved. 

grade 3–4 neutropenia and transaminitis both occurred in 3 patients (8.6%). The most common grade 3–4 AE among patients who received AC-THP was neutropenia (3, 8.1%) followed by anemia (2, 5.4%). Grade 3–4 thrombocytopenia occurred in 3 TcbHP-treated patients (4.6%), which was not observed in patients who received THP or AC-THP.

## Discussion

Only limited data have been available regarding the pCR rate obtained after neoadjuvant treatment with dual HER2 blockade in combination with chemotherapy in Chinese HER2-positive early-stage BC patients (24). Previous studies have found biological differences in the treatment sensitivity of BC patients in terms of race and ethnic origin (25-27), so we aimed to evaluate the efficacy and safety of neoadjuvant pertuzumab plus trastuzumab in combination with chemotherapy in Chinese patients with HER2-positive early or locally advanced BC. The pCR rate of our real-world study was 46.8% which is similar to that reported in previous clinical trials (39.3–68%) evaluating neoadjuvant pertuzumab plus trastuzumab dual anti-HER2 therapy in early or locally advanced HER2-positive BC (10,20,22,28). The pCR rate in this context was also concordant with other real-world studies of neoadjuvant treatment with double HER2 blockade in routine clinical regimens of HER2-positive early or LABC which confirmed the notable pCR benefit of neoadjuvant pertuzumab plus trastuzumab in previous randomized clinical trials (29-32).

In our study, univariate and multivariate analyses revealed that both HR-negative status and Ki-67 <15% were independent predictors of pCR in the HER2-positive population treated with neoadjuvant pertuzumab plus trastuzumab. The pCR rate of HR-negative patients was significantly higher than that of HR-positive patients, which has been found in previous randomized clinical trials such as NeoSphere and TRYPHAENA (10,20,21) and was confirmed in other real-world studies (33-35). The difference in pCR between the HR-negative and HR-positive groups could be explained by the cross-talking between ER and HER2 signaling pathways (36). We also found that Ki-67 <15% was associated with a higher pCR rate (68.2%) than Ki-67 ≥15% (44.0%). However, in a Hungarian real-world study, Boér *et al*. reported that among the HER2-positive patients treated with neoadjuvant pertuzumab plus trastuzumab, the group with the expression of Ki-67 ≥60% achieved a statistically higher pCR rate than those with Ki-67 <60% (31). This difference may be secondary to underpowering of both studies, with the Hungarian study only including 82 patients. A larger population will be needed to explore the relationship between the Ki-67 level and pCR rate in this context in the future.

There was no significant difference in the pCR rates among different neoadjuvant chemotherapy regimens such as with or without anthracycline treatment in the presence of dual anti-HER2 therapy, similar to previous clinical trials (20,28). The pCR rates were also not statistically correlated with neoadjuvant treatment cycles or neoadjuvant targeted therapy cycles in our study.

Untch *et al*. reported that the pCR rate was significantly higher in the albumin-bound paclitaxel group than in the solvent-based paclitaxel group for the neoadjuvant primary BC patients in a phase 3 randomized trial (37). Recently, a meta-analysis including 5 studies and 2,335 patients found that neoadjuvant therapy with albumin-bound paclitaxel was associated with a statistically higher pCR rate compared with conventional taxanes (38). In our study, the pCR rate of the albumin-bound paclitaxel group (61.1%) was higher than that of the conventional taxane group (43.3%) for HER2-positive early or LABC patients with neoadjuvant chemotherapy plus dual anti-HER2 therapy, though this was not statistically significant (P=0.056). The discrepancy between our result and previous studies might be due to a small sample size of the albumin-bound paclitaxel subgroup.

Neoadjuvant therapy enables some patients to become eligible for BCS. Boér *et al*. found the rate of BCS increased from 3.6% to 33% after neoadjuvant chemotherapy combined with trastuzumab and pertuzumab among patients with stage II and III HER2-positive BC (31). An Indian study reported a breast conservation rate as high as 51.1% for the patients treated with neoadjuvant pertuzumab plus trastuzumab in combination with chemotherapy though this was a small study involving 45 patients, and it included patients with oligometastatic disease (33). González-Santiago *et al*. noted 58.7% of patients undergoing BCS after neoadjuvant treatment with dual HER2 blockade for HER2-positive BC (34). The breast conservation rate in our study was 2.7%, even after neoadjuvant trastuzumab and pertuzumab plus chemotherapy, which was much lower than that of previous studies. This result might be due to multiple economic and social factors. First, to ensure adequate tumor resection with BCS, it is best to locate the tumor area with marker clips before neoadjuvant therapy. But during the study period, the marker clips were not available in Hunan province, so

© Annals of Translational Medicine. All rights reserved. 

most patients chose mastectomy. Second, standard of care involves the administration of radiation therapy for patients undergoing BCS. Therefore, some patients eligible for BCS may have preferred mastectomy in consideration of the cost of radiotherapy.

In terms of AEs, our study found neoadjuvant trastuzumab and pertuzumab combined with different chemotherapy regimens were generally well tolerated with no patient having to stop therapy due to AEs. Compared with TRYPHAENA trial and NeoSphere trial (10,20), there were no other new or unexpected safety signals. In our study, anemia was the most common AE yet most cases were mild to moderate and manageable, consistent with a Korean real-world study (32). The most common grade 3–4 AE was nausea and vomiting in our study, whereas, in other previous clinical trials, neutropenia and febrile neutropenia were the most frequently reported grade ≥3 toxicities (10,20). This could be due to the use of pegylated recombinant human granulocyte colony-stimulating factor in our study. Diarrhea was also reported as the most common AE in some other previous studies (10,20,34), yet the incidence of diarrhea in this study was only 22.2%. Although a mild mean declination in cardiac function was observed in 7.8% of patients in our study, no patients experienced serious cardiac dysfunction, this is consistent with the PEONY trial and NeoSphere trial. Our study confirmed the cardiac safety of neoadjuvant dual HER2 blockade plus chemotherapy in real-world BC patients.

Our study presented the largest cohort real-world data on evaluating the efficacy and safety of neoadjuvant pertuzumab plus trastuzumab in combination with chemotherapy in Chinese patients with HER2-positive early or LABC. We presented valuable clinical data about neoadjuvant dual HER2 blockade in Chinese patients. There are several limitations to this study. First, the study was a retrospective study with limited statistical power and partial toxicity data. Second, while the total sample size was sufficient for drawing conclusions about the population as a whole, some subgroups contained small numbers of patients. Finally, the follow up duration was inadequate to evaluate long-term outcome, specifically event-free and overall survival, and safety.

## Conclusions

In summary, our study confirmed the benefit of neoadjuvant pertuzumab plus trastuzumab in combination with chemotherapy on pCR with a tolerable safety profile in routine clinical practice in Chinese patients with HER2-positive BC. These data are consistent with those previously reported in well-controlled randomized trials. We also demonstrated that HR-negativity and Ki-67 <15% were positively associated with pCR in HER2-positive BC in this patient population treated with neoadjuvant dual HER2 blockade and chemotherapy.

## Acknowledgments

The authors appreciate the academic support from the AME Breast Cancer Collaborative Group.
*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6054/rc

*Data Sharing Statement:* Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6054/dss

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6054/coif). NZ received an honorarium as a speaker for a Roche event; the content was independently developed, without input from the sponsor. NZ also received a research grant from Roche. This was paid to the institution, and the sponsor did not have any input into the design, conduct, analysis or reporting of the research. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Clinical Research Ethics Board of Xiangya Second Hospital, Central South University (No. LYF2021182). In addition, all the relevant ethics committees approved the study. Written informed consent was provided by each participant for the use of their data.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons

© Annals of Translational Medicine. All rights reserved. 

Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

## References

1. Owens MA, Horten BC, Da Silva MM. HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. Clin Breast Cancer 2004;5:63-9.
2. Ross JS, Slodkowska EA, Symmans WF, et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 2009;14:320-68.
3. Yao M, Fu P. Advances in anti-HER2 therapy in metastatic breast cancer. Chin Clin Oncol 2018;7:27.
4. Gianni L, Dafni U, Gelber RD, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. Lancet Oncol 2011;12:236-44.
5. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365:1273-83.
6. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol 2014;32:3744-52.
7. Franklin MC, Carey KD, Vajdos FF, et al. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. Cancer Cell 2004;5:317-28.
8. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-19.
9. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 2015;372:724-34.
10. 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.
11. Petruolo O, Sevilimedu V, Montagna G, et al. How Often Does Modern Neoadjuvant Chemotherapy Downstage Patients to Breast-Conserving Surgery? Ann Surg Oncol 2021;28:287-94.
12. Shin HC, Han W, Moon HG, et al. Breast-conserving surgery after tumor downstaging by neoadjuvant chemotherapy is oncologically safe for stage III breast cancer patients. Ann Surg Oncol 2013;20:2582-9.
13. Cance WG, Carey LA, Calvo BF, et al. Long-term outcome of neoadjuvant therapy for locally advanced breast carcinoma: effective clinical downstaging allows breast preservation and predicts outstanding local control and survival. Ann Surg 2002;236:295-302; discussion 302-3.
14. Wuerstlein R, Harbeck N. Neoadjuvant Therapy for HER2-positive Breast Cancer. Rev Recent Clin Trials 2017;12:81-92.
15. 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;384:164-72.
16. Symmans WF, Wei C, Gould R, et al. Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype. J Clin Oncol 2017;35:1049-60.
17. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005;23:3676-85.
18. 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;375:377-84.
19. 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;15:640-7.
20. 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;24:2278-84.
21. Swain SM, Ewer MS, Viale G, et al. Pertuzumab,

© Annals of Translational Medicine. All rights reserved. 

trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol 2018;29:646-53.
22. 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.
23. Ogston KN, Miller ID, Payne S, et al. A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. Breast 2003;12:320-7.
24. Lv M, Guo H, Wang C, et al. Neoadjuvant docetaxel with or without carboplatin plus dual HER2 blockade for HER2-positive breast cancer: a retrospective multi-center Chinese study. Gland Surg 2020;9:2079-90.
25. Killelea BK, Yang VQ, Wang SY, et al. Racial Differences in the Use and Outcome of Neoadjuvant Chemotherapy for Breast Cancer: Results From the National Cancer Data Base. J Clin Oncol 2015;33:4267-76.
26. Tiwari SR, Mishra P, Dilawari A, et al., editors. Lower pathologic complete response rate with dual-HER2 blockage and chemotherapy in African Americans and ethnic minorities. Cancer Res 2020;80:abstr P2-10-10.
27. Zhao F, Steiner M, Ibraheem A, et al., editors. Racial disparities in pathological complete response among breast cancer patients receiving neoadjuvant chemotherapy. Cancer Res 2021;81:abstr SS1-06.
28. 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;19:1630-40.
29. Hall BJ, Bhojwani AA, Innes H, et al. Real-world evidence regarding the efficacy and toxicity of neoadjuvant trastuzumab and pertuzumab in the management of HER2-positive early-breast cancer. J Clin Oncol 2019;37:e12108.
30. Fasching PA, Hartkopf AD, Gass P, et al. Efficacy of neoadjuvant pertuzumab in addition to chemotherapy and trastuzumab in routine clinical treatment of patients with primary breast cancer: a multicentric analysis. Breast Cancer Res Treat 2019;173:319-28.
31. Boér K, Kahán Z, Landherr L, et al. Pathologic Complete Response Rates After Neoadjuvant Pertuzumab and Trastuzumab with Chemotherapy in Early Stage HER2-Positive Breast Cancer - Increasing Rates of Breast Conserving Surgery: A Real-World Experience. Pathol Oncol Res 2021;27:1609785.
32. Kim JY, Nam SJ, Lee JE, et al. Real World Evidence of Neoadjuvant Docetaxel/Carboplatin/Trastuzumab/Pertuzumab (TCHP) in Patients with HER2-Positive Early or Locally Advanced Breast Cancer: A Single-Institutional Clinical Experience. Cancer Res Treat 2022;54:1091-8.
33. Arora S, Gogia DA, Deo S, et al. Neoadjuvant pertuzumab plus trastuzumab in combination with anthracycline- free chemotherapy regimen in patients with HER2 positive breast cancer-Real-world data from a single center in India. Cancer Treat Res Commun 2021;29:100483.
34. González-Santiago S, Saura C, Ciruelos E, et al. Real-world effectiveness of dual HER2 blockade with pertuzumab and trastuzumab for neoadjuvant treatment of HER2-positive early breast cancer (The NEOPETRA Study). Breast Cancer Res Treat 2020;184:469-79.
35. Tiwari SR, Calhoun B, Abraham J, et al. Efficacy and safety of neoadjuvant docetaxel, carboplatin, trastuzumab/pertuzumab [TCH-P] in non-metastatic HER2+ breast cancer: The Cleveland Clinic experience. J Clin Oncol 2015;33:abstr 531.
36. Giuliano M, Trivedi MV, Schiff R. Bidirectional Crosstalk between the Estrogen Receptor and Human Epidermal Growth Factor Receptor 2 Signaling Pathways in Breast Cancer: Molecular Basis and Clinical Implications. Breast Care (Basel) 2013;8:256-62.
37. Untch M, Jackisch C, Schneeweiss A, et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. Lancet Oncol 2016;17:345-56.
38. Li Y, Lu X, Lin Q, et al. Is nab-paclitaxel better than conventional taxanes as neoadjuvant therapy for breast cancer? A meta-analysis. J Int Med Res 2020;48:300060520943473.

**Cite this article as:** Zhou M, Wang S, Wan N, Yuan S, Hu X, Zhou W, Qing B, Liu M, Sun W, Fan P, Wang J, Cao H, Xu H, Dai B, Tang P, Qian L, Zhao X, Xiao J, Zhou H, Hu J, Ding L, Tripodi D, Zdenkowski N, O'Keefe TJ, Sanchez AM, Chen L, Zhang P, Xu F. Efficacy and safety of neoadjuvant pertuzumab plus trastuzumab in combination with chemotherapy regimen in Chinese patients with HER2-positive early breast cancer: a real-world retrospective multi-center cohort study. Ann Transl Med 2022;10(24):1387. doi: 10.21037/atm-22-6054

© Annals of Translational Medicine. All rights reserved. 