Dual HER2 Blockade in Neoadjuvant Treatment of HER2+ Breast Cancer: A Meta-Analysis and Review

Chaokun Wang, MS1, Jing Chen, MS1, Xiangyun Xu, MS1, Xiaochen Hu, MS1, Dejiu Kong, MS1, Gaofeng Liang, MD2, and Xinshuai Wang, MD1

Abstract

Background: To investigate the pathologic complete response (pCR) rates of dual human epidermal growth factor receptor 2 (HER2) blockade in a neoadjuvant setting for HER2+ breast cancer. Methods: We searched randomized clinical trials (RCTs) using dual HER2 blockade in a neoadjuvant setting for HER2+ breast cancer in PubMed, the Cochrane Library, Embase and ClinicalTrials.gov up to July 5, 2020, and all included studies were assessed according to the Cochrane Collaboration tool for assessing the risk of bias of RCTs, and the statistical analyses were performed using STATA 14.0 software. Results: A total of 9 RCTs involving 2758 patients were included. Meta-analysis indicated that the pCR rates of lapatinib/pertuzumab/neratinib plus trastuzumab versus trastuzumab [relative risk (RR) = 1.31; 95% confidence interval (CI): 1.21-1.43; p < 0.001] and lapatinib plus trastuzumab versus lapatinib (RR = 1.39; 95%CI: 1.25-1.53; p < 0.001) showed a significant statistical difference between dual HER2-blockade treatment and single-agent treatment in a neoadjuvant setting for HER2+ breast cancer. Additionally, there was no statistically significant difference in disease-free survival (HR = 0.72; 95% CI: 0.47-1.09; p = 0.123), incidence of serious adverse events (SAEs) (RR = 1.04; 95%CI: 0.81-1.33; p = 0.778) and cardiotoxicity(RR = 1.30; 95%CI: 0.81-2.08; p = 0.280), and the pCR rate was unaffected by hormone receptor status. Conclusions: The pCR rate of neoadjuvant dual-target therapy for HER2+ breast cancer was significantly higher than that of single-target therapy. Furthermore, the results indicated that the safety of dual-target therapy is similar to that of single-target therapy.

Keywords
breast cancer, neoadjuvant, trastuzumab, lapatinib, pertuzumab, meta-analysis

Abbreviations
(DFS), disease-free survival; (HER2), human epidermal growth factor receptor 2; (pCR), pathologic complete response; (RCTs), randomized clinical trials; (SAEs), serious adverse events.

Introduction

Breast cancer is the most common malignant tumor in women worldwide, with 24 million new patients and 523,000 deaths annually.1 Approximately 15% to 20% of breast cancers exhibit upregulated levels of HER22 (referred to as HER2+ breast cancer), a 185-kDa tyrosine kinase transmembrane receptor encoded by a gene located on chromosome 17q12-21.32. HER2 overexpression results in a highly invasive tumor and worse prognosis without appropriate treatment. For primary resectable HER2+ breast cancer, neoadjuvant anti-HER2 therapy has become a routine treatment,3 with trastuzumab representing the first targeted

1 Henan Key Laboratory of Cancer Epigenetics, Cancer hospital, The First Affiliated Hospital, College of Clinical Medicine, Medical College of Henan University of Science and Technology, Luoyang, China
2 Medical College, Henan University of Science and Technology, Luoyang, China

Corresponding Author:
Xinshuai Wang, Henan Key Laboratory of Cancer Epigenetics, Cancer hospital, The First Affiliated Hospital, College of Clinical Medicine, Medical College of Henan University of Science and Technology, Luoyang 471003, China. Email: xshuaiw@126.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
Materials and Methods

Search Strategy
We searched PubMed, the Cochrane Library, Embase and ClinicalTrials.gov up to July 5, 2020, using subject headings and random words. The search strategy included the following terms: breast cancer, receptor ErbB-2, trastuzumab, lapatinib, pertuzumab, neratinib and neoadjuvant chemotherapy. The search terms were linked with “AND” or “OR” respectively and followed the Cochrane Handbook by using a combination of subject terms and free words, with searches of the literature included.

Study Inclusion/Exclusion Criteria
Studies needed to meet the following inclusion criteria to be eligible for the meta-analysis: 1) randomized clinical trials; 2) studies of HER2+ breast cancer and neoadjuvant dual-blockade anti-HER2 therapy; 3) involvement of at least 2 treatment options; 4) inclusion of data related to pathologic complete response, progression-free survival, disease-free survival (DFS), overall survival, and safety. Exclusion criteria for literature included the following: 1) similar studies were repeatedly published; 2) studies did not include neoadjuvant therapy; 3) corresponding data could not be obtained directly or indirectly; 4) review articles, case reports, comments, or letters.

Quality Assessment
The quality of the literature was evaluated using the Cochrane bias risk-assessment tool, including use of the random-allocation method, allocation scheme hiding, the blind method, and assessment of the integrity of results data, selective report research results, and other sources of bias. Two investigators (Chaokun Wang, Jing Chen) independently assessed quality, and in the event of disagreement, decisions were made based on discussions or evaluation by a third investigator.

Results

Included Studies
We selected a total of 805 articles databases through systematic searches and screening, initially identifying 697 articles after remove duplicates, with 78 articles identified by study titles and abstracts. Eight of these studies were reviews, with 53 articles not meeting the inclusion criteria. Seventeen articles13-29 were obtained following a review of the entire text, with one representing a meeting abstract (TRIO-US B07)13 and the remaining RCTs. Through detailed reading, it was found that 6 literatures had the same study population, so they were excluded. A total of 1113,15-19,23,26-29 papers were included in the study. The detailed process is shown in Figure 1.

Study Characteristics and Quality Assessment
Of the 11 articles included, the NeoALTTO study included 4 articles, of which the pCR rate was mainly reported in 2012, others studies mainly reported long-term survival, adverse events and secondary analysis, which were determined as different populations. Among the remaining 10 articles, the NBRST, NeoSphere and PEONY studies reported the results of pertuzumab plus trastuzumab dual HER2-blockade therapy versus single-targeted therapy. The NSABP FB-7 study reported the results of neratinib plus trastuzumab versus trastuzumab single-targeted therapy, and the remaining 7 studies involved lapatinib plus trastuzumab therapy single-target dual HER2-blockade therapy as compared with single-targeted therapy. Information regarding the included studies is shown in Table 1. Quality evaluation was performed according to the PRISMA scale. Because the TRIO-US B07 abstract was a
Figure 1. Flowchart describing study selection for the meta-analysis.

Table 1. Characteristics of the Studies Used for Meta-Analysis.

| Trial          | Phase | Chemotherapy | Clinical stage | HER2 therapy | n   | HR+  | HR−  | tpCR (%) | pCR (%) |
|----------------|-------|--------------|----------------|--------------|-----|------|------|----------|---------|
| NBRST          | NA    | NA           | T1-4           | H            | 178 | 111  | 67   | 72(40.4%) | 33(29.7%) |
|                |       |              |                | H+P          | 119 | 73   | 46   | 68(57.1%) | 35(48%)  |
| NeoALTTO       | III   | Paclitaxel   | T2-4           | H            | 149 | 75   | 74   | 44(29.53%)| 17(22.67%)| 27(36.49%)|
|                |       |              |                | L            | 154 | 80   | 74   | 38(24.68%)| 13(16.25%)| 25(33.78%)|
|                |       |              |                | L+H          | 152 | 77   | 75   | 78(51.31%)| 32(41.56%)| 46(61.33%)|
| NeoSphere      | II    | Docetaxel    | T2-4           | P            | 96  | 46   | 50   | 31(29%)   | 10(20%)  | 21(36.8%) |
|                |       |              |                | H+P          | 107 | 50   | 57   | 45(45.8%) | 13(26%)  | 36(63.2%) |
|                |       |              |                | L+P          | 119 | 73   | 46   | 68(57.1%) | 35(48%)  | 33(71.7%) |
|                |       |              |                | L+H          | 152 | 77   | 75   | 78(51.31%)| 32(41.56%)| 46(61.33%)|
| NSABP B-41     | III   | AC, Paclitaxel| IIA-IIIA       | H            | 177 | 122  | 55   | 93(52.5%) | 57(46.7%)| 36(65%)   |
|                |       |              |                | L            | 171 | 100  | 71   | 91(53.2%) | 48(48%)  | 43(60.6%) |
|                |       |              |                | L+H          | 171 | 108  | 63   | 106(62.0%)| 60(55.6%)| 46(73%)   |
| TRIO US B07    | II    | DC           | I-III          | H            | 30  | NA   | NA   | 13(43%)   | 10(33%)  | 17(58%)   |
|                |       |              |                | L            | 28  | NA   | NA   | 7(25%)    | 4(13%)   | 12(42%)   |
|                |       |              |                | L+H          | 48  | NA   | NA   | 25(52%)   | 20(41%)  | 32(68%)   |
| CHER-LOB       | II    | Paclitaxel→FEC| II-III         | H            | 36  | 21   | 15   | 9(25%)    | 5(23.8%) | 41(26.6%)|
|                |       |              |                | L            | 39  | 24   | 15   | 10(26.3%) | 5(20.8%) | 5(38.4%) |
|                |       |              |                | H+L          | 46  | 28   | 18   | 21(46.7%)| 10(35.7%)| 10(58.8%) |
| ICORG 10-05    | II    | DC           | IIA-IIIC       | H            | 36  | NA   | NA   | 19(52.8%) | NA       | NA        |
|                |       |              |                | L            | 10  | NA   | NA   | 2(20%)    | NA       | NA        |
|                |       |              |                | H+L          | 33  | NA   | NA   | 17(51.5%) | NA       | NA        |
| EORTC10054     | IIb   | DC→FEC      | IIA-IIIC       | H            | 52  | 27   | 25   | 27(52%)   | 14(52%)  | 13(52%)   |
|                |       |              |                | L            | 22  | 14   | 8    | 8(36%)    | 6(43%)   | 2(25%)   |
| CALGB 40601    | I/II  | Paclitaxel  | II-III         | H            | 117 | 69   | 45   | 54(46%)   | 28(14%)  | 26(54%)   |
|                |       |              |                | L            | 62  | 35   | 25   | 20(32%)   | 10(20%)  | 10(37%)   |
|                |       |              |                | H+L          | 116 | 68   | 47   | 65(56%)   | 28(41%)  | 37(79%)   |
| NSABP FB-7     | II    | Paclitaxel→AC| IIB-IIIC       | H            | 41  | 27   | 14   | 16(39%)   | 8(29.6)  | 8(57.1%)  |
|                |       |              |                | N            | 42  | 29   | 13   | 14(33.3%) | 8(27.6)  | 6(46.2%)  |
|                |       |              |                | H+N          | 42  | 23   | 19   | 21(50%)   | 7(30.4)  | 14(73.7%)|
| PEONY          | III   | Docetaxel   | T2-T4          | H            | 110 | 56   | 54   | 24(21.8%) | 14(25%)  | 10(18.5%) |
|                |       |              |                | H+P          | 219 | 117  | 102  | 86(39.3%) | 39(33.3%)| 47(46%)   |

Abbreviations: DC: Docetaxel-Carboplatin; AC: Doxorubicin-Cyclophosphamide; FEC: Fluorouracil-Epirubicin-Cyclophosphamide; H, trastuzumab; L, lapatinib; P, pertuzumab; N, neratinib; HR+, hormone receptor positive; HR−, hormone receptor negative; pCR, pathologic complete response; tpCR, total pathologic complete response; DFS, disease-free survival; NA, not available; SAE, serious adverse events.
summary of the meeting, bias evaluation was uncertain, whereas the results for the remaining studies indicated high-quality studies with low bias. The detailed evaluation results are shown in Figure 2.

**PCR After Different Anti-HER2 Therapy**

The pCR results for lapatinib, pertuzumab or neratinib combined with trastuzumab as compared with trastuzumab alone are shown in Figure 3. The results indicated that the RR value of the pCR of dual HER2-blockade therapy was 1.31 (95% confidence interval: 1.21-1.43; p < 0.001), which differed significantly from that of single-agent treatment.

The RR for pCR in the lapatinib combined with trastuzumab group relative to the lapatinib group was 1.39 (95% CI: 1.25-1.53; p < 0.001), which differed significantly from that of single-agent treatment (Figure 4).

**Hazard Rates for DFS**

Figure 5 shows the DFS results of lapatinib or pertuzumab combined with trastuzumab treatment as compared with trastuzumab treatment alone. The results suggested that the hazard ratio (HR) for DFS following dual HER2-blockade treatment was 0.72 (95% CI: 0.47-1.09; p = 0.123) as compared with that of trastuzumab treatment alone.

**Analysis of Adverse Events**

The forest plot of SAE outcomes for lapatinib or pertuzumab combined with trastuzumab dual-targeted therapy as compared with trastuzumab alone is shown in Figure 6A. The results showed that SAE incidence and resistance to treatment following dual targeted therapy had an RR value of 1.04 (95% CI: 0.81-1.33; p = 0.778). Figure 6B shows the forest plot for cardiotoxicity related to lapatinib or pertuzumab combined with trastuzumab treatment as compared with trastuzumab treatment alone. Due to the heterogeneity of the 6 included literatures (I² = 65.1%, p = 0.014), the random effect model was adopted for analysis. The results showed an RR value for dual HER2-blockade therapy plus trastuzumab treatment of 1.30 (95% CI: 0.81-2.08; p = 0.280).

**Subgroup Analysis**

To clarify differences of pCR between targeted therapies involving lapatinib, pertuzumab or neratinib combined with trastuzumab and trastuzumab alone, we performed subgroup analysis between treatment groups (lapatinib + trastuzumab, pertuzumab + trastuzumab). The results showed that compared with trastuzumab treatment alone, the RR for dual HER2-blockade treatment of pCR with lapatinib was 1.30 (95% CI: 1.28-1.14; p < 0.001), whereas that with pertuzumab was 1.37 (95% CI: 1.21-1.55; p = 0.001) (Figure 7A). Additionally, we performed subgroup analysis to clarify the relationship between hormone receptor (HR) status and therapeutic effect, finding that HR+ status resulted in an RR value for pCR treatment using dual HER2-blockade therapy relative to trastuzumab treatment alone of 1.23 (95% CI: 1.09-1.38; p = 0.001), whereas in cases of HR- status, the RR value was 1.53 (95% CI: 1.34-1.76; p < 0.001). Similarly, for pCR treated with dual HER2-blockade therapy as compared with lapatinib treatment alone, HR+ status returned an RR value of 1.28 (95% CI: 1.11-1.49; p < 0.001), whereas that for HR- status was 1.65 (95% CI: 1.35-2.02; p = 0.001) (Figure 7B, C).

**Publication Bias**

To assess the publication bias in this meta-analysis, as shown in Figure 8, evaluation of publication bias revealed no significant publication bias among the included studies (p = 0.404).
Figure 3. Forest plots of RR for dual block versus single-agent trastuzumab in HER2+ breast cancer women in the neoadjuvant.

Figure 4. Forest plots of RR for dual blockade versus single-agent lapatinib treatment in HER2+ breast cancer patients receiving neoadjuvant therapy.
Discussion

HER2 is a tyrosine kinase transmembrane receptor and an important marker of tumor invasion and poor prognosis. As a therapeutic target, its status affects breast cancer classification, risk assessment, and treatment strategies. Moreover, as a tyrosine kinase receptor, HER2/HER1 [also known as epidermal growth factor receptor (EGFR)] and HER3/HER4 can form dimers to play a key role in activating intracellular signaling pathways associated with breast cancer progression. Trastuzumab inhibits the cleavage of HER2 and specifically binds to the extracellular segment, thereby blocking the formation of HER2 homologous dimers, whereas pertuzumab prevents the formation of HER2/HER3 dimers by anchoring to HER2 domain two. The characteristics of different targets of these 2 drugs provide a complementary mechanism for dual-target therapy. Unlike trastuzumab, as a small-molecule EGFR tyrosine kinase inhibitor, lapatinib blocks ligand-induced heterodimeric signaling. These characteristics provide a molecular basis for dual HER2-blockade therapy. Numerous studies have focused on dual HER2-blockade therapy, however, their results are inconsistent, especially in aspects of long-term survival and adverse drug reactions. Therefore, in the present study, we systematically searched and screened high-quality studies to evaluate the therapeutic effects, long-term survival status, and adverse reactions associated with dual HER2-blockade therapy relative to single-target therapy in neoadjuvant settings of breast cancer.

This meta-analysis suggested dual anti-HER2 therapy can improve the pCR rate in neoadjuvant chemotherapy for HER2+ breast cancer. However, in terms of long-term survival, there was no statistically significant difference in DFS (HR = 0.72; 95% CI: 0.47-1.09; p = 0.123), since in many of these included studies the primary outcome was pCR rate, survival analysis was not the main objective. Further investigations are needed to determine whether dual HER2 blockade therapy can improve long-term survival benefits.

Of the 11 included studies, one was an abstract from the TRIO-US B07 meeting, and the rest were reports from high-quality RCTs. Subgroup analysis of combined-drug therapies revealed that compared with trastuzumab treatment alone, combined therapy with lapatinib or pertuzumab increased the pCR rate by 28% and 37%, respectively, suggesting that combined treatment with pertuzumab might be efficacious than that with lapatinib. However, this result was not statistically significant; therefore, further studies is needed.

Another key factor effecting clinical treatment strategies is the HR status. In clinical studies, it has been demonstrated that HR+ breast cancer patients are more likely to benefit from dual HER2 blockade therapy. However, our findings are inconsistent with previous research, our results suggested that hormone receptor status and dual HER2 blockade therapy had no significant effect on the outcome. Many neoadjuvant clinical trials have demonstrated that dual HER2 blockade (trastuzumab plus neratinib, trastuzumab plus lapatinib, trastuzumab plus pertuzumab) increase the pathologic complete response rate. Nevertheless, the efficacy of different trials was not consistent. The reasons may comprise differences in pathologic complete response definition, tumor size, duration of anti-HER2 treatment, standard chemotherapy protocols and HR status. The percentage of HR+ patients varied in different trials, which may have affected the pathologic complete response rate.
For instance, the percentage of HR+ and HR− patients in the NeoALTTO19 and NeoSphere23 trials were equivalent, however, in the CHER-LOB,14 NSABP-B41,26 and CALGB-4060127 trials, more than 60% of patients were HR+. Furthermore, several studies have shown intratumoral heterogeneity was observed in HER2+ breast cancer, which can also affect the therapeutic efficacy of anti-HER2 and biologic characteristics of cancer.36 These neoadjuvant trials have demonstrated the efficacy of dual HER2 blockade in HER2+ breast cancer. Previous studies showed that compared with single HER2 blockade, the pCR rate of dual HER2 blockade was statistically significantly improved in the range from 16% to 19%, which was not related to chemotherapy regimen.37 This finding is consistent individual researches, regardless of the type of anti-HER2 treatment and chemotherapy, the pCR rate in the HR− subgroup was significantly increased.14,19,23,26,27

In terms of safety, SAE incidence and cardiotoxicity following dual HER2-blockade therapy were 1.04 (95%CI: 0.81-1.33; p = 0.778) and 1.30 (95%CI: 0.81-2.08; p = 0.280), respectively, as compared with trastuzumab treatment alone,
indicating that dual HER2-blockade therapy does not increase SAE incidence or cardiotoxicity relative to single-agent treatment, which increases our confidence in using dual-targeted therapy.

Here, we analyzed outcome indicators, including reported therapeutic effects, long-term survival, and adverse reactions, and found that dual HER2-blockade therapy is superior to trastuzumab or lapatinib single-agent therapy. However, this meta-analysis has several limitations. First, the number of studies included was relatively small, with one representing a summary of a meeting and only 2 related to dual HER2-blockade therapy involving trastuzumab. Moreover, the RCTs outlined in the included studies are still in progress, and follow-up reports will be used in future analyses.

Conclusions

In summary, this meta-analysis suggested that dual-target therapy can improve pCR rates relative to trastuzumab or lapatinib single-target therapy, with safety similar to that of single-agent therapy.

Authors’ Note

This is a meta-analysis, the data source has published articles, so no ethical approval is required.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Xinshuai Wang https://orcid.org/0000-0002-9024-170X

References

1. Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer
groups, 1990 to 2015: a systematic analysis for the global burden of disease study. *JAMA Oncol.* 2017;3(4):524-548.

2. Krishnamurti U, Silverman JF. HER2 in breast cancer: a review and update. *Adv Anat Pathol.* 2014;21(2):100-107.

3. Chia SK. Neoadjuvant and adjuvant therapy for HER2 positive disease. *Am Soc Clin Oncol Educ Book.* 2015:e41-48.

4. Butterbaugh ST, Patel R, Romond EH, Mathew A. Trastuzumab use in patients with durable complete response in HER2-amplified metastatic breast cancer: to continue or not to continue. *Ann Oncol.* 2017;28(12):3098-3099.

5. Austin CD, De Maziere AM, Pisacane PI, et al. Endocytosis and sorting of ErbB2 and the site of action of cancer therapeutics trastuzumab and geldanamycin. *Mole Biol Cell.* 2004;15(12):5268-5282.

6. Bachman KE, Argani P, Samuels Y, et al. The PIK3CA gene is mutated with high frequency in human breast cancers. *Cancer Biol Theryp.* 2004;3(8):772-775.

7. Nahta R, Takahashi T, Ueno NT, Hung MC, Esteva FJ. P27(kip1) down-regulation is associated with trastuzumab resistance in breast cancer cells. *Cancer Res.* 2004;64(11):3981-3986.

8. Diermeier S, Horvath G, Knuechel-Clarke R, Hofstaedter F, Szollosi J, Brockhoff G. Epidermal growth factor receptor coexpression modulates susceptibility to Herceptin in HER2/neu overexpressing breast cancer cells via specific erb-receptor interaction and activation. *Exp Cell Res.* 2005;304(2):604-619.

9. Gallardo A, Lerma E, Escuin D, et al. Increased signalling of EGFR and IGF1R, and deregulation of PTEN/Pi3K/Akt pathway are related with trastuzumab resistance in HER2 breast carcinomas. *British J Cancer.* 2012;106(8):1367-1373.

10. Lu Y, Zi X, Zhao Y, Mascarenhas D, Pollak M. Insulin-like growth factor-I receptor signaling and resistance to trastuzumab (Herceptin). *J National Cancer Institute.* 2001;93(24):1852-1857.

11. Nagy P, Friedlander E, Tanner M, et al. Decreased accessibility and lack of activation of ErbB2 in JIMT-1, a herceptin-resistant, MUC4-expressing breast cancer cell line. *Cancer Res.* 2005;65(2):473-482.

12. Fan R, Chiu CY, Jung J, et al. A comparison study of fixed and mixed effect models for gene level association studies of complex traits. *Gene Epidemiol.* 2016;40(8):702-721.

13. Hurvitz SA, Miller JM, Dickmann R, et al. Abstract S1-02: Final analysis of a phase II 3-arm randomized trial of neoadjuvant trastuzumab or lapatinib or the combination of trastuzumab and lapatinib, followed by six cycles of docetaxel and carboplatin with trastuzumab and/or lapatinib in patients with HER2+ breast cancer (TRIO-US B07). *Cancer Res.* 2014;73:S1-02.

14. 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(16):1989-1995.

15. Guarneri V, Dieci MV, Frassoldati A, et al. Prospective biomarker analysis of the randomized CHER-LOB study evaluating the dual anti-HER2 treatment with trastuzumab and lapatinib plus chemotherapy as neoadjuvant therapy for HER2-positive breast cancer. *Oncologist.* 2015;20(9):1001-1010.

16. 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(2):325-332.

17. Toomey S, Eustace AJ, Fay J, et al. Impact of somatic PI3 K pathway and ERBB family mutations on pathological complete response (pCR) in HER2-positive breast cancer patients who received neoadjuvant HER2-targeted therapies. *Breast Cancer Res.* 2017;19(1):87.

18. Beitsch P, Whitworth P, Baron P, et al. Pertuzumab/Trastuzumab/ CT Versus Trastuzumab/CT therapy for HER2+ breast cancer: results from the prospective neoadjuvant breast registry symphony trial (NBRST). *Ann Surg Oncol.* 2017;24(9):2539-2546.

19. Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet (London, England).* 2012;379(9816):633-640.

20. de Azambuja E, Holmes AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol.* 2014;15(10):1137-1146.

21. Salgado R, Denkert C, Campbell C, et al. Tumor-infiltrating lymphocytes and associations with pathological complete response and event-free survival in HER2-positive early-stage breast cancer treated with lapatinib and trastuzumab: a secondary analysis of the Neo ALTO trial. *JAMA Oncol.* 2015;1(4):448-454.

22. Scarlitti M, Nuciforo P, Bradbury I, et al. High HER2 expression correlates with response to the combination of lapatinib and trastuzumab. *Clin Cancer Res.* 2015;21(3):569-576.

23. 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(1):25-32.

24. 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(6):791-800.

25. Bianchini G, Kiermaier A, Bianchi GV, et al. Biomarker analysis of the neo sphere study: pertuzumab, trastuzumab, and docetaxel versus trastuzumab plus docetaxel, pertuzumab plus trastuzumab, or pertuzumab plus docetaxel for the neoadjuvant treatment of HER2-positive breast cancer. *Breast Cancer Res.* 2017;19(1):16.

26. Robidoux A, Tang G, Rastogi P, et al. Lapatinib for HER2-positive operable breast cancer (safety and tolerability): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2013;14(12):1183-1192.

27. Carey LA, Berry DA, Cirrincione CT, et al. Molecular heterogeneity: an area ripe for oncological research and development. *Lancet Oncol.* 2017;18(S1):16.
28. 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(1):133.

29. 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*. 2019;6(3):e193692.

30. Radenkovic S, Konjevic G, Isakovic A, Stevanovic P, Gopcevic K, Jurisic V. HER2-positive breast cancer patients: correlation between mammographic and pathological findings. *Radiat Prot Dose*. 2014;162(1-2):125-128.

31. Montemurro F, Valabrega G, Aglietta M. Lapatinib: a dual inhibitor of EGFR and HER2 tyrosine kinase activity. *Exp Opin Biol Therap*. 2007;7(2):257-268.

32. 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.

33. 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.

34. Advani P, Cornell L, Chumsri S, Moreno-Aspitia A. Dual HER2 blockade in the neoadjuvant and adjuvant treatment of HER2-positive breast cancer. *Breast Cancer (Dove Med Press)*. 2015;7:321-335.

35. 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(18):4594-4603.

36. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature*. 2012;490(7418):61-70.

37. Bria E, Carbognin L, Furlanetto J, et al. Impact of neoadjuvant single or dual HER2 inhibition and chemotherapy backbone upon pathological complete response in operable and locally advanced breast cancer: sensitivity analysis of randomized trials. *Cancer Treat Rev*. 2014;40(7):847-856.