Article published online: 2026-01-09

Original Article

Assessment of Response to Neoadjuvant Chemotherapy with Single and Dual HER2 Blockade in HER2-Positive Breast Cancers: A Single-Center Experience

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Ind J Med Paediatr Oncol

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Abstract

Introduction Breast cancer remains the leading cause of morbidity and mortality among women and has now become a molecular spectrum rather than a single disease. The human epidermal growth factor receptor 2 (HER2) overexpressing subtype is a rather aggressive form of breast cancer, and its prognosis is improving at a faster pace in recent times with the advent of multiple strategies with targeted agents.

Objectives In this study, we planned to compare dual and single HER2 blockades—docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) and trastuzumab, docetaxel, and carboplatin (TCH)—in the neoadjuvant setting and compare the pathological complete response rates for each protocol, and to assess the toxic effect profile of the regimens.

Materials and Methods We enrolled 30 patients randomized in a 1:2 fashion to TCHP ($n = 9$) and TCH ($n = 21$). The patients' age, tumor staging, and N staging were well matched.

Results The completion rates of neoadjuvant therapy were 100% in the TCHP arm and 90% in the TCH arm. Breast conservation surgery rates were 22.2 and 5%, respectively, in the TCHP and TCH arms. The pathological complete response rate was 66.7% (6/9; 95% confidence interval [CI]: 29.9–92.5) in the TCHP arm compared with 15.8% (3/19; 95% CI: 3.4–39.6) in the TCH arm, with an absolute difference of 50.9% (95% CI: 12.8–74.5). No grade 3 or higher treatment-related adverse events were observed.

Conclusion With no added grade 3 adverse events documented in the TCHP arm, we concluded that the addition of pertuzumab would serve as a valuable strategy in the HER2+ subset in the neoadjuvant setting in the population of South Indian origin.

Keywords
- NACT
- HER2+
- breast cancer
- trastuzumab
- pertuzumab
- dual blockade

Introduction

Breast cancer is a molecularly heterogeneous disease comprising various molecular subtypes, each having a disparate natural history and response to therapy. One of the subtypes, defined by the overexpression or amplification of the human epidermal growth factor receptor 2 (HER2) oncogene, is seen in approximately 15% of all breast cancer patients in the West, while the prevalence has been twice as high in the Indian subcontinent.[1]

DOI https://doi.org/10.1055/s-0045-1815709.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Historically, HER2 gene amplification has been associated with an aggressive disease course, early relapse, and increased mortality, and was considered an unfavorable subtype until the advent of HER2-targeted therapies.[2] This incorporation of HER2-targeted agents in (neo)adjuvant treatment of this subset has improved the outcomes significantly.

In patients with locally advanced breast cancer (LABC), neoadjuvant chemotherapy (NACT) helps downstage locally advanced tumors, increasing the feasibility of breast conservation surgery (BCS). Responsiveness of tumor to chemotherapy and achievement of pathological complete response (pCR; no residual viable tumor in the breast or lymph nodes; ypT0/is, ypN0) in the surgical specimen after NACT are known to have better event-free survival (EFS) and overall survival (OS).[3]

However, there are reported racial and ethnic variations in response to NACT, with some ethnic minorities demonstrating significantly lower pCR rates, especially in patients with HER2-positive and triple-negative tumors.[4,5] In the population of Indian origin, there is a paucity of data regarding NACT with dual HER2 blockade—both in trials and in real-world settings. In addition, most of the patients in resource-constrained settings are treated with a single blockade as opposed to the current standard of care, the dual HER2 blockade. Hence, we conducted this study to evaluate and compare the safety and efficacy of the TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab) and TCH (trastuzumab, docetaxel, carboplatin) chemotherapy regimens for patients with early, locally advanced HER2-positive breast cancer in the neoadjuvant setting to estimate the magnitude of benefit offered by dual blockade over single blockade in a real-world setting.

Materials and Methods

Study Design and Patients

The study was designed to be an open-label, prospective, randomized trial conducted in the Department of Medical Oncology, Tirunelveli Medical College, during the period from 2023 to 2025. The study population comprised those who fulfilled the eligibility criteria.

Inclusion Criteria

All women aged $\geq$18 years with early and locally advanced HER2-positive breast cancer (defined as HER2 3+ by immunohistochemistry [IHC] or HER2 2+ by IHC with validated dual probe fluorescence in situ hybridization [FISH] positivity as per the American Society of Clinical Oncology/College of American Pathologists [ASCO/CAP] guidelines), with clinical stage $\geq cT_2$ and $\geq cN_1$, Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$2, left ventricular ejection fraction (LVEF) $\geq$55%, and oligometastatic stage 4 disease planned in curative intent as assessed clinically were included in the study. Both hormone receptor–positive (HR+) and hormone receptor–negative patients were enrolled in the study.

Exclusion Criteria

Patients with extensive in situ disease in which the extent of invasive component could not be clearly defined, those with tumors that were not clinically palpable, those with metastatic breast cancer in whom curative intent of therapy could not be planned due to disease extent, those who had received pretreatment with any other neoadjuvant therapy, those unwilling to participate in the study, those with decompensated cardiac disease, those with impaired organ function, and those who were pregnant were excluded from the study.

Primary and Secondary Endpoints

The primary endpoint of the study was the achievement of pCR as defined by the absence of residual invasive or in situ tumor cells in the primary tumor in the breast or in the axillary lymph nodes. Secondary endpoints were median time to response and assessment of toxicity profile.

Procedures

Patients who fulfilled the key eligibility criteria were enrolled in the study and were randomly assigned (2:1) to one of the two study arms—trastuzumab plus docetaxel plus carboplatin (TCH) and trastuzumab plus pertuzumab plus docetaxel plus carboplatin (TCHP). Neoadjuvant cycles were administered at intervals of every 3 weeks with granulocyte colony-stimulating factor support. Trastuzumab was dosed at 8 mg/kg in cycle 1 and at 6 mg/kg from cycle 2; pertuzumab was dosed at 840 mg in cycle 1 and at 420 mg from cycle 2; docetaxel was dosed at 75 mg/m^2 and carboplatin was dosed at area under the curve (AUC) of 6 based on estimated glomerular filtration rate (eGFR) estimated by the modification of diet in renal disease (MDRD) formula. Baseline imaging for metastatic workup was done using contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis, together with bone scan or by positron emission tomography (PET) CT, as per the clinician's discretion.

Tumor response assessment by clinical examination was done before the administration of every cycle. Blood counts and renal and liver function were monitored before every cycle of chemotherapy. Any adverse event of grade 3 or higher by common terminology for criteria for adverse effects (CTCAE) was reported. Monitoring of cardiac function with LVEF was performed by two-dimensional echocardiography every three cycles.

A total of six neoadjuvant cycles were administered during the study, and at the completion of neoadjuvant therapy, those with a favorable response were subjected to the standard of care treatment with modified radical mastectomy (MRM) or BCS. The surgical specimen was examined microscopically for the absence of neoplastic cells, and the results were taken into the study and statistical analysis was performed.

Statistical Analysis

Statistical analysis was performed using standard statistical software (SPSS version 20). Continuous variables were expressed as median with range or mean $\pm$ standard deviation, as appropriate. Categorical variables were summarized as frequencies and percentages. Baseline clinicopathological characteristics between the two treatment arms were compared using the chi-squared test or Fisher's exact test for

categorical variables and the independent samples *t*-test or Mann–Whitney *U* test for continuous variables, as applicable. The primary endpoint, pCR, was compared between the TCHP and TCH arms using Fisher's exact test. Secondary endpoints, including BCS rates, treatment completion rates, nodal downstaging rates, and toxicity profiles, were analyzed using descriptive statistics and compared between groups using Fisher's exact test. The median time to clinical response and median time to complete clinical response were compared between treatment arms using the Mann–Whitney *U* test. Subgroup analyses were performed based on hormone receptor status to evaluate differences in pCR rates.

Ethical Approval

The study was undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all the enrolled patients. The study was approved by the Tirunelveli Medical College Institutional Research Ethics Committee (Protocol ID: 20242869; Approval date: February 2, 2024).

Results

Patients were enrolled for the trial from the Department of Medical Oncology, Tirunelveli Medical College, from 2023 to 2025. After screening, 30 eligible patients with HER2+ breast cancer were enrolled into the trial. Nine patients were randomized to receive NACT with dual HER2 blockade consisting of docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) and 21 patients were randomized to receive neoadjuvant therapy with single HER2 blockade consisting of docetaxel, carboplatin, and trastuzumab (TCH). The enrolled patients were planned to receive six cycles of NACT, and the consort diagram has been provided in ►**Fig. 1**.

In the TCHP arm, 100% of the patients enrolled completed all six cycles of planned neoadjuvant therapy. In the TCH arm, of the 21 patients enrolled, 19 patients (90%) completed the planned neoadjuvant cycles. One patient developed acute fulminant liver failure due to Hepatitis B viral re (HBsAg) CONSORT Diagram activation and expired after two cycles of TCH, while one patient dropped out.

Baseline patient demographics are summarized in ►**Table 1**.

The median age was 51 years (18–62 years) in the TCHP arm and 55 years (44–75 years) in the TCH arm. Most of the women in the TCHP arm were premenopausal (66.6%), while most women in the TCH arm were postmenopausal (84.2%). The hormone receptor–positive subgroup was 66.6% in the TCHP arm and 36.8% in the TCH arm. The clinical stages of the enrolled patients were well matched, with 55.5% of T4 disease in the TCHP arm and 63.1% of T4 disease in the

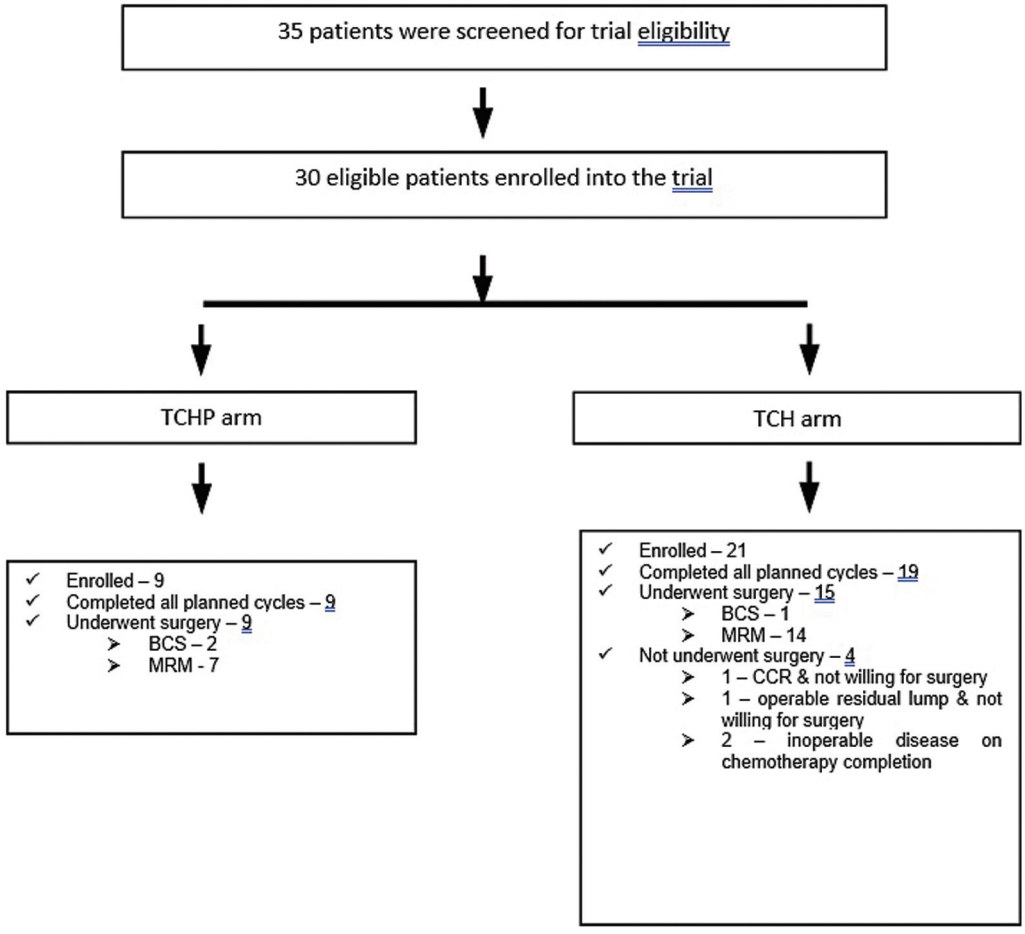

Fig. 1

Table 1 Baseline patient demographics

	TCHP arm ($n = 9$)	TCH arm ($n = 19$)
Median age (yrs)	51 (18–62)	55 (44–75)
Menopausal status		
Premenopausal	66.6% (6)	15.7% (3)
Postmenopausal	33.3% (3)	84.2% (16)
Hormone receptor (HR) status		
HR +	66.6% (6)	36.8% (7)
HR –	33.3% (3)	63.1% (12)
Clinical tumor staging		
T2	33.3% (3)	10.5% (2)
T3	11.1% (1)	21% (4)
T4b	55.5% (5)	52.6% (10)
T4c	–	10.5% (2)
Clinical nodal staging		
N0	11.1% (1)	10.5% (2)
N1	33.3% (3)	52.6% (10)
N2	55.5% (5)	21% (4)
N3	–	15.7% (3)

TCH arm; 88.9% in the TCHP arm were node positive and 89.5% in the TCH arm were node positive. All patients tolerated chemotherapy well, and no dose adjustments were made.

At the end of six cycles of neoadjuvant therapy, 100% of patients in the TCHP arm underwent surgery, while the surgical completion rates in the TCH arm were 78.9%. Two patients (10.5%) in TCH arm had inoperable disease even after completion of planned neoadjuvant cycles. BCS was achieved in 22.2% (2/9; 95% confidence interval [CI]: 2.8–60.0) of patients in the TCHP arm and 5.3% (1/19; 95% CI: 0.1–26.0) of patients in the TCH arm.

The pCR rate was 66.7% (6/9; 95% CI: 29.9–92.5) in the TCHP arm and 15.8% (3/19; 95% CI: 3.4–39.6) in the TCH arm. The absolute difference in pCR rates between the two treatment arms was 50.9% (95% CI: 12.8–74.5). The median time to observe a measurable clinical response was one cycle in the TCHP arm and two cycles in the TCH arm, and the median time to achieve a complete clinical response was four cycles and six cycles, respectively. Nodal downstaging was observed in 88.9% (8/9; 95% CI: 51.8–99.7) of patients in the TCHP arm compared with 52.6% (10/19; 95% CI: 28.9–75.6) in the TCH arm.

In the HR+ subgroup, the pCR rate was 50% (3/6; 95% CI: 11.8–88.2) in the TCHP arm compared with 14.3% (1/7; 95% CI: 0.4–57.9) in the TCH arm. These subgroup analyses were exploratory. All the patients who failed to attain pathological complete rates in the TCHP arm were in the HR+ subgroup, while this was not the case with the TCH arm.

The most common adverse events documented were grade 2 asthenia, followed by grade 2 diarrhea. There were no documented chemotherapy-related grade 3 adverse reactions. With the prophylactic colony stimulating factors, no patients experienced grade 3 neutropenia with any of the regimens. No cardiotoxicity events were documented.

Discussion

The advent of epidermal growth factor (EGF) in human biology came into the limelight with the discovery by Stanley Cohen in 1962.[6,7] This discovery, together with the work of Harold Varmus and Michael Bishop on the discovery of oncogenes, led to the understanding of HER2 as an oncogene as it stands today. *ERBB* has two parts—*v-erbA* and *v-erbB*—of which *v-erbB* is transforming[8] and is an oncogene whose sequence is similar to human eGFR.

HER Dynamics and Rationale for Anti-HER2 Therapy and Combination Strategy

The HER family, comprising HER1, HER2, HER3, and HER4, is a type 1 transmembrane receptor with an extracellular ligand-binding domain, transmembrane domain, and an intracellular tyrosine kinase domain with the ability to dimerize and catalyze intracellular signaling pathways upon ligand binding. In HER signaling, HER heterodimers are preferred over homodimers, and the dimerization partner selection is a key determinant in signaling activity, with HER2-containing dimers possessing the strongest catalytic signal.[9] In addition, HER2 and HER3 are structurally incomplete molecules, that is, the extracellular domain of HER2 is in a constitutively active conformation, and hence lacks ligand binding activity and HER3 has no ATP binding site in the intracellular domain, rendering it catalytically inactive, and they are interdependent on each other for the completion of the signaling pathway. Evidence says that not only are HER2 and HER3 obligate partners but also their complex forms are the strongest active signaling forms among the HER family.[10]

Trastuzumab is the first humanized monoclonal antibody that has shown meaningful efficacy in the management of breast cancer in the clinics.[11] Trastuzumab binds to extracellular domain IV of HER2 and suppresses the intracellular signaling, inhibits cell cycle arrest, and mediates antibody-dependent cellular cytotoxicity. **Pertuzumab** is another humanized monoclonal antibody against extracellular domain II of HER2, and effectively prevents HER2 heterodimerization with other HER proteins, especially HER3, creating synergism with trastuzumab in blocking the downstream signaling pathways and averting cell growth. In addition, pertuzumab also prevents the emergence of resistance to trastuzumab due to incomplete inhibition of the HER family.[12]

The current study demonstrates that patients with HER2+ breast cancer who are candidates for neoadjuvant therapy have a better probability of achieving a pCR with the dual HER2 blockade. The pCR rates, as per protocol definition, was 66.6% with dual blockade and 15.7% with chemotherapy and single HER2 blockade. The pCR with dual blockade is almost four times that of the pCR with a single anti-HER2 strategy. While the pCR rates with the use of trastuzumab and chemotherapy in neoadjuvant setting has set the pCR rates to be around 31 to 50% across various trials,[13–17] with the

studies by Buzdar et al, from MD Anderson, claiming the highest of 50% in a phase 3 study (ACOSOG Z1041[Alliance]),[14] and another benchmark of 66% in a small scale study,[13] the pCR rates of single HER2 blockade with chemotherapy in Indian counterparts have continued to linger on the lower end of the spectrum, with Joel A et al, quoting a pCR of 37.6%.[18] In addition to the lower pCR rates, around 10.5% of patients in the single blockade arm in the current study had chemo-resistant disease. Having proven beyond doubt that pCR is a surrogate marker of EFS, these lower pCR rates and resistant subgroup make a significant number of patients in a high-risk scenario for disease recurrence. This need creates the perfect position for the synergistic partner, pertuzumab, to step in.

Pertuzumab stepped into the neoadjuvant scenario with the phase 2 trial NeoSphere, in which pertuzumab was added to trastuzumab and docetaxel and compared with single blockade with trastuzumab plus docetaxel and pertuzumab plus docetaxel. While pertuzumab with docetaxel had the lowest pCR rates of 24%, trastuzumab plus docetaxel had pCR of 29%, and the dual blockade arm with THP had attained a pCR of 45.8%, with a significant *p*-value of 0.0141.[19] The 5-year updated analysis of the NeoSphere trial showed the longevity and sustainability of the benefits attained by the addition of a second anti-HER2 agent, with better PFS in those who attained pCR (85 vs. 76%; hazard ratio [HR] = 0.54).[20] This significance translated similarly in disease free survival (DFS) benefit (84 vs. 81%).[20] The cardiac safety of adding pertuzumab to the management of HER2+ breast cancer was evaluated by TRYPHAENA, a phase 2 trial. In this study, they concluded that the protocol with TCHP had the least cardiac toxicity of 3.9%, along with the highest pCR rates of an unprecedented 66.2%.[21] While these data are of the Western population, Indian studies by Shalabh Arora et al have demonstrated a comparable pCR rate of 55.6%, with 70% of the study population having stage II disease.[22] In this study, we have an overall pCR of 66.6% in the TCHP arm, which is similar to and comparable to the western counterparts. Unlike in other trials such as NeoSphere, considering the fact that 60% patients included in the TCHP arm of this trial had stage IIIB disease at presentation, and more than 60% being positive for HR, we hypothesize that pertuzumab-mediated synergism and signal interruption is better in our population. While the underlying molecular mechanism remains unknown, the addition of pertuzumab clearly surpasses its best results in trials in our population.

HR+ Subset

In this study, the HR+ subgroup has pCR rates around 50% in the TCHP arm. In comparison, the NeoSphere trial had a pCR of 26% in the HR+ subgroup[19]; the Indian trial by Arora et al demonstrated a pCR of 40.2% in the HR+ subset.[22] The reason for the higher pCR in the HR+ subset needs to be explored.

This response in the HR+ subgroup remains lower than that in the HR– subgroup in this study, with pCR rates in the HR+ and HR– subsets being 50 and 100%, respectively even with dual blockade. This differential response of tumors based on HR status may be explained by the activation of complementary signaling pathways, including activation of PI3KCA mutations due to intrinsic mutation or loss of PTEN; bidirectional crosstalk of HER2 and HR signaling pathways, cyclin D1–CDK4/6 axis, and over-expression of MUC4 (mucin4) leading to masking of the epitope to trastuzumab.[23–28]

Safety Concerns

In addition to this efficacy betterments similar to the landmark trials, there were no documented additional toxicities or new safety signals with the addition of pertuzumab in this study. This stands in line with the TRYPHAENA and NeoSphere trials, which proved that pertuzumab conferred no added cardiotoxicity. This efficacy with no grade 3 adverse effects adds value to dual blockade. The decreased probability of grade 3 CTCAE with the TCHP protocol would significantly decrease the health care costs and man-hours. A better efficacy coupled with a fair tolerability and no added cardiotoxicity makes TCHP a better neoadjuvant strategy in HER2+ breast cancer. Although the addition of pertuzumab exerts some financial toxicity at the start of therapy, it would defer the use of Ado-Trastuzumab Emtansine (T-DM1) in a significant proportion of patients, proving to be a financially sensible option, in addition to avoiding the added distress regarding the risks of nonattainment of pCR and disease recurrence at a later stage of therapy.

Limitations

The study has a few limitations, including being a small-scale, single-center study with a limited study population ($n = 30$, as taken by the number of population accrued in the study period), thus needing large-scale phase 3 studies to ensure generalizability. Despite its limitations, the study demonstrates that TCHP is a safe, tolerable, and sensible protocol in the neoadjuvant setting without adding health care costs on supportive care.

Conclusion

To summarize, this real-world data support the use of the neoadjuvant TCHP protocol in HER2+ breast cancer with higher pCR and BCS rates and an acceptable toxicity profile.

Authors' Contributions

V.A. reviewed the manuscript and designed the protocol. B.A. was responsible for manuscript preparation and data collection.

Patient Consent

Written informed consent was obtained from all the participants.

Acknowledgments

The authors would like to thank the Department of Medical Oncology, Tirunelveli Medical College, Tirunelveli.

Funding

None

Conflict of Interest
None declared.

References

1 Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 2014;106(05):dju055
2 Borg A, Tandon AK, Sigurdsson H, et al. HER-2/neu amplification predicts poor survival in node-positive breast cancer. Cancer Res 1990;50(14):4332–4337
3 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(9938):164–172
4 Tiwari SR, Mishra P, Dilawari A, et al. Abstract P2–10–10: lower pathologic complete response rate with dual-HER2 blockage and chemotherapy in African Americans and ethnic minorities. Cancer Res 2020;80(4, Supplement):2–10
5 Zhao F, Miyashita M, Hattori M, et al. Racial disparities in pathological complete response among patients receiving neoadjuvant chemotherapy for early-stage breast cancer. JAMA Netw Open 2023;6(03):e233329
6 Cohen S. Isolation of a mouse submaxillary gland protein accelerating incisor eruption and eyelid opening in the new-born animal. J Biol Chem 1962;237:1555–1562
7 Cohen S. The stimulation of epidermal proliferation by a specific protein (EGF). Dev Biol 1965;12(03):394–407
8 Yamamoto T, Nishida T, Miyajima N, Kawai S, Ooi T, Toyoshima K. The erbB gene of avian erythroblastosis virus is a member of the src gene family. Cell 1983;35(01):71–78
9 Tzahar E, Waterman H, Chen X, et al. A hierarchical network of interreceptor interactions determines signal transduction by Neu differentiation factor/neuregulin and epidermal growth factor. Mol Cell Biol 1996;16(10):5276–5287
10 Sliwkowski MX, Schaefer G, Akita RW, et al. Coexpression of erbB2 and erbB3 proteins reconstitutes a high affinity receptor for heregulin. J Biol Chem 1994;269(20):14661–14665
11 Baselga J. Treatment of HER2-overexpressing breast cancer. Ann Oncol 2010;21(Suppl 7):vii36–vii40
12 Ishii K, Morii N, Yamashiro H. Pertuzumab in the treatment of HER2-positive breast cancer: an evidence-based review of its safety, efficacy, and place in therapy. Core Evid 2019;14:51–70
13 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 (16):3676–3685
14 Buzdar AU, Suman VJ, Meric-Bernstam F, et al. Disease-free and overall survival among patients with operable HER2-positive breast cancer treated with sequential vs concurrent chemotherapy: the ACOSOG Z1041 (alliance) randomized clinical trial. JAMA Oncol 2019;5(01):45–50
15 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(9712):377–384
16 Swain SM, Tang G, Brauer HA, et al. NSABP B-41, a randomized neoadjuvant trial: genes and signatures associated with pathologic complete response. Clin Cancer Res 2020;26(16):4233–4241
17 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(12):2024–2031
18 Joel A, Georgy JT, Thumaty DB, et al. Neoadjuvant chemotherapy with biosimilar trastuzumab in human epidermal growth factor receptor 2 overexpressed non-metastatic breast cancer: patterns of use and clinical outcomes in India. Ecancermedicalscience 2021;15:1207
19 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(01):25–32
20 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(06):791–800
21 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 (09):2278–2284
22 Arora S, Gogia DA, Deo S, Sharma D, Mathur SR. 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
23 Loibl S, Majewski I, Guarneri V, et al. PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol 2016;27(08):1519–1525
24 Baselga J, Cortés J, Im SA, et al. Biomarker analyses in CLEOPATRA: a phase III, placebo-controlled study of pertuzumab in human epidermal growth factor receptor 2-positive, first-line metastatic breast cancer. J Clin Oncol 2014;32(33):3753–3761
25 Chandarlapaty S, Sakr RA, Giri D, et al. Frequent mutational activation of the PI3K-AKT pathway in trastuzumab-resistant breast cancer. Clin Cancer Res 2012;18(24):6784–6791
26 Rimawi MF, De Angelis C, Schiff R. Resistance to anti-HER2 therapies in breast cancer. Am Soc Clin Oncol Educ Book 2015; 35(01):e157–e164
27 Xia W, Bacus S, Hegde P, et al. A model of acquired autoresistance to a potent ErbB2 tyrosine kinase inhibitor and a therapeutic strategy to prevent its onset in breast cancer. Proc Natl Acad Sci U S A 2006;103(20):7795–7800
28 Wang YC, Morrison G, Gillihan R, et al. Different mechanisms for resistance to trastuzumab versus lapatinib in HER2-positive breast cancers: role of estrogen receptor and HER2 reactivation. Breast Cancer Res 2011;13(06):R121

