



# Advances in neoadjuvant therapy for HER2-positive breast cancers: a narrative review

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**Background and Objective:** Breast cancer (BC) is currently the most frequently diagnosed cancer and the primary cause of cancer-related death among women worldwide. Human epidermal growth factor receptor type 2 (HER2)-positive BC accounts for 14.5–15% of all BCs, with a relatively poor prognosis. Neoadjuvant therapy (NAT) has become a preferred treatment option for HER2+ BCs. With the continuous emergence of various clinical trials and new treatment concepts in BC, the NAT model has changed from chemotherapy alone to the neoadjuvant combination of anti-HER2-targeted therapy with chemotherapy, neoadjuvant endocrine therapy, and so on. Therefore, an up-to-date review is needed to inform the selection of NAT strategies for HER2+ BCs.

**Methods:** This review was administrated with literature from the PubMed database. Manuscripts were searched using the following keywords: “neoadjuvant” or “preoperative”, “breast cancer” or “breast neoplasm”, “HER2+” or “HER2-positive”, titles and abstracts were screened and evaluated independently by two authors. Information relating to the efficacy and safety profile of NAT for patients with HER2+ BCs were included and analyzed qualitatively. Only English-language articles were included.

**Key Content and Findings:** This review discusses the neoadjuvant situation for the surgical management of HER2-positive BCs around the world. In this paper, we describe the efficacy assessment of NAT, analyze clinical effect and toxicity of chemotherapy, and targeted therapy, including monoclonal antibody, tyrosine kinase inhibitors (TKIs) and antibody-drug conjugates (ADCs), and other neoadjuvant treatments in HER2+ BC. The data shows while overall survival is the standard endpoint for efficacy, pathological complete response have been implemented more and more frequently in clinical trials for its convenience. Dual-targeted therapy plus chemotherapy exhibited favorable efficacy in most cases, meanwhile other treatment strategies such as combinations without chemotherapy or including CDK4/6 agents may be applicable in specific situation.

**Conclusions:** As an important part of BC treatment, NAT is lingering in the stage of continuous development, especially for patients with HER2-positive BC. The challenges we are facing today in this field are dose de-escalation without reducing efficacy and choose suitable combination of agents in clinical practice. Moreover, new biomarkers are warrant for individualize treatment.

**Keywords:** HER2-positive breast cancer; neoadjuvant therapy (NAT); targeted therapy; triple-positive breast cancer; chemotherapy

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## Introduction

Breast cancer (BC) has become the most frequently diagnosed cancer and the primary cause of cancer-related death in women aged 20–59 years worldwide (1,2). According to Cancer Statistics 2022, BC alone accounts for over one-third of all newly diagnosed diseases in women worldwide. Female BC incidence rates slowly increased by about 0.5% annually from 2014 through 2018 (1). Mortality patterns also can reflect incidence trends. In recent years, BC mortality has slowly declined, from 2–3% annually during the 1990s and 2000s to 1% annually from 2013 to 2019, which perhaps reflects the slight but steady increase in incidence (1).

The activation of human epidermal growth factor receptor type 2 (HER2) by the amplification and/or overexpression of its related kinase receptor protein, also known as HER2-positive BC, has been reported in 14.5–15% of all BCs (3–5). The amplification and overexpression of HER2 were historically associated with poor prognosis in BC (6–9). Over the past two decades, several HER2-targeted therapies have been developed and investigated, including pertuzumab, trastuzumab, lapatinib, ado-trastuzumab emtansine (T-DM1), and fam-trastuzumab deruxtecan (T-DXd, DS-8201), which have improved the treatment efficacy in patients with HER2-positive BC (10–13). In recent years, various targeted therapies and clinical trials have been implemented to improve the outcomes of operable HER2-positive BCs. However, the treatment resistance to HER2-targeted therapy and its occasional intolerable adverse events remain hugely challenging; there is a clear, urgent demand for more novel therapies.

The current standard management for nonpalpable BC is neoadjuvant treatment combined with localized surgical excision (14). Neoadjuvant therapy (NAT) has become a preferred option for surgical management of HER2-positive BCs (15–17). The use of NAT for operable BC has increased significantly over the past several years. Initially, the interest of investigators in NAT was focused on operability and improving eligibility for breast-conserving surgery. It has become clear that the use of NAT can increase the chances of surgical success. Following NAT, both tumor size and stage can be reduced, and inoperable BC can change into operable BC (18). In addition, NAT can improve the breast-conserving rate and reduce the stage of non-breast-conserving BC to breast-conserving BC.

Later, the neoadjuvant therapies came to be recognized as a human *in vivo* system to explore predictive biomarkers,

surrogate endpoints, and the efficacy of therapies including novel agents, making it an attractive setting for drug development (19). Further, indications for NAT have evolved to recognize its critical role in guiding escalation and de-escalation of subsequent therapy, particularly in HER2-positive BC. The application of NAT facilitates the obtainment of drug sensitivity information to screen out insensitive patients with a poor prognosis, and adjust adjuvant therapy to improve long-term survival according to whether the pathologic complete response (pCR) rate has been achieved.

With the increasing understanding of tumor biological behavior, NAT is recommended by clinicians for patients with HER2-positive BC. The application of NAT can assist in judging the sensitivity of patients to the therapies used, and thus adjust the regimen according to the different residual situations after surgery. With the continuous emergence of various clinical trials and new treatment concepts in BC, the NAT model has changed from comprising chemotherapy alone to a neoadjuvant combination of anti-HER2-targeted therapy with chemotherapy, neoadjuvant endocrine therapy, and so on.

As an important part of BC treatment, NAT is subject to continuous development, especially for patients with HER2-positive BC. However, fast development and revolution in new agents and treatment combinations may be hard for clinicians to follow and thus lead to incorrect choice of the optimal treatment strategy. Therefore, we performed this up-to-date review to help clinicians encounter with the important achievements of neoadjuvant treatment for HER2-positive BC in recent years and provide reference in daily clinical practice. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/gS-22-439/rc>).

## Methods

Manuscripts were searched using the search term of (“neoadjuvant” OR “preoperative”) AND (“breast cancer” OR “breast neoplasm”) AND (“HER2+” OR “HER2-positive”). Only manuscripts written in English and from PubMed databases were included.

After initial enrollment, unrelated articles were excluded on the basis of title and abstract by two authors independently. Subsequently, manuscripts containing similar and/or important information were read in full text, critical study results were discussed and interpreted by all three

**Table 1** The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	2022.6
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters)	("neoadjuvant" OR "preoperative") AND ("breast cancer" OR "breast neoplasm") AND ("HER2+" OR "HER2-positive")
Timeframe	1987.1–2022.6
Inclusion and exclusion criteria (study type, language restrictions, etc.)	Retrospective study, preclinical studies, case report and studies not written in English were excluded
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Manuscripts following the before mentioned criteria were downloaded from PubMed and uploaded in EndNote 20, then screened by two authors independently based on its title and abstract to decide whether or not it should be included in the subsequent analysis  Manuscripts containing important information were read in full text, critical study results were discussed and interpreted by all three authors. When there are different opinions, correspondent author was in charge to made the final decision
Any additional considerations, if applicable	None

authors. When there are different opinions, corresponding author was in charge to made the final decision (*Table 1*).

### Efficacy assessment of NAT

Overall survival (OS) has been regarded as the gold standard of endpoint in clinical trials of oncology, as it is objective, simple to measure, and interpret (20).

However, extended follow-up time, higher costs, and larger sample sizes are required when OS is used as an endpoint in clinical trials, especially for patients with early-stage cancers who receive NAT. Therefore, in the neoadjuvant setting, disease-free survival (DFS) and pCR began to be accepted as a surrogate endpoint for accelerated approval by the Food and Drug Administration (FDA) (21). Although DFS has always been used as a primary endpoint in studies involving HER2-positive BC patients, the association between DFS and OS in patients had not been validated until a meta-analysis was conducted in recent years (22). The association between pCR and DFS and OS had remained unclear because of the ununified definition of pCR (16,23). However, after pCR was defined as an absence of residual tumor cells in the breast and/or axillary lymph nodes, it was shown that pCR could be used as a suitable outcome in clinical trials of HER2-positive patients who received neoadjuvant chemotherapy (NACT) (24).

### NACT

Over decades, many clinical trials have demonstrated that NACT could reduce the size of most breast tumors/neoplasms and decrease the incidence of positive nodes. The greatest increase of lumpectomy after NAT has occurred in HER2-positive BC women.

The National Surgical Bowel and Breast Project (NSAPB) B-18, conducted in 1997, was the first study to demonstrate the benefits of NACT in BC. The results showed that breast tumor size was reduced in 80% of patients after NAT [anthracycline + cyclophosphamide (AC)], and 36% had a clinical complete response (cCR) (16,25). Subsequently, with the great success of HER2-targeted therapies in the treatment of advanced HER2-positive BC, researchers began to try to include HER2-targeted therapies in neoadjuvant regimens in combination with chemotherapy in the treatment of HER2+ BC. The results showed that the combination of HER2-targeted agents and chemotherapy in NAT achieved higher pCR rates than chemotherapy alone (26). The NeoSphere trial is a milestone in neoadjuvant therapy of patients with HER2-positive breast cancer, as the proportion of patients who achieved pCR in docetaxel/trastuzumab/pertuzumab (THP) group was significantly higher than patients in trastuzumab/docetaxel (45.8% *vs.* 29%) group (27,28). In addition, no

increased cardiotoxicity was observed in patients received dual HER2 blockade. The NeoSphere trial demonstrated that the addition of pertuzumab to trastuzumab/docetaxel also improved DFS, lifting the veil of the dual HER2-targeted therapies era.

The TRYPHAENA study investigated neoadjuvant dual HER2 blockade with standard anthracycline-based regimen [5-fluorouracil/epirubicin/cyclophosphamide (FEC)] and nonanthracycline chemotherapy regimens. The results revealed similar pCR rates between these two groups (29). Since then, the neoadjuvant nonanthracycline regimens has become the standard treatment. The BCIRG-006 trial compared chemotherapy with or without trastuzumab plus either anthracycline or nonanthracycline chemotherapy. The results demonstrated that compared with the AC-TH regimen containing anthracyclines, the docetaxel, carboplatin, and trastuzumab (TCH) regimen showed better efficacy (30). In line with these studies, the results in BERENICE trial provide reassurance regarding the cardiotoxicity of anthracyclines as NAT for HER2-positive BC (31). Then the combination of docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) become a common standard option in neoadjuvant setting based on the results in the TRAIN-2 study and bring changes to National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer (32). A 9-year follow-up study also confirmed that the inclusion of anthracyclines in treatment of HER2-positive BC provided higher pCR rates and progression-free survival (PFS) (33).

## Neoadjuvant targeted therapy

### *Monoclonal antibody*

Accumulating evidence has indicated that trastuzumab is associated with favorable efficacy in the adjuvant treatment of HER2-positive BC, therefore, studies have begun to focus on the addition of monoclonal antibody drugs in the neoadjuvant setting.

The clinical efficacy between standard NACT and NACT with trastuzumab was first tested in a phase III randomized clinical trial (RCT) in 2004, an early termination was performed based on the significantly higher pCR rate in the NACT with trastuzumab group, alone with extended DFS shown by follow-up examination (26,34). Subsequently, studies with a larger sample size have been conducted to validate the conclusion. The NOAH trial

showed that compared with chemotherapy alone regimen, patients with HER2+ locally advanced or inflammatory BC achieved a higher pCR rate and prolonged event-free survival (EFS) when receiving chemotherapy plus trastuzumab regimen (35). These studies both demonstrated encouraging results of chemotherapy plus trastuzumab for patients who desire breast-conserving surgery.

Currently, dual HER2-blockade plus chemotherapy is the standard of care for HER2+ BC in NAT, which was based on the results of the NeoSphere trial. In this trial, patients were divided into 4 groups to receive the following treatments: (A) trastuzumab and chemotherapy; (B) pertuzumab and trastuzumab and chemotherapy; (C) trastuzumab and pertuzumab; or (D) pertuzumab and chemotherapy in the neoadjuvant setting. The results revealed a significantly higher pCR rate in the dual HER2-blockade plus chemotherapy group than that in the other groups (27). Prolonged PFS and DFS rates were observed at the 5-year follow-up in the dual HER2-blockade group, which was consistent with the previous conclusion (28). Given the toxicity incurred by chemotherapy, there is a trend in de-escalation strategies. In the WSG-ADAPT study, a phase II RCT, neoadjuvant efficacy and safety of dual HER2-blockade with trastuzumab and pertuzumab were compared with the trastuzumab and pertuzumab plus chemotherapy regimen in patients with HER2+/HR- BC. Disappointingly, a reduced pCR rate of 36.3% was reported in the chemotherapy-free cohort versus 90.5% in the chemotherapy-containing cohort (36). Notably, these results also revealed dual HER2-blockade plus chemotherapy associate with better clinical benefit in HER2+/HR- BC than HER2+/HR+ BC. This study indicated that NACT is still necessary when using monoclonal antibodies in the treatment of HER2-positive BC at the current stage.

In the recent PEONY phase III RCT, which focused specifically on Asian patients, a 39.9% pCR rate was achieved in patients treated with pertuzumab and trastuzumab plus docetaxel regimen. Compared with the NeoSphere trial, the pCR rate was relatively low, which might be due to the assessment performed by the independent review committee (37).

### *Tyrosine kinase inhibitors (TKIs)*

Compared with monoclonal antibodies, TKIs are more convenient in administration and have less cardiotoxicity. Furthermore, theoretically, dual HER2-blockade with TKIs and monoclonal antibodies has better efficacy than the

combination of 2 monoclonal antibodies.

The first head-to-head comparison of lapatinib and trastuzumab with the same chemotherapy regimen in the neoadjuvant treatment of patients with HER2-positive BC was performed in the GeparQuinto study, which revealed a superior pCR rate with trastuzumab containing regimens (38). However, no significant statistical difference in DFS and OS between the 2 treatment arms was reflected after a 3-year follow-up, which might have been due to prolonged anti-HER2 treatment in the lapatinib arm (39). In the CHER-Lob study, patients with HER2-positive BC administered with chemotherapy plus trastuzumab and lapatinib achieved a higher pCR rate compared with chemotherapy plus either trastuzumab or lapatinib (46.7% *vs.* 25% *vs.* 26.3%, respectively). Survival analysis of the CHER-Lob study was updated after 9 years, and improved long-term outcomes were reflected in the dual HER2-blockade group and has a positive correlation with the pCR rate (40,41). Consistently, the phase III NeoALTTO trial suggested a higher pCR rate of 51.3% in the dual HER2-targeted arm than in the other 2 single HER2-targeted agent arms (42). Although no statistical difference between EFS and OS was shown in the follow-up evaluation because of limited sample size, the association between pCR rates and long-term clinical benefit has been confirmed (43). Nevertheless, the CALGB 40601 study failed to demonstrate a difference in pCR rates between combined treatment with paclitaxel and trastuzumab plus lapatinib and paclitaxel plus either trastuzumab or lapatinib regimens. However, favorable results for recurrence-free survival (RFS) and OS have been found after a 7-year follow-up (44,45). The unexpected pCR rate in the GALGB 40601 study might owing to molecular heterogeneity or different tumor immune microenvironment and need to be further investigated in the future.

In summary, it has been challenging to arrive at a definitive conclusion regarding the clinical benefits of dual HER2-blockade with lapatinib and trastuzumab due to different definitions of pCR and administration dose in each study (46).

Besides lapatinib, other TKIs, such as neratinib and pyrotinib, have been used in NAT for patients with HER2-positive BC in recent years.

In the case of neratinib, a phase II RCT has been carried out to evaluate its efficacy and safety. Unfortunately, although 50% pCR rates were achieved in the trastuzumab and neratinib with the paclitaxel arm, no statistical significance could be detected due to an insufficient sample

size (47). Other clinical trials investigating the role of neratinib in treating HER2+ BC patients are ongoing.

Moreover, in recent years, the clinical effect and safety profile of pyrotinib have been preliminarily explored in several studies and exhibit promising results when combined with trastuzumab and chemotherapy in NAT (48,49). The NeoATP study included patients with HER2+ stage IIA–IIIC BC who received combination therapy with pyrotinib and trastuzumab plus paclitaxel, resulting in a high pCR rate of 69.81% (50). In addition, a chemotherapy-free neoadjuvant regimen with pyrotinib, letrozole, and dalpiciclib in the MUKDEN 01 trial demonstrated a 29.5% pCR rate in primary analysis in triple-positive BC (51).

### *Antibody-drug conjugates (ADCs)*

ADCs have attracted great attention with their encouraging efficacy in metastatic BC patients. The clinical effect has been assessed in the KRISTINE study, which is a phase III RCT focusing on excluding chemotherapy in NAT for HER2-positive BC treatment. An inferior pCR rate was revealed in the T-DM1 plus pertuzumab arm compared with the docetaxel, carboplatin, and trastuzumab plus pertuzumab arm (55.7% *vs.* 44.4%). Despite the decreased proportion of pCR, the treatment arm without systemic chemotherapy was less toxic (52). In contrast, in the I-SPY2 phase II trial, no statistical difference between T-DM1 plus pertuzumab and THP was found. The pCR rate in different HER2-positive BC subtypes has been further studied (53,54). T-DXd presents with a durable anti-tumor effect in the adjuvant setting of HER2-positive BC and its usage in the neoadjuvant setting is under investigation (55).

### **Other treatments**

Regarding triple-positive BC patients, several clinical trials have enrolled patients to receive treatment regimens including CDK4/6 drugs, such as the beforementioned MUKDEN 01 study. Although preclinical studies have indicated a greater anti-tumor effect when immune checkpoint inhibitors are combined with standard dual HER2-blockade, the IMpassion050 trial failed to detect and improved pCR rate, and further studies are warranted for long-term effect (56). In addition, neoadjuvant radiotherapy has been also manipulated in inoperable BC to downstage tumor burden, which might allow patients to become eligible for surgery (57).

## Conclusions

The current standard of care for patients with HER2-positive BC in the neoadjuvant setting is dual HER2-blockade with chemotherapy. Recently, the pCR rate has been one of the most commonly used surrogate endpoints in clinical trials because of its short follow-up time and convenient assessment. Overall, regardless of the categories of anti-HER2 agents, treatment regimens with dual HER2-blockade exhibit a much better pCR rate and following EFS and OS results than with single HER2-blockade. However, the clinical effect in dual HER2-blockade with 2 monoclonal antibodies versus a monoclonal antibody and TKI is hard to measure owing to different pCR definitions and agent doses, which need further advancement through head-to-head studies. When combined with monoclonal antibodies, ADCs have demonstrated encouraging pCR rates and long-term outcomes, which might be a favorable treatment option for patients who are unable to tolerate chemotherapy-induced adverse events. The future research in this field mainly focuses on de-escalation strategies by eliminate dose and treatment cycles or use new agents with less toxicity and choose suitable treatment regimen for specific subtype within HER2-positive breast cancer. Yet the idea of discard chemotherapy in neoadjuvant setting remains challenging. Biomarker-based de-escalation strategies are under investigation to avoid unnecessary treatment for personalized treatment in the future.

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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.

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