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The Role of Neoadjuvant Treatment in HER-2 Positive Breast Cancer: What a Surgeon Should Know

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Abstract

This review aims to provide an updated overview of neoadjuvant strategies in Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancer, with a specific focus on surgical implications. We explore the role of targeted therapies, critical trial data, and future treatment directions. Particular attention is given to the impact of Neoadjuvant Therapy (NAT) on surgical outcomes such as Breast-Conserving Surgery (BCS) rates, axillary management, and reoperation risk. By offering a critical synthesis of current evidence, this review intends to support breast surgeons in understanding and applying neoadjuvant protocols in clinical practice.

Abbreviations

HER2: Human Epidermal Growth Factor Receptor 2; NAT: Neoadjuvant Therapy; pCR: Pathologic Complete Response; BCS: Breast-Conserving Surgery; ALND: Axillary Lymph Node Dissection; TAD: Targeted Axillary Dissection; HR: Hormone Receptor; T-DM1: Trastuzumab Emtansine; T-DXd: Trastuzumab Deruxtecan; ADC: Antibody-Drug Conjugate; TKI: Tyrosine Kinase Inhibitor; CNS: Central Nervous System; TILs: Tumor-Infiltrating Lymphocytes; PET: Positron Emission Tomography; ESMO: European Society for Medical Oncology; NCCN: National Comprehensive Cancer Network; EGFR: Epidermal Growth Factor Receptor

Introduction

Human Epidermal Growth Factor Receptor 2 (HER2)-positive breast cancer, representing 15%–30% of all breast cancers, is characterized by the overexpression of the HER2 receptor and is associated with aggressive clinical behavior and poor prognosis [1,2]. The introduction of targeted therapies, such as trastuzumab and pertuzumab, has revolutionized treatment and significantly improved survival [3,4]. Despite these advances, treatment resistance and recurrence remain significant challenges [5,6], underscoring the need for multimodal approaches, such as Neoadjuvant Therapy (NAT) [7–21].

Methods

This review employed a narrative approach. A comprehensive literature search was performed in PubMed, Scopus, and Web of Science databases from January 2010 to March 2025. The following search terms were used individually and in combination: "HER2-positive breast cancer", "Trastuzumab", "Pertuzumab", "Antibody-Drug Conjugate (ADC)", "surgical outcomes", "Pathologic Complete Response (pCR)", and "axillary management". The inclusion criteria encompassed clinical trials, meta-analyses,

guidelines, and high-quality narrative reviews published in the English language. Exclusion criteria included preclinical studies, single case reports, non-peer-reviewed articles, and publications without clear relevance to neoadjuvant HER2-positive breast cancer.

The final selection included 63 peer-reviewed articles. Priority was given to large randomized controlled trials, landmark studies, and publications from high-impact journals. The selection process involved independent screening of titles and abstracts by two authors, with discrepancies resolved through discussion.

Clinical Efficacy of Neoadjuvant Therapy

Pathologic Complete Response (pCR): Achieving a pCR, defined as the absence of invasive cancer in breast and axillary nodes post-therapy, is a surrogate marker for improved disease-free and overall survival in HER2+ patients [22,23]. Studies such as CTNeoBC and NeoALTTO confirm that dual HER2 blockade with trastuzumab and pertuzumab significantly increases pCR rates (up to 60%) [24–28,48]. pCR is highest in Hormone Receptor (HR)-negative/HER2+ subtypes.

Impact on Survival: Meta-analyses show strong correlations between pCR and long-term outcomes. For HER2+ patients, those achieving pCR exhibit up to 70%–80% improvement in event-free and overall survival compared to those with residual disease [29,30].

Surgical Implications

Conversion to Breast-Conserving Surgery (BCS): NAT often enables conversion from mastectomy to lumpectomy. Trials like BrighTNess (Figure 1) for triple negative breast cancer reported significant increases in BCS eligibility following NAT, which is also confirmed specifically in the TECHNO trial for HER2-positive (Figure 2). Tumor shrinkage also facilitates better cosmetic outcomes and fewer reoperations [31,32].

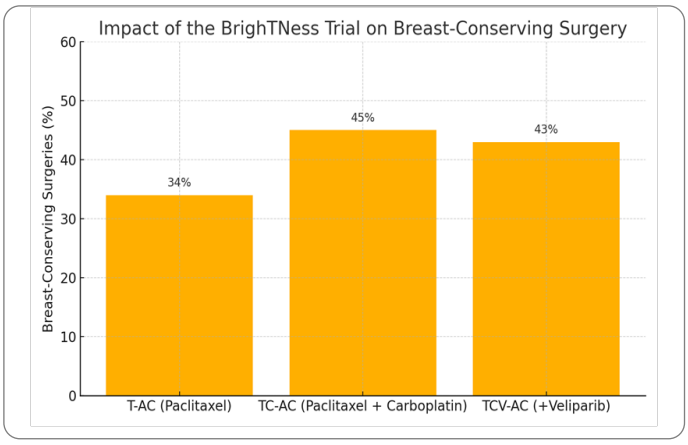

Figure 1: The usage of carboplatin has significantly improved the chance to receive BCS, whereas veliparib has no impact on the outcome.

Margin Status and Reoperation Rates: NAT improves the likelihood of achieving negative margins at the time of initial surgery, thereby reducing the risk of re-excision. This effect is particularly evident in patients undergoing BCS, where margin status is a critical determinant of success. For instance, the First Surgical National Consensus Conference of the Italian Breast Surgeons Association (ANISC) highlighted that NAT significantly enhances the rate of margin-negative resections in HER2-positive breast cancer, enabling more effective surgical planning and reducing reoperation rates [33]. Furthermore, findings from the TECHNO trial and other large-scale datasets suggest that patients treated with NAT have fewer margin-positive resections and improved cosmetic outcomes, supporting a more conservative surgical approach [32].

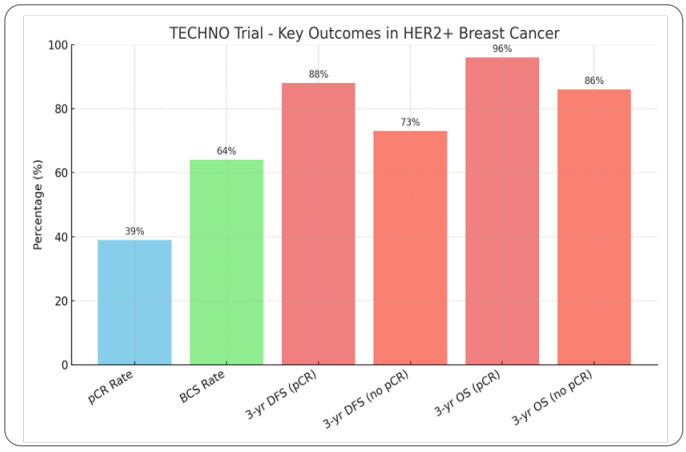

Figure 2: A graphic resume of main results coming from TECHNO trial.

Axillary Management: NAT can significantly downstage axillary lymph node disease, converting Clinical Node-Positive Disease (cN1) to Pathological Node-Negative Disease After Neoadjuvant Therapy (ypN0) status. This response enables a shift from ALND to less invasive techniques such as Sentinel Lymph Node Biopsy (SLNB) or TAD [33]. TAD, which involves the removal of both sentinel and pre-marked positive nodes, has demonstrated high identification rates and a low false-negative rate in patients treated with NAT. This approach has been endorsed by trials such as ACOSOG Z1071, SENTINA, and, more recently, by Weber et al. [34], who showed that omitting ALND in select patients post-NAT does not compromise oncologic outcomes but significantly reduces surgical morbidity, such as lymphedema, seroma, and shoulder dysfunction [35–37]. These findings support a tailored surgical approach to the axilla based on treatment response (Figure 3) (Table 1,Table 2).

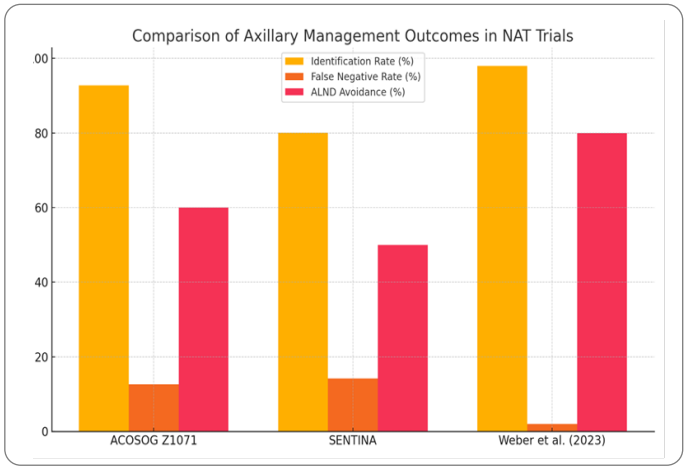

Figure 3: A comparative chart for the ACOSOG Z1071, SENTIN and Weber et al.

trials, comparing the following: identification rate (ability to correctly identify target lymph nodes), false negative rate (risk of underestimating residual disease), estimated percentage of ALND avoidance (reduction in radical axillary dissections).

Table 1: Common Side Effects of Neoadjuvant Therapies.

Side Effect	Description	Notes/References
Hypertension	Significant increase in grade ≥3 hypertension, especially with bevacizumab.	Requires careful monitoring [38, 39]
Left-Ventricular Dysfunction	Impaired heart pumping function, more common with anthracyclines + bevacizumab.	Severe; may require therapy adjustment [38, 39]
Mucositis	Inflammation and ulceration of mucous membranes, often in the gastrointestinal tract.	Can cause significant discomfort [38]
Febrile Neutropenia	Fever and infection risk due to neutropenia; potentially life-threatening.	More frequent with certain regimens [38]
Infection	Increased risk due to immunosuppressive effects of chemotherapy.	Requires prevention and monitoring [38]
Pain	Pain from either the malignancy or the treatment itself.	May require analgesics [38]
Hand-Foot Syndrome	Redness, swelling, and pain in the palms and soles, associated with specific chemotherapy agents.	Affects quality of life [38]
Neutropenia	Low neutrophil count increasing infection risk.	May require G-CSF or dose adjustment [38]
Fatigue	Persistent cancer-related fatigue impacting daily functioning.	Very common and debilitating [40]

Table 2: Management of side Effects.

Strategy	Description	Notes/References
Pharmacologic Interventions	- Antiemetics (e.g., ondansetron, aprepitant) - G-CSF for neutropenia - Dexrazoxane for cardiotoxicity	Standard supportive medications [41]
Monitoring and Early Detection	- Regular echocardiography - Use of biomarkers (e.g., troponins, natriuretic peptides)	Crucial in high-risk patients [41]
Lifestyle Modifications	Healthy diet, regular exercise, smoking cessation	Improves treatment tolerance [41]
Psychosocial Support	Psychological counseling, support groups, anxiety/depression management	Enhances patient resilience [41]
Multidisciplinary Approach	Collaboration among oncologists, cardiologists, nutritionists, and mental health providers	Comprehensive care strategy [41]
Patient Education	Informing patients about side effects and encouraging prompt reporting	Enables timely intervention
Tailored Treatment Plans	Adjust regimens based on individual risk factors (e.g., avoid anthracyclines in cardiac patients)	Personalized medicine approach [42]

Combination Therapies and Emerging Agents

Dual HER2 Blockade: Dual HER2 blockade with trastuzumab and pertuzumab is considered the gold standard in NAT for HER2-positive breast cancer [19]. The NeoALTTO trial [48] demonstrated significantly higher pCR rates when trastuzumab was combined with lapatinib or pertuzumab compared to trastuzumab alone. The CTNeoBC pooled analysis [28] confirmed that dual blockade achieves the most pronounced survival benefit in HR-negative subgroups. For patients with residual disease post-NAT, the KATHERINE trial [44] established the superiority of Trastuzumab Emtansine (T-DM1) over trastuzumab alone, reducing the risk of invasive disease recurrence by 50%.

Novel Agents: Among the most promising emerging therapies, Trastuzumab Deruxtecan (T-DXd), an ADC, has shown remarkable efficacy in heavily pretreated HER2-positive metastatic patients, including those with brain metastases, as demonstrated in DESTINY-Breast03 [50,54,56]. Likewise, margetuximab, an Fc-optimized anti-HER2 antibody, offers improved Antibody-Dependent Cellular Cytotoxicity (ADCC) over trastuzumab [50].

In addition, tucatinib, a HER2-selective Tyrosine Kinase Inhibitor (TKI), has demonstrated Central Nervous System (CNS) activity in the HER2CLIMB trial, making it an important option for patients with brain involvement [51]. Furthermore, pyrotinib, a pan-HER TKI, is under evaluation in multiple Asian trials with encouraging results in terms of response rate and pCR in the neoadjuvant setting [45].

Immunotherapy: Immunotherapy is an emerging frontier in HER2-positive breast cancer. Preliminary studies suggest that combining HER2-targeted therapies with immune checkpoint inhibitors such as atezolizumab or pembrolizumab may enhance immune response, particularly in tumors with high levels of Tumor-Infiltrating Lymphocytes (TILs). Early-phase trials, including the PANACEA study [52], have reported encouraging responses in HER2-enriched subtypes. The integration of immunotherapy into the neoadjuvant setting may expand treatment options for patients with poor responses to standard regimens, although further randomized data are required to establish efficacy (Table 3).

Table 3: Summary of Key Clinical Trials on NAT in HER2-positive breast cancer.

Study	Treatment Combination	Main Findings / pCR Rate	Implication
NeoALTTO [48]	Lapatinib + Trastuzumab + Chemotherapy	pCR: 51.3% (vs 29.5% with trastuzumab alone)	Dual HER2 blockade improves pCR significantly in early HER2+ BC
I-SPY 2 [43]	Neratinib + Standard Chemo-therapy	Higher pCR with neratinib addition	Targeted therapy with neratinib enhances neoadjuvant efficacy
PREDIXHER2 [44]	T-DM1 vsTrastuzumab + Pertuzumab	Similar pCR rates in both arms	T-DM1 may be a viable de-escala-tion strategy
PHERGain [46]	Trastuzumab + Pertuzumab guided by Positron Emission Tomography (PET) (no chemo in responders)	Excellent outcomes in PET-re-sponders; some achieved pCR without chemo	PET-guided de-escalation is feasi-ble in selected patients
Panphila [47]	Pyrotinib + Trastuzumab + Chemotherapy	Favorable pCR rate (specific % not reported)	Pyrotinib may improve outcomes as dual HER2/Epidermal Growth Factor Receptor (EGFR) blockade
WSG-ADAPT HER2+/ HR− [49]	Trastuzumab + Pertuzumab ± Weekly Paclitaxel	pCR: 90.5% with chemo + dual blockade	Dual HER2 blockade + chemo highly effective
Pyrotinib + TAC [45]	Pyrotinib + Docetaxel + Liposomal Doxorubicin + Cyclophosphamide (TAC)	pCR: 37.0%	Pyrotinib combined with TAC is effective in HER2+ breast cancer

Current Guidelines and Recommendations

ESMO and NCCN recommend neoadjuvant systemic therapy with dual HER2 blockade—trastuzumab and pertuzumab—combined with taxane-based chemotherapy as the standard for patients with stage II–III HER2-positive breast cancer [10,16,50]. This regimen has demonstrated high pCR rates and improved long-term survival outcomes, particularly in HR-negative tumors.

For patients who achieve pCR after NAT, current guidelines support continuation of anti-HER2 therapy to complete one full year of treatment. This often consists of trastuzumab alone or in combination with pertuzumab, depending on nodal status and initial disease burden [50,51].

In cases where pCR is not achieved, adjuvant treatment with T-DM1 is strongly recommended, as demonstrated by the KATHERINE trial, which showed superior invasive disease-free survival compared to continued trastuzumab in patients with residual disease (Figure 4). De-escalation strategies are being actively explored in clinical trials, notably PHERGain and WSG-ADAPT HER2+/HR− [53]. These studies are investigating whether selected patients—identified through early response imaging or biomarkers—can safely avoid chemotherapy altogether and be treated effectively with anti-HER2 agents alone or with minimal systemic toxicity. Interim results suggest promising pCR rates and low recurrence risk in low-burden, high-response subsets [54–56].

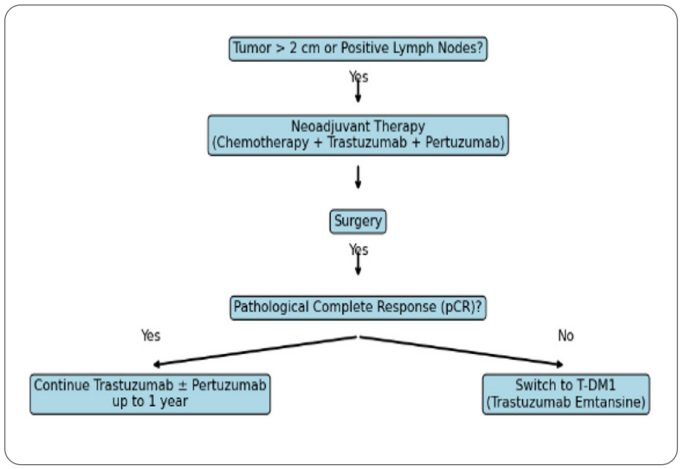

Figure 4: Flowchart based on European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines.

Discussion

NAT not only improves oncologic control but also significantly enhances surgical management in HER2-positive breast cancer [57–59]. Evidence from trials such as TECHNO and BrighTNess demonstrates increased eligibility for BCS following tumor shrinkage, with rates increasing from below 50% to over 70% post-NAT. Moreover, the ANISC consensus and data from Untch et al. [32] confirm that NAT leads to higher rates of margin-negative resections, reducing the need for reoperations.

In addition to these advances in breast surgical management, the ability of NAT to downstage axillary disease has been transformative. The ACOSOG Z1071 and SENTINA trials established the foundation for replacing full Axillary Lymph Node Dissection (ALND) with Targeted Axillary Dissection (TAD), minimizing morbidity without compromising oncologic safety. More recently, Weber et al. [34] validated this strategy in a large contemporary cohort, confirming its role in tailored surgical de-escalation.

At the systemic level, dual HER2 blockade with trastuzumab and pertuzumab remains a cornerstone, supported by data from NeoALTTO and CTNeoBC, which demonstrate elevated pCR rates, particularly in HR-negative tumors. For patients with residual disease, the KATHERINE trial showed that adjuvant T-DM1 significantly improves invasive disease-free survival compared to trastuzumab alone [60].

The emergence of novel anti-HER2 agents, such as T-DXd margetuximab, tucatinib, and pyrotinib, introduces opportunities to overcome resistance to first-line therapies and address metastases, including those in the CNS. Immunotherapy combinations, particularly those involving checkpoint inhibitors like atezolizumab, are also under active investigation and may shape the future of treatment for HER2-enriched subtypes.

Despite these advancements, a major unmet need persists in the identification of robust biomarkers to guide treatment stratification. Trials such as PHERGain and WSG-ADAPT HER2+/HR− are pioneering de-escalation strategies guided by early imaging (e.g., 18F-FDG-PET) and TILs. These approaches aim to individualize therapy, potentially sparing selected patients from the toxicity of chemotherapy while preserving efficacy.

In summary, NAT in HER2-positive breast cancer has evolved from a purely oncologic intervention into a multidimensional strategy that optimizes surgical outcomes, improves survival, and paves the way for precision oncology through de-escalation and emerging targeted modalities.

Conclusion

NAT is transformative in HER2+ breast cancer, significantly impacting survival and surgical outcomes. Surgeons must understand its implications on margin status, axillary approach, and reoperation risk. Future directions include individualized therapy guided by response and molecular profiling, with growing roles for novel anti-HER2 agents and immunotherapy.

Simple Summary

NAT improves surgical outcomes for HER2-positive breast cancer by reducing tumor size and lymph node involvement, thereby increasing eligibility for BCS and decreasing the need for axillary dissection. This enhances margin clearance, lowers local recurrence rates, and provides early information about tumor biology and treatment responsiveness, which is critical for surgical planning.

Conflicts of Interest

The authors declare no conflicts of interest.

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