



Current Treatment Approaches for Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer in Adjuvant and Neoadjuvant Settings

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Abstract

Breast cancer (BC) is the second most common cancer and the second leading cause of mortality among women globally. Approximately 20 to 25% of BC patients have amplification of the human epidermal growth factor receptor 2 (HER2) genes, a marker of poor prognosis. However, the introduction of anti-HER2-therapies (trastuzumab, followed closely by lapatinib, pertuzumab, trastuzumab emtansine, and neratinib) has changed the natural history of HER2-positive BC and improved the outcome in HER2-positive BC patients. The preeminence of anti-HER2 combination therapy in achieving complete inhibition of the various HER receptor dimers has been demonstrated in clinical studies. However, despite these therapeutic advances, tumors expressing estrogen receptor have poorer responses to targeted therapy and are more likely to relapse. A better understanding of resistance to existing anti-HER2 agents, along with the role played by the microenvironment and of interconnected signaling pathways, can permit tailor-made therapeutic options for each patient. This review aimed to evaluate treatment approaches for BC patients with HER2-positive disease in the adjuvant and neoadjuvant settings, also exploring the possibilities of extended duration of anti-HER2 maintenance therapy.

Keywords

- ▶ adjuvant
- ▶ human epidermal growth factor receptor 2 positive breast cancer
- ▶ neoadjuvant

Introduction

Cancer was estimated to be the cause of 9.6 million deaths in 2018, making it the second leading cause of mortality.¹ Breast cancer (BC) is the most frequently diagnosed cancer in women. Overall, it is the second leading cause of death in women.² In 2018, there were over 2 million new cases of BC and over 627,000 women died due to this disease.³ In India, BC is ranked as the most common cancer among females,

with the age-adjusted rate of 25.8/100,000 women and mortality 12.7/100,000 women.⁴

BC has evolved to be a heterogeneous disease clinically and pathologically. Amplification of the human epidermal growth factor receptor 2 (HER2) genes occurs in 20 to 25% of patients.⁵ Human epidermal growth factor receptor 2 is a transmembrane protein with tyrosine kinase activity encoded by the ERBB2 gene. The cell proliferation and tumor

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growth results from ligand-dependent and independent signaling through HER2.⁶

HER2 overexpression is characterized by poorly differentiated high-grade tumors with reduced responses to traditional therapies and decreased survival.^{7,8}

However, the effective advancement of HER2-directed therapies over the last two decades, initially in the palliative and then in the curative-intent settings, has dramatically improved the results in women affected by BC.⁹ A considerable number of HER2-targeted agents are available including monoclonal antibodies (MAbs), small-molecule inhibitors, and antibody–drug conjugates (ADC).¹⁰ The introduction of anti-HER2-therapies (trastuzumab, followed closely by lapatinib, pertuzumab, and trastuzumab emtansine) has changed the natural history of HER2-positive BC. Discovery of these therapies has resulted in a significant improvement in survival of both early and advanced settings.¹⁰⁻¹²

Currently, the standard of care in HER2-positive early BC includes neoadjuvant treatment with a combination of sequential chemo and HER2-targeted therapy, followed by breast surgery and radiotherapy (if indicated).¹³ This is ensued by 12 months of HER2-directed therapy, and depending on the tumor biology, endocrine adjuvant therapy.¹³ This article reviews the current treatment approaches for BC patients with HER2-positive disease in the adjuvant and neoadjuvant settings.

The Function of Human Epidermal Growth Factor Receptors and Their Inhibitors

The human epidermal growth factor (EGF), HER1, HER2, HER3, and HER4 are receptor tyrosine kinases involved in signal transduction pathways that modulate cellular processes.¹⁴ All HER receptors excluding HER3 consist of an extracellular ligand-binding domain and intracellular tyrosine kinase domain (T). The ligand (L) binds the receptor's extracellular domain, homodimerization, and heterodimerization, leading to tyrosine kinase domain phosphorylation and activation of downstream signaling pathways.¹⁴ Many novel HER2-targeting agents including the MAb trastuzumab, pertuzumab, and ADC trastuzumab emtansine (T-DM1), and the tyrosine kinase inhibitors (TKIs) like lapatinib and neratinib, have been developed; these agents target the signal transduction pathway downstream from HER2 (► Fig. 1 and ► Table 1).^{8,15,16}

Human Epidermal Growth Factor Receptor 2 Inhibitors

Trastuzumab is a humanized MAb. It is the first HER2-targeting drug introduced to BC clinics and remains a major component of the most effective regimens used to treat HER2-positive BC. Pertuzumab is an alternative monoclonal anti-HER2 antibody, which binds HER2 at a different location than trastuzumab. It inhibits the formation of HER2-HER3 heterodimers.¹⁵ Lapatinib is a reversible small-molecule TKIs, which has activity against the tyrosine kinase ATP-binding pocket of HER1 as well as HER2.⁸

Trastuzumab emtansine is an ADC. This new drug enables targeted delivery of cytotoxic molecules to the tumor, thereby increasing efficiency and simultaneously reducing toxicity.¹⁵

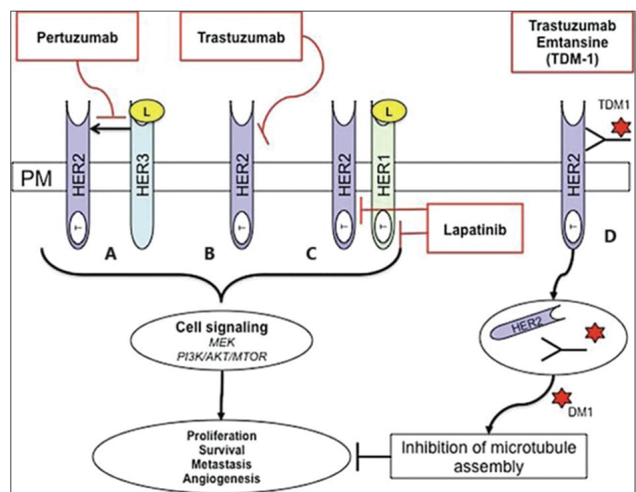


Fig. 1 Human epidermal growth factor receptor 2 (HER2) targeted therapies for the treatment of metastatic breast cancer.¹⁴

Table 1 Antihuman epidermal growth factor receptor 2 blocking agents and mechanisms of action¹⁶

Class of compounds	Agent (s)	Mechanism of action
Monoclonal antibody	Trastuzumab	Prevent formation of HER2-containing heterodimers, antibody-dependent cell-mediated cytotoxicity (ADCC), disruption of downstream signaling pathways, inhibition of cleavage of HER2, and promoting endocytosis of HER2 receptor
	Pertuzumab	It exerts its function by binding with an epitope on the extracellular domain of HER2 receptors, therefore preventing the formation of HER2-containing heterodimers
Antibody drug conjugates	T-DM1	Trastuzumab's action Selective delivery of the antimicrotubule agent DM1
Small-molecule inhibitors	Lapatinib	Reversible and dual small molecular inhibitor of HER2 and HER1 with prolonged inhibition of tyrosine phosphorylation in tumor cells
	Afatinib, neratinib	Irreversible dual inhibitor of EGFR and HER2

Abbreviations: EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine.

Human Epidermal Growth Factor Receptor 2 Inhibitors and Tumor Resistance

While BC will be cured in some patients treated in the adjuvant setting, a fraction is predicted to eventually recur. Tumors harbor de novo or acquire resistance to therapeutic inhibitors of HER2.^{17,18} General mechanisms of resistance to HER2-targeted therapies transpire at three levels. The first involves mechanisms inherent in the target, such as molecular changes in the target receptor; the p95HER2 expression, which is a truncated HER2 receptor; and HER2 gene amplification.¹⁹ Second, resistance involving parallel signaling

pathways bypassing HER2 inhibition, like amplified activation of HER3, unusual activation of pathways downstream of the receptor, and compensatory crosstalk with other pathways, can also occur.¹⁹ The third mechanism involves resistance due to defects in the apoptosis pathway in tumor cells or extrinsic host factors contributing to the action of the drugs.¹⁹

Biological Insights into Improved Human Epidermal Growth Factor Receptor 2 Targeting

Inhibition of Human Epidermal Growth Factor Receptor Family Dimerization

The dimerization of HER family members is a known mechanism of resistance to anti-HER2 therapy.²⁰ All members of the HER family can form dimers together, but HER2 and HER3 form a predominantly potent heterodimer, which is important in BC growth and development. Although HER3 does not exert tyrosine kinase activity on its own, HER2 dimerization considerably increases downstream signaling activity^{21,22} and provides an escape mechanism for HER2 inhibition.^{23,24} Pertuzumab is a humanized MAb bound to the HER2 dimerization domain. It is an inhibitor of HER2/HER3 dimerization and also induces antibody-dependent cellular cytotoxicity. Although pertuzumab has some clinical activity of its own when used in combination with trastuzumab, the dual binding to HER2 results in synergistic action.⁸

In the pertuzumab and trastuzumab (CLEOPATRA) phase III clinical evaluation trial, 808 patients with metastatic BC (MBC) who had not previously received anti-HER2 therapy for metastatic disease were treated with the combination of pertuzumab and trastuzumab with docetaxel. Median progression-free survival as investigators assessed, increased by 6 months (hazard ratio [HR]: 0.65, $p < 0.001$), and the objective response rate improved by 10.8%.²⁵ The combination also leads to a marked increase in overall survival (OS) by almost 16 months compared with standard trastuzumab plus docetaxel (HR: 0.68, $p < 0.001$).²⁶ Since this research, pertuzumab plus trastuzumab has replaced trastuzumab as the standard of care for first-line metastatic BC.

Many TKIs such as lapatinib and neratinib have recently been developed to target the downstream signal transduction pathway from HER2. It is effective against HER2 amplification in early as well as metastatic BC when given in combination with trastuzumab.^{27,28} However, most HER2 somatic mutations were resistant to lapatinib in preclinical studies.²⁹ Neratinib has emerged as a potent inhibitor of HER2 activity as yet another HER2-targeting TKI. It is an irreversible pan-inhibitor of HER2 and HER1/EGFR and has been found to be more effective in blocking HER2 activation than lapatinib.^{30,31}

Optimizing Human Epidermal Growth Factor Receptor 2-Targeted Therapy for Breast Cancer

The advancement of HER2-targeted therapies has revolutionized women's treatment of HER2-positive BC. These

targeted therapies have improved their outcomes significantly (► **Table 1**).^{8,15,16} In a series of key trials, trastuzumab was tested in the adjuvant setting, with the success of anti-HER2 therapy in (MBC). Major international trials were the Herceptin Adjuvant (HERA) Trial study, the National Surgical Adjuvant Breast and the Bowel Project (NSABP) B-31 trial, the BC International Research Group 006 trial, and the North Central Cancer Treatment Group N9831 of more than 13,000 women with HER2-positive early BC.

Patients treated with trastuzumab in the HERA trial experienced a 46% lower risk of a first event (HR: 0.54; 95% confidence interval [CI]: 0.43–0.67; $p < 0.0001$) than patients under observation, at 1-year median follow-up. This corresponded to an absolute disease-free survival (DFS) benefit favoring trastuzumab of 8.4% at 2 years.³²

Present Standards of Care in Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer

For HER2-positive early BC, the current standard of care includes trastuzumab (with or without pertuzumab) and chemotherapy,⁸ established on the basis of benefit of trastuzumab over standard care in both the adjuvant and neoadjuvant settings, shown in several clinical studies.^{8,32-35} In the phase III HERA trial, 1 year of adjuvant trastuzumab was associated with significant improvements in both 10-year rates of DFS (69 vs. 63%; HR: 0.76) and 12-year rates of OS (79% vs. 73%; HR: 0.74) compared with observation.^{8,32,33}

In the phase III NeoAdjuvant Herceptin (NOAH) trial, HER2-positive patients treated with trastuzumab plus chemotherapy had a significantly higher rate of pathologic complete response (pCR) compared with patients who received chemotherapy only (38.5 vs. 19.5%; HR: 0.29, $p = 0.0135$) and these patients remained disease-free longer (5-year event-free survival [EFS] 58 vs. 43%; HR: 0.64, $p = 0.016$).³⁵ Even though trastuzumab has demonstrated efficacy in early BC, a significant proportion of patients in due course of time will progress.⁸ In the HERA trial, after 10 years of follow-up, 28.8% of patients treated with trastuzumab experienced disease progression.^{8,32,33} Likewise, in the NOAH trial, at only 5 years posttreatment with trastuzumab, 42% of patients treated experienced a disease recurrence.³⁵ This establishes that for several patients with HER2-positive BC, there is still a significant unmet need, and research in recent years has focused on identifying novel approaches to adjuvant and neoadjuvant therapy that can improve outcomes for these patients.⁸

Human Epidermal Growth Factor Receptor 2-Targeted Adjuvant Therapy Other Approaches

Many novel HER2-targeting agents have been studied including dual HER2 blockade. These agents have the potential for being used as adjuvant therapy for patients with nonmetastatic HER2-positive BC.

Lapatinib

Lapatinib has been evaluated as prospective adjuvant therapy for HER2-positive BC, either alone or in combination with

trastuzumab. In the Tykerb Evaluation after Chemotherapy trial, lapatinib was compared with placebo in women with HER2-positive early BC, who had previously received adjuvant chemotherapy but not trastuzumab.³⁶ The study results showed that single-agent lapatinib failed to demonstrate a significant DFS benefit over placebo (HR: 0.83, 95% CI: 0.70–1.00). However, exploratory analyses showed a marginal benefit for patients with HER2-positive disease confirmed by central fluorescence in situ hybridization.³⁶ Patients who received single-agent lapatinib had poorer outcomes relative to patients who received trastuzumab in the adjuvant lapatinib and/or trastuzumab treatment optimization (ALTTO) trial (HR: 1.34).³⁷ Lapatinib and trastuzumab combination appeared to improve outcomes, as patients who received both lapatinib and trastuzumab, either in combination (L + T) or in sequence (T → L), showed significant DFS rates (L + T: 88% and T → L: 87%) as compared with patients who received single agent (lapatinib L: 82%). However, at the 5 years of follow-up, the combination did not sufficiently improve either DFS or OS compared with single-agent trastuzumab.³⁸ At present, lapatinib is not being further studied, either alone or in combination with trastuzumab, in the adjuvant setting.

Neratinib

Neratinib studies had been successful in the adjuvant setting. A multicenter, randomized, double-blind, placebo-controlled, phase III study, neratinib after trastuzumab-based adjuvant therapy in HER2-positive BC (ExteNET) compared neratinib (240 mg daily) to placebo.³⁹ This study was conducted at 495 centers across America, Europe, Asia, Australia, and New Zealand. The women included in this study were with stage I to III HER2-positive BC, who had completed neoadjuvant and adjuvant trastuzumab for up to 2 years (amended to 1 year) before randomization. Included patients were stage I to III node positive and node negative with tumors >1 cm in size. In this study, neratinib improved invasive DFS (iDFS) by 2 years by 2.3% over placebo (HR: 0.67, $p = 0.009$).³⁹

This improvement was most discrete in patients with hormone receptor (HR) -positive tumors (HR: 0.51, $p = 0.001$). This study suggested that neratinib may provide a treatment option for this subset of patients who have a long-term constant risk of relapse on trastuzumab.

Furthermore, at 5-year follow-up, the benefit with neratinib was maintained with a 2.5% absolute improvement in iDFS (90.2 vs. 87.7%; HR: 0.73, $p = 0.008$) for the whole population.⁴⁰ This improvement in iDFS was most apparent in HR-positive patients (91.2 vs. 86.8%; HR: 0.60, $p = 0.002$).⁴⁰ It was observed that patients who have completed adjuvant trastuzumab <1 year prior to the start of the study showed the maximum benefit with neratinib.⁴⁰

Pertuzumab

APHINITY study examined the pertuzumab (P) and trastuzumab (T) combination as adjuvant treatment, compared with standard trastuzumab plus chemotherapy (C) in 4805 patients with HER2-positive early BC.⁴¹ The study included patients who had either node-positive disease or node-negative disease (pN0) and a tumor size of >1.0 cm.

Eligible patients were with pN0, T1b tumors with high-risk features. A total of 4805 patients were randomized to C and T plus either P ($n = 2400$) or placebo ($n = 2405$).⁴¹

This study reached its primary end point of improved iDFS at 3 years (94.1 vs. 93.2%; HR: 0.81, $p = 0.045$), the gain magnitude was small, and there was no related change in OS (97.7% for both groups; HR: 0.89, $p = 0.467$).

Analysis in the subgroup suggested a somewhat greater effect on ER-negative tumors (HR: 0.76, $p = 0.085$). Treatment with pertuzumab was associated with an increase in grade ≥ 3 diarrhea (9.8 vs. 3.7%).⁴¹ Results from key phase III trials are summarized in ►Table 2.

Ado-trastuzumab Emtansine

T-DM1 is an immunoconjugate of trastuzumab with a microtubule inhibitor. It is a derivative of fungal toxin emtansine (DM1), which has three capabilities: anti-HER2 function of trastuzumab, DM1-induced cytotoxicity, and tissue-specific expression.⁴²

The KATHERINE trial compared adjuvant therapy with T-DM1 to adjuvant trastuzumab in patients with HER2-positive early BC who had residual disease after neoadjuvant therapy involving a minimum of six cycles of taxane-based chemotherapy and 9-week trastuzumab.⁴² Patients randomized received either 14 cycles of ado-trastuzumab emtansine or 14 cycles of trastuzumab. Treatment with 14 cycles of adjuvant T-DM1 resulted in a significant improvement in the rates of iDFS compared with adjuvant trastuzumab.⁴³

iDFS favored T-DM1 in all prespecified patient subgroups. At 3 years, a larger proportion of patients receiving T-DM1 remained free of distant recurrence (89.7 vs. 83.0%; HR: 0.60). There was a trend toward improved OS in patients receiving T-DM1 (although the OS data are not yet mature). This study concluded that adjuvant T-DM1 in patients with invasive residual disease demonstrated a statistically significant benefit with clinically meaningful improvements in iDFS compared with trastuzumab, and tailoring therapy based on pathological response improves outcomes.⁴³

Neoadjuvant Therapy for Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer

Trastuzumab as neoadjuvant therapy provides significant clinical benefits and decreases the rate of distant metastasis.⁴⁴ Clinical studies have shown that trastuzumab-based neoadjuvant therapy has a higher rate of pCR (defined as the absence of residual cancer in the breast or axillary lymph node pathology) in the treatment of HER2-positive BC.⁴⁵

At first, a small randomized trial was conducted to determine whether the addition of trastuzumab to chemotherapy in the neoadjuvant setting could increase (pCR) rate in patients with HER2-positive disease. This study confirmed the role of trastuzumab in the neoadjuvant scenario.⁴⁶ Another multicenter, open-label, randomized phase III study was NOAH trial.⁴⁷ A sustained improvement in the EFS rate with neoadjuvant therapy involving trastuzumab was achieved after a 5.4-year follow-up (58 vs. 43%; HR: 0.64). A strong association with pCR was revealed in patients given trastuzumab.

Table 2 Disease-free survival and overall survival rates for phase III adjuvant trials of novel human epidermal growth factor receptor 2 inhibitors⁸

Agent/trial	Disease setting	Regimen	n	Follow-up	DFS	OS
Lapatinib						
ALTO trial	Stage I–III adjuvant therapy	Lapatinib + trastuzumab	8,381	6 y	85% (HR: 0.86)	93% (HR: 0.86)
Piccart-Gebhart et al ³⁷		Lapatinib (34 w) → Trastuzumab (12 w)			84% (HR: 0.93)	92% (HR: 0.88)
Moreno-Aspitia et al ³⁸		Trastuzumab			82%	91%
		Lapatinib			82% (HR: 1.34)	93% (HR: 1.36)
TEACH—Goss et al ³⁶	Stage I–III delayed adjuvant therapy. Prior trastuzumab unless contraindicated	Lapatinib	3,147	47.4 mo	87% (HR: 0.83)	94% (HR: 0.99)
Neratinib		Placebo		48.3 mo	83%	94%
ExteNET—Martin et al ⁴⁰	Stage I–III delayed adjuvant therapy. Prior trastuzumab	Neratinib	2,840	5 y	90.2% (HR: 0.73)	Not mature
Pertuzumab		Placebo			87.7%*	
APHINITY—von Minckwitz et al ⁴¹	Stage II–III adjuvant therapy	Pertuzumab (plus chemo and trastuzumab)	4,805	36 mo	94.1% (HR: 0.81)*	97.7% (HR: 0.89)
		Placebo (plus chemo and trastuzumab)			93.2%*	97.7%

Abbreviations: ALTO, adjuvant lapatinib and/or trastuzumab treatment optimization; Chemo, chemotherapy; DFS, disease-free survival; ET, endocrine therapy; HR, hazard ratio; OS, overall survival.

pCR improved from 22 to 43% ($p < 0.001$).³⁵ In the trial of Taxol Epirubicin Cyclophosphamide Herceptin Neoadjuvant (TECHNO), 217 HER2-positive patients obtained four cycles of EC (epirubicin and cyclophosphamide) followed by four cycles of TH (paclitaxel and trastuzumab) as neoadjuvant therapy. pCR was obtained in nearly 38.7%. Three-year DFS (88 vs. 71%; $p = 0.003$) and OS (96 vs. 85%; $p = 0.007$) were improved.⁴⁸

Other trials, such as the American Z1041 trial,⁴⁹ Gepar Quattro study,⁵⁰ and HannaH trial,⁵¹ also enrolled HER2-positive BC patients with comparable inclusion criteria as TECHNO. These trials also evaluated treatment with chemotherapy plus trastuzumab as concurrently or consequence regimens (► **Table 3**).

Other Therapy in the Neoadjuvant Setting

The GeparQuinto⁵² phase III trial compared the efficacy of two HER2-targeted drugs, lapatinib and trastuzumab, with the combination of four cycles of chemotherapy with EC, followed by docetaxel. The results of the study indicated that the arm of trastuzumab showed ~7% more pCR than the arm of lapatinib (30.3 vs. 22.7%; $p = 0.04$).⁵²

The lapatinib with trastuzumab for HER2-positive early BC (NeoALTO) trial,²⁷ an international, randomized, open-label, multicenter, phase III study, compared the efficacy of lapatinib or trastuzumab monotherapy, or the concomitant lapatinib and trastuzumab regimen, in addition

to paclitaxel, in the neoadjuvant setting. In the combination arm, noticeable progress on pCR of 51% was observed, which is almost twice as much as the other two monotherapies against HER2 (29.5% in trastuzumab alone and 24.7% in lapatinib alone, $p < 0.001$).²⁷ Other studies with the dual inhibitory regimen, NSABP B-41 study,⁵³ NeoSphere trial,^{54,55} and the TRYPHAENA trial⁵⁶ details are illustrated in ► **Table 3**.

Novel Strategies to Overcome Resistance to Human Epidermal Growth Factor Receptor 2-Targeted Therapy

Replacement of Current Antihuman Epidermal Growth Factor Receptor 2 Therapies for Improved Antihuman Epidermal Growth Factor Receptor 2 Drugs Antibody–Drug Conjugates

ADCs provide a wider therapeutic window by providing more effective and specific drug delivery. ADCs leverage target selectivity of MABs to deliver cytotoxic drugs to antigen-expressing cells to enhance tumor selectivity and reduce damage to normal cells.⁵⁷ Several anti-HER2 ADCs in clinical development are listed in ► **Table 4**.

Novel Tyrosine Kinase Inhibitors

There are several novel TKIs in clinical development listed in ► **Table 5**.

Table 3 Optimal clinical trials in the neoadjuvant setting for human epidermal growth factor receptor 2-positive breast cancer⁵⁷

Drug or study name	Neoadjuvant chemotherapy	Number of patients	Pathological complete response (%)	Comments	References
The NSABP B-41 trial	AC → TH or TL or THL	181 versus 174 versus 174	52.5% versus 53.2% versus 62.0%	H + L no better. All patients received anthracyclines	Robidoux et al ⁵³
Pertuzumab The NeoSphere trial	Do + H versus Do + P versus P + H	107 versus 107 versus 96	29.0% versus 45.8% versus 24.0% versus 16.8%	≥0.6. Combination P + H results in better pCR	Gianni et al ^{54,55}
The TRYPHAENA trial	FEC + HP → Do + HP versus FEC → Do + HP versus TCHP	223 patients in total	62% versus 57% versus 66%	TCH + P is an active combination	Schneeweiss et al ⁵⁶

Abbreviations: A, Adriamycin; BC, breast cancer; C, cyclophosphamide; Do, docetaxel; E, epirubicin; F, 5FU; H, trastuzumab; human epidermal growth factor receptor 2; L, lapatinib; M, methotrexate; P, pertuzumab; pCR, pathologic complete response; T, paclitaxel; TC, docetaxel plus carboplatin; T-DM1, trastuzumab emtansine.

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Table 4 Human epidermal growth factor receptor 2-directed antibody-drug conjugates in clinical development

Agent	Anti-HER2 MAb/payload (target)	Drug to antibody ratio	Linker drug	Phase of development	ORR in HER2 ⁺ positive	ORR in HER2 low (IHC 1+/2+/IS)
T-DM1 ⁵⁸	T-DM1 (antitubulin)	3.5	Noncleavable	US FDA approved	43.6%	–
Trastuzumab deruxtecan (DS-8201a) ⁵⁹	Trastuzumab/exatecan derivative (topoisomerase I inhibitor)	8	Cleavable	II/III NCT03248492 NCT03529110 NCT03523585	54.5%	50%
SYD985 ⁶⁰	Duocarmycin derivative (alkylating agent)	2.8	Cleavable	III NCT03262935	33%	HR ⁺ 27% HR ⁻ 40%
XMT-1522 ⁶¹	XMT-1519/monomethyl auristatin (antitubulin)	12	Cleavable	I NCT02952729	Unknown	Unknown

Abbreviations: ADC, antibody-drug conjugate; HR⁻, hormone receptor-negative; HR⁺, hormone receptor-positive; IHC, immunohistochemistry; MAb, monoclonal antibody; NCT, ClinicalTrials.gov identifier; ORR, overall response rate; T-DM1, trastuzumab emtansine; US FDA, United States Food and Drug Administration.

Escalating or De-escalating Adjuvant Therapy in Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer

Recently, many studies have investigated modifications of the schedule of treatment with trastuzumab by either making it shorter and less toxic (de-escalation) or more effective with dual HER2 inhibition or extended treatment duration (escalation).⁶³

Seven randomized trials investigated whether a shorter regimen of adjuvant trastuzumab may be as effective as 1-year of trastuzumab, but with fewer side effects. In four trials, trastuzumab was given in combination with chemotherapy in the experimental arm with the objective to investigate drug synergism (FinHer, E2198, SOLD, and Short-HER trials), and three trials compared 6- to the 12-month duration of trastuzumab (the Hellenic trial, PHARE, and PERSEPHONE).

The FinHer study randomized⁶⁴ 1,010 women with axillary node-positive or high-risk node-negative BC to obtain

three cycles of docetaxel or vinorelbine, followed by three cycles of fluorouracil (F), epirubicin (E), and cyclophosphamide (C) in both groups. Two-hundred thirty-two patients with HER2-positive BC were further treated with trastuzumab or no additional therapy. Even though trastuzumab was given for a shorter duration, distant DFS (83.3 vs. 73%) and OS (91.3 vs. 82.3%) favored the trastuzumab arm after a median of 8 years.⁶⁴

In the SOLD trial,⁶⁵ 2,176 patients with early-stage HER2-positive BC were randomized (1:1) to the 9-week trastuzumab arm or the 12-month trastuzumab arm. Both arms received three cycles of docetaxel (80 mg/m² or 100 mg/m²) and trastuzumab (q3 weekly), followed by three cycles of chemotherapy.⁶⁵ The 9-week arm received no further treatment, while those in the 12-month arm received additional 14 cycles of trastuzumab every 3 weeks. The trial failed to establish that 9 weeks of adjuvant trastuzumab was non-inferior to the standard 12 months in terms of DFS.⁶⁵ The

Table 5 New antihuman epidermal growth factor receptor 2 agents and combinations⁶²

	Novel HER2 antibodies
Agent	Mechanism of action
Margetuximab (MGAH22)	Optimized Fc domain for enhanced binding to the activating low-affinity Fc receptor, FcγRIIIA
MCLA-128	IgG1 bispecific antibody with enhanced ADCC activity targeting both HER2 and HER3 receptors
ZW-25	The bispecific antibody directed against two distinct epitopes of HER2
ADC	
SYD 985	Trastuzumab with an alkylant prodrug DUBA (duocarmycin derivate) payload
DS-8201	HER2 antibody attached to topoisomerase I inhibitor (DXd) payload
TKIs	
Neratinib	Oral TKI that irreversibly inhibits HER1, HER2 and HER 4
Tucatinib	Oral TKI, ATP competitive, selectively inhibits HER2 relative to EGFR
Pozotinib	Irreversible oral TKI, pan-HER kinase inhibitor
Pyrotinib	Irreversible oral, TKI pan-HER kinase inhibitor
Immune approaches	
Atezolizumab	Anti-PD-L1 antibody
Pembrolizumab	Anti-PD-L1 antibody
CDK4/6 inhibitor	
Palbociclib	CDK4/6 inhibitor
Abemaciclib	CDK4/6 inhibitor
Ribociclib	CDK4/6 inhibitor
PI3K inhibitors	
Alpelisib	α-specific PI3K inhibitor
Copanlisib	Pan-class PI3K inhibitor
Taselisib	β-sparring PI3K inhibitor

Abbreviations: ADC, antibody-drug conjugates; ADCC, antibody-dependent cell-mediated cytotoxicity; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; NR, not reported; ORR, overall response rate; PI3K, phosphatidylinositol-3-kinase; T, trastuzumab; TKI, tyrosine kinase inhibitor.

shorter trastuzumab treatment was safer to the heart than the longer treatment. In the 9-week group, there were 22 protocol-defined cardiac adverse events compared with 42 in patients receiving 1 year of trastuzumab ($p = 0.012$).⁶⁵

In the short-HER study,^{66,67} patients were randomly selected to receive 1 year of trastuzumab plus chemotherapy ("long" group) or 9 weeks of trastuzumab plus chemotherapy ("short" group). The primary end points were DFS and OS. The secondary end points included failure rate at 2 years and the incidence of cardiac events.^{66,67} The 5-year DFS was not noninferior (87.5 vs. 85.4% in the long and short groups, respectively, HR: 1.15, 90% CI: [0.91, 1.46]). In an analysis of DFS in patients with the earlier-stage disease (stage I and II) as compared with those with locally advanced disease (stage III), the shorter duration was not inferior to the longer one. There was no difference in OS at 5 years.⁶⁶

PERSEPHONE was a noninferiority trial, which randomized patients of early BC to 6 months of trastuzumab versus the standard 12 months in 4,088 patients between 2007 and

2015.^{68,69} Patients were randomized to receive either 6-month or 12-month trastuzumab delivered every 3 weeks intravenously (loading dose of 8 mg/kg followed by maintenance doses of 6 mg/kg) or subcutaneously (600 mg), given in combination with chemotherapy (concurrently or sequentially). The margin of noninferiority was 3% difference in DFS of the 6-month arm versus 12-month arm. Randomization was done before the tenth cycle of trastuzumab. The researchers found nearly identical results between the two treatment arms at a mean follow-up of 5 years: DFS was 89.4% for women in the 6-month arm and 89.8% for women in the 12-month arm indicating a noninferiority of 6-month trastuzumab in women with carefully selected early BC and adding an option of 6-month trastuzumab in resource-limited setting.^{68,69}

Seven-Year Follow-Up of Adjuvant Paclitaxel and Trastuzumab Trial

This study included 410 HER2-positive BC patients with tumors 3 cm or smaller and negative nodes. They received

12 weeks of paclitaxel (80 mg/m²) with trastuzumab followed by 9 months of trastuzumab.⁷⁰ The main end point was DFS. It also analyzed recurrence-free interval, BC-specific survival, and OS.

After a median follow-up of 4 years, the first study from the Adjuvant Paclitaxel and Trastuzumab trials revealed an intrusive DFS of 98.7 over 3 years, and at 7 years, DFS was 93.3%. In patients with HR-positive tumors, the 7-year DFS was 94.6%, while in HR-negative patients, the 7-year DFS was 90.7%. Key secondary outcomes at 7 years included the relapse-free interval of 97.5%, BC-specific survival of 98.6%, and OS of 95%.⁷⁰ This long-term data support the use of adjuvant paclitaxel and trastuzumab as a treatment option for patients with tumor size <3 cm and node-negative HER2-positive BC. However, it is important to note that ~50% of the patients were <1 cm and another 41.2% were T-size 1 to 2 cm. This regimen represents an important step in de-escalating therapy in early BC with the intent to preserve the quality of life and yet achieve excellent oncological outcomes for node-negative HER2-positive early BC.⁷⁰

Extended Duration of Antihuman Epidermal Growth Factor Receptor 2 Therapy

In 2017, neratinib was approved by the Food and Drug Administration for extended adjuvant treatment of patients with early-stage HER2-positive BC after adjuvant trastuzumab-based therapy.⁷¹

So far, the overall approach has stepped up treatment by adding more targeted HER2 agents. Yet, the initiation of treatment is burdened by high cost and severe toxicity, and in some cases may be overtreatment. Therefore, it is important to update the current treatment approaches and de-escalation is a research goal to minimize adverse effects without sacrificing patient outcomes.

Challenges and Future Directions

Targeting Human Epidermal Growth Factor Receptor 2/ER Crosstalk

Although HER2 inhibition is highly effective in improving outcomes in HER2-positive BC patients, tumors expressing estrogen receptor (ER) have poorer responses to targeted therapy and are more likely to relapse.^{33,72,73} Current theories have revealed that in patients with HER2-positive/ER-positive tumors, a key mechanism of trastuzumab resistance could be crosstalk between HER2 and ER, most likely through PI3K pathway. It has been observed in preclinical studies with HER2-positive/ER-positive tumor models that inhibition of HER2 results in an increase in ER signaling.⁷⁴

PI3K is a main component of the HER2 signaling pathway. It plays a very important role in regulating ER expression in BC. A suggested solution to the issue of HER2/ER crosstalk is to combine HER2 inhibition with ER inhibition, blocking both mechanisms. Preclinical studies have found that this strategy is effective for ER-positive tumors with *PIK3CA* mutations, where coadministration of PI3K inhibitors with hormone therapy increased responses.⁷⁵ In a few studies, the

combination of HER2 and ER inhibition improved outcomes over inhibition of either pathway alone.⁷⁶⁻⁷⁸ In the neoadjuvant setting, the simultaneous targeting of both pathways did not affect response.⁷⁹

Conclusion

BC is a very common, complex, and heterogeneous disease. Highly malignant with poor outcomes after recurrence and metastasis, HER2-positive BC accounts for 20 to 25% of all BC. Anti-HER2 therapy is the keystone for early and advanced HER2-positive BC.

Trastuzumab has been breakthrough drug for anti-HER2 treatment. One-year treatment with trastuzumab is a standard for adjuvant therapy. Pertuzumab also showed an overall benefit in (neo) adjuvant therapy. Double-targeted adjuvant therapy can be beneficial in high-recurrence risk groups (positive lymph nodes or ER/progesterone receptor-negative patients). Extended adjuvant therapy with neratinib needs balancing therapy with adverse effects and its effects on quality of life. Treatment of residual disease after neoadjuvant therapy with T-DM1 shows promise and must be offered where possible.

Although trastuzumab, pertuzumab, lapatinib, neratinib, and T-DM1 are promising drugs, some patients may show no response or develop drug resistance after a period of treatment. There are several new anti-HER2 agents and combination studies in clinical development. With the introduction of any new treatment or regimen, care must be taken about the risks and therapeutic benefits.

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Conflicts of Interest

There are no conflicts of interest.

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