Current treatment approaches for breast cancer patients with HER2-positive disease in the adjuvant, and neo-adjuvant setting

Rashmi Purushottam Surti*

ABSTRACT

Breast cancer (BC) is the second most common cancer and the 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, and T-DM 1) has changed the natural history of HER2-positive BC and improved the prognosis and survival in HER2-positive BC patients. The approval of trastuzumab and pertuzumab linked with a taxane as a first-line treatment and follow-up treatment with the antibody-drug conjugate T-DM1 has undeniably contributed to attaining these outcomes. The Tyrosine Kinase Inhibitor lapatinib is another commonly used treatment in combination with capecitabine, approved on the basis of an improvement in progression-free survival. The superiority of combination anti-HER2 therapy to achieve more complete inhibition of the various HER receptor dimers has been demonstrated in clinical studies. Nonetheless, studies have also suggested that some HER2-amplified tumors may benefit from anti-HER2 therapy combined with only a single chemotherapy agent or in the absence of any chemotherapy. However, despite therapeutic advances, tumors expressing estrogen receptor (ER) 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. The aim of this review is to evaluate treatment approaches for BC patients with HER2-positive disease in the adjuvant, and neo-adjuvant setting.

Keywords: Breast cancer, HER2

INTRODUCTION

Breast cancer is a heterogeneous disease, with approximately 20% to 25% of patients having amplification of the human epidermal growth factor receptor 2 (HER2) genes. HER2 is a transmembrane protein with tyrosine kinase activity encoded by the ERBB2 gene. Ligand-dependent and independent signaling through HER2 results in cell proliferation and tumor growth. HER2 overexpression is associated with poor clinical prognosis, poorly differentiated, high-grade tumors reduced responses in younger patients to traditional therapies and decreased survival. However, the successful development of HER2-directed therapies in the past two decades, first in the palliative and...
then the curative-intent settings, BC-specific outcomes are now dramatically improved for affected women.\textsuperscript{9} A substantial number of HER2-targeted agents are available including monoclonal antibodies, small molecule inhibitors, and antibody-drug conjugates.\textsuperscript{10} The introduction of anti-HER2- therapies (trastuzumab, followed closely by lapatinib, pertuzumab, and T-DM1) has changed the natural history of HER2-positive BC and led to notable improvements in survival of both early and advanced settings.\textsuperscript{10,12}

Neo-adjuvant treatment with a combination of sequential chemotherapy and HER2-targeted therapy, followed by breast surgery, radiotherapy (if indicated), completion of 12 months of HER2-directed therapy, and depending on the tumor biology, endocrine adjuvant therapy is currently the standard of care in HER2-positive early BC.\textsuperscript{13} This article will review current treatment approaches for BC patients with HER2-positive disease in the adjuvant, and neoadjuvant setting.

**Table 1: Anti-HER2 blocking agents- mechanisms of action.**\textsuperscript{16}

<table>
<thead>
<tr>
<th>Class of compounds</th>
<th>Agent (S)</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoclonal antibody</strong></td>
<td>Trastuzumab</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Pertuzumab</td>
<td>It exerts its function by binding with an epitope on the extracellular domain of HER2 receptors, therefore preventing the formation of HER2-containing heterodimers.</td>
</tr>
<tr>
<td><strong>Antibody-drug conjugates</strong></td>
<td>Trastuzumab-DM1</td>
<td>Trastuzumab's action Selective delivery of the antimicrotubule agent DM1</td>
</tr>
<tr>
<td><strong>Small-molecule inhibitors</strong></td>
<td>Lapatinib</td>
<td>Reversible and dual molecular inhibitor of HER2 and HER1 with prolonged inhibition of tyrosine phosphorylation in tumor cells.</td>
</tr>
<tr>
<td></td>
<td>Afatinib, neratinib</td>
<td>Irreversible dual inhibitor of EGFR and HER2</td>
</tr>
</tbody>
</table>

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; p95HER2, carboxy-terminal fragments of HER2; EGFR, epidermal growth factor receptor.

**Figure 1: HER2 Targeted therapies for the treatment of metastatic BC.**\textsuperscript{14}

**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 within the plasma membrane (PM). These factors are involved in signal transduction pathways that modulate cellular processes.\textsuperscript{14} All factors except HER3 consist of an extracellular ligand-binding domain and intracellular tyrosine kinase domain (T). The ligand (L) binds the receptor’s extracellular domain, homo-dimerization, and hetero-dimerization leads to tyrosine kinase domain...
phosphorylation and activation of downstream signalling pathways. There is an emergence of several novel HER2-targeting agents, including the monoclonal antibody trastuzumab and pertuzumab, the antibody-drug conjugate trastuzumab emtansine (also known as T-DM1), and the tyrosine kinase inhibitors (TKIs) lapatinib and neratinib, which target the signal transduction pathway downstream from HER2 (Figure 1 and Table 1).

**HER2-INHIBITORS**

Trastuzumab is a humanized monoclonal antibody. It is the first HER2-targeting drug introduced to BC clinics and remains a key component of the most effective regimens used to treat HER2-positive BC now. Pertuzumab is an alternative monoclonal anti-HER2 antibody. It binds HER2 at a different location than trastuzumab. It prevents the formation of HER2-HER3 heterodimers. Lapatinib is a reversible small-molecule TKI which has dual activity against the tyrosine kinase ATP-binding pocket of HER1 and HER2.

Trastuzumab-emtansine (T-DM1) is an antibody-drug conjugate (ADC). This new drug allows for targeted delivery of cytotoxic molecules to the tumor, thereby increasing efficiency and reducing toxicity at the same time.

**HER2-INHIBITORS AND TUMOR RESISTANCE**

Although BC will be cured in some patients treated in the adjuvant setting, it is predicted that a fraction will eventually recur. Tumors harbor de novo or acquire resistance to therapeutic inhibitors of HER2. General mechanisms of resistance to HER2-targeted therapies that occur at three levels. The first comprises mechanisms intrinsic to the target, such as molecular changes in the target receptor; the expression of p95HER2, which is a truncated HER2 receptor; and HER2 gene amplification. Secondly, resistance involving parallel signaling pathways bypassing HER2 inhibition, such as increased activation of HER3, aberrant activation of pathways downstream of the receptor, and compensatory crosstalk with other pathways, can also occur. The third mechanism includes resistance due to defects in the apoptosis pathway in tumor cells or in extrinsic host factors participating in the action of the drugs.

**BIOLOGICAL INSIGHTS INTO IMPROVED HER2 TARGETING**

**Inhibition of HER family dimerization**

A known mechanism of resistance to anti-HER2 therapy is the dimerization of HER family members. All members of the HER family can form dimers together, nevertheless, HER2 and HER3 form a mainly potent heterodimer that is important in BC development and growth. Though HER3 does not exert tyrosine kinase activity on its own, dimerization with HER2 drastically increases downstream signaling activity and provides a mechanism of escape from HER2 inhibition. Pertuzumab is a humanized monoclonal antibody that binds to the dimerization domain of HER2. It is an inhibitor of HER2/HER3 dimerization and also induces antibody-dependent cellular cytotoxicity (ADCC). While pertuzumab has some clinical activity of its own, when used along with trastuzumab, the dual binding to HER2 leads to synergistic action.

In the Phase III Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study, 808 patients with metastatic BC 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 (PFS) as assessed by investigators improved by 6 months (HR 0.65, p<0.001) and there was a 10.8% improvement in objective response rate. The combination also leads to a marked improvement in overall survival (OS) by almost 16 months compared to standard trastuzumab plus docetaxel (HR 0.68, p<0.001). Ever since this study, pertuzumab plus trastuzumab has replaced trastuzumab as the standard of care for first-line metastatic BC.

Recently, several TKIs like, lapatinib and neratinib have been developed that target the signal transduction pathway downstream from HER2. In both early and metastatic BC, it is effective against HER2 amplification when given in combination with trastuzumab. But, in preclinical studies, most HER2 somatic mutations were resistant to lapatinib. One more HER2-targeting TKI, neratinib has emerged as a potent inhibitor of HER2 activity. It is an irreversible pan-inhibitor of HER2 and HER1/EGFR and has been found to be more effective than lapatinib in blocking HER2 activation.

**OPTIMIZING HER2-TARGETED THERAPY FOR BREAST CANCER**

The development of HER2-targeted therapies has revolutionized the management of women with HER2-positive BC. These targeted therapies have significantly improved their outcomes (Table 1).

With the success of anti-HER2 therapy in MBC, trastuzumab was evaluated in the adjuvant setting in a series of pivotal trials. Major international studies of adjuvant trastuzumab with a planned enrollment of >13,000 women with HER2-positive EBC were: the Herceptin® Adjuvant (HERA) trial, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial, the North Central Cancer Treatment Group (NCCCTG) N9831 trial and the Breast Cancer International Research Group (BCIRG) 006 trial. At a 1-year median follow-up, patients treated with trastuzumab in the HERA trial experienced a 46% lower risk of a first event (hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.43-0.67; p<0.0001) than patients under observation. This corresponded to an absolute DFS benefit favoring trastuzumab of 8.4% at 2 years.
CURRENT STANDARDS IN HER2-POSITIVE EARLY BREAST CANCER

For HER2-positive early BC, the current standard of care includes trastuzumab (with or without pertuzumab) and chemotherapy, given either before or after surgery. This is based on results from several clinical trials which demonstrated a significant benefit of trastuzumab in standards of care in both the adjuvant and neoadjuvant settings.\(^3\) In the phase III Herceptin Adjuvant (HERA) trial, 1 year of adjuvant trastuzumab was associated with significant improvements in both 10-year rates of disease-free survival (DFS; 69% versus 63%; HR 0.76) and 12-year rates of OS (79% versus 73%; HR 0.74) compared to observation.\(^2\)\(^3\)

In the phase III Neo-adjuvant Herceptin (NOAH) trial, HER2-positive patients treated with trastuzumab plus chemotherapy had a significantly higher rate of pathologic complete response (pCR) than patients who only received chemotherapy (38.5% versus 19.5%; HR 0.29, p=0.0135) and these patients remained disease-free longer (5-year event-free survival [EFS] 58% versus 43%; HR 0.64, p=0.016).\(^5\) Even though trastuzumab has demonstrated efficacy in early BC, a significant proportion of patients will eventually progress. In the HERA trial, after 10 years of follow up, 28.8% of patients treated with trastuzumab experienced disease progression. Likewise, in the NOAH trial, at only 5 years post-treatment with trastuzumab, 42% of patients treated, experienced a disease recurrence.\(^6\)

Thus, clearly, for many 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.

**Novel approaches to HER2-targeted adjuvant therapy**

Many novel HER2-targeting agents have been studied including dual HER 2 blockade. These agents are potential adjuvant therapy for patients with HER2-positive BC.

**Lapatinib**

Lapatinib has been evaluated as a potential adjuvant therapy for HER2-positive BC, either alone or in combination with trastuzumab. In the Tykerb Evaluation after Chemotherapy (TEACH) trial, lapatinib was compared to placebo in women with HER2-positive early BC. Women had previously received adjuvant chemotherapy but not trastuzumab. The study found that single-agent lapatinib failed to demonstrate a significant DFS benefit over placebo (HR 0.83, 95% CI 0.70–1.00). It was found that there was a marginal benefit for patients with HER2-positive disease confirmed by central fluorescence in situ hybridization.\(^6\) In the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial, patients who received single-agent lapatinib had poorer outcomes compared to patients who received trastuzumab (HR 1.34).\(^7\) 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%) compared to 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 to single-agent trastuzumab.\(^8\) At present, lapatinib is not being further investigated in the adjuvant setting, either alone or in combination with trastuzumab.

**Neratinib**

Studies of neratinib in the adjuvant setting have been promising. Phase III study, Neratinib after trastuzumab-based adjuvant therapy in HER2-positive BC (ExteNET) compared neratinib (240 mg daily) to placebo.\(^9\) This was a multicenter, randomized, double-blind, placebo-controlled, conducted at 495 centers in Europe, Asia, Australia, New Zealand, and North and South America. Women included in the study were with stage I–III HER2-positive BC, who had completed neoadjuvant and adjuvant trastuzumab up to 2 years (amended to 1 year) before randomization. Patients with stage I–III node-positive and node-negative patients with tumors greater than 1 cm in size were included. In this study, neratinib improved invasive DFS by 2 years by 2.3% over placebo (HR 0.67, p=0.009).\(^10\)

This improvement was most discrete in patients with hormone receptor (HR)-positive tumors (HR 0.51, p=0.001). This study results suggested that neratinib might provide an additional treatment option for this subset of patients who have an ongoing, long-term, and fairly constant risk of relapse on trastuzumab. Also at a 5-years follow-up, the benefit with neratinib was maintained with a 2.5% absolute improvement in invasive DFS (90.2% versus 87.7%; HR 0.73, p=0.008) for the whole population.\(^10\) This improvement in invasive DFS was most apparent in HR-positive patients (91.2% versus 86.8%; HR 0.60, p=0.002).\(^11\) It was observed that patients who have completed adjuvant trastuzumab less than 1 year prior to the start of the study showed the maximum benefit with neratinib.\(^10\)

**Pertuzumab**

Pertuzumab in addition to chemotherapy and trastuzumab as adjuvant therapy in participants with HER2-positive primary BC, (APHINITY) study examined the pertuzumab (P) and trastuzumab (T) combination as adjuvant treatment, compared to standard trastuzumab plus chemotherapy(C) in 4805 patients with HER2-positive early BC.\(^4\) Study included patients who had either node-positive disease or node-negative disease (pN0) and a tumor size of >1.0 cm. Patients with pN0, T1b tumors with high-risk features were initially eligible. 4805 patients were randomized to C and T plus either P (n=2400) or Pla (n=2405).\(^11\)
This study met its primary endpoint of improved invasive DFS at 3 years (94.1% versus 93.2%; HR 0.81, p=0.045), the magnitude of the benefit was modest and there was no associated improvement in OS (97.7% in both groups; HR 0.89, p=0.467). Subgroup analysis suggested a somewhat greater effect on ER-negative tumors (HR 0.76, P=0.085). Pertuzumab treatment was associated with an increase in grade ≥3 diarrhea (9.8% versus 3.7%).

Results from key phase III trials are summarized in Table 2.

Table 2: Disease-free survival and overall survival rates for phase III adjuvant trials of novel HER2 inhibitors.8

<table>
<thead>
<tr>
<th>Agent/trial</th>
<th>Disease setting</th>
<th>Regimen</th>
<th>N</th>
<th>Follow-up</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation (ALTTO) trial</td>
<td>Lapatinib trastuzumab+</td>
<td>8381</td>
<td>6 years</td>
<td>85% (HR 0.86)</td>
<td>93% (HR 0.86)</td>
</tr>
<tr>
<td>Piccart-Gebhart et al17</td>
<td>Stage I–III adjuvant therapy</td>
<td>Lapatinib (34 w) → Trastuzumab (12 w)</td>
<td></td>
<td></td>
<td>84% (HR 0.93)</td>
<td>92% (HR 0.88)</td>
</tr>
<tr>
<td>Moreno-Aspitia et al18</td>
<td>• Trastuzumab • Lapatinib</td>
<td></td>
<td></td>
<td></td>
<td>82%</td>
<td>91%</td>
</tr>
<tr>
<td>TEACH Goss et al16</td>
<td>Stage I–III delayed adjuvant therapy. Prior trastuzumab unless contraindicated</td>
<td>• Lapatinib • Placebo</td>
<td>3147</td>
<td>47.4 mo</td>
<td>87% (HR 0.83)</td>
<td>94% (HR 0.99)</td>
</tr>
<tr>
<td>Neratinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ExteNET (Martin et al40)</td>
<td>• Neratinib • Placebo</td>
<td>2840</td>
<td>5 years</td>
<td>90.2% (HR 0.73)*</td>
<td>87.7%*</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>APHINITY Von Minckwitz et al41</td>
<td>• Pertuzumab (plus chemo and trastuzumab) • Placebo (plus chemo and trastuzumab)</td>
<td>4805</td>
<td>36 mo</td>
<td>94.1% (HR 0.81)*</td>
<td>93.2%*</td>
</tr>
</tbody>
</table>

Chemo, chemotherapy; DFS, disease-free survival; ET, endocrine therapy; mo, months; OS, overall survival, invasive DFS.

Ado-trastuzumab emtansine (T-DM1)

Ado-trastuzumab emtansine (T-DM1) is an immunoconjugate of trastuzumab with an effective microtubule inhibitor agent. 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 following neoadjuvant therapy including a minimum of six cycles of taxane-based chemotherapy and nine weeks of trastuzumab.42 Patients were randomized to either 14 cycles of ado-trastuzumab emtansine versus 14 cycles of trastuzumab. Treatment with 14 cycles of adjuvant T-DM1 resulted in a significant improvement in rates of invasive disease-free survival (iDFS) compared to adjuvant trastuzumab.43

iDFS favored T-DM1 in all prespecified patient subgroups. At 3 years, a greater proportion of patients receiving T-DM1 remained free of distant recurrence (89.7% versus 83.0%; HR 0.60). There was a trend towards improved overall survival (OS) in patients receiving T-DM1. The study concluded that adjuvant T-DM1 demonstrated both statistically significant and
clinically meaningful improvements in iDFS compared to trastuzumab in patients with invasive residual after neoadjuvant therapy.43

**Neoadjuvant therapy for HER2-positive breast cancer**

Trastuzumab as neoadjuvant therapy provides significant clinical benefits and reduces the rate of distant metastasis.44 Clinical studies have revealed that trastuzumab-based neoadjuvant therapy has a higher pCR (termed as the absence of residual cancer in the breast or axillary lymph node pathology) in the treatment of HER2-positive BC.55

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.37 After a median follow-up of 5.4 years, neoadjuvant treatment with trastuzumab improved the 5-year DFS rate as 58% to 43% (p<0.001), with an unadjusted HR of 0.64. A strong association with improved the 5-year OS (96% versus 85%; p=0.007) was improved.48

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

**Other therapy in the neoadjuvant setting**

The GeparQuinto 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.52 The study results confirmed that the trastuzumab arm showed ~7% more pCR than lapatinib arm (30.3% versus 22.7%; p=0.04).52

Table 3: Optimal clinical trials in the neoadjuvant setting for HER2-positive breast cancer.57

<table>
<thead>
<tr>
<th>Drug or study name</th>
<th>Neoadjuvant chemotherapy</th>
<th>No. of patients</th>
<th>Pathological complete response (%)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>The NSABP B-41 trial</td>
<td>AC → TH or TL or THL</td>
<td>181 versus 174 versus 174</td>
<td>52.5% versus 53.2% versus 62.0%</td>
<td>H + L no better. All patients received anthracyclines</td>
<td>Robidoux et al53</td>
</tr>
<tr>
<td>Pertuzumab The NeoSphere trial</td>
<td>Do+H vs Do+P+H vs Do+P vs P + H</td>
<td>107 versus 107 versus 96</td>
<td>29.0% versus 45.8% versus 24.0% versus 16.8%</td>
<td>≥T2; Combination P+H result in better pCR</td>
<td>Gianni et al54,55</td>
</tr>
<tr>
<td>The TRYPHAENA trial</td>
<td>FEC+HP → Do + HP vs FEC → Do + HP vs TCHP</td>
<td>223 patients in total</td>
<td>62% versus 57% versus 66%</td>
<td>TCH+P is an active combination</td>
<td>Schneeweiss et al56</td>
</tr>
</tbody>
</table>

T paclitaxel; F 5FU, E epirubicin, C cyclophosphamide, A adriamycin, M methotrexate, D docetaxel, TC docetaxel plus carboplatin, H trastuzumab, P pertuzumab, L lapatinib, T-DM1 trastuzumab-maytansine.

The Lapatinib with trastuzumab for HER2-positive early BC (NeoALTTO) trial, 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.57 In the combination arm, prominent progress on pCR of 51%, was observed which is almost twice as much as the other two monotherapies against HER 2 (29.5% in trastuzumab alone and 24.7% in lapatinib alone, p<0.001).57 Other studies with the dual inhibitory regimen, NSABP B-41 study, NeoSphere trial and the TRYPHAENA trial details are illustrated in Table 3.53-56

**NOVEL STRATEGIES TO OVERCOME RESISTANCE TO HER2-TARGETED THERAPY**

**Replacement of current anti-HER2 therapies for improved anti-HER2 drugs**

ADCs

ADCs offer a wider therapeutic window by more efficient and specific drug delivery. To improve tumor selectivity and reduce damage to normal cells, ADCs exploit target selectivity of monoclonal antibodies (MAbs) to deliver
cytotoxic drugs to antigen-expressing cells. Several anti-HER2 ADCs in clinical development are listed in Table 4.

**Novel TKIs**

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

**Escalating or de-escalating adjuvant therapy in HER2+ 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).

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 concomitantly with chemotherapy in the experimental arm with the aim to investigate drug synergism (FinHer, E2198, SOLD, and Short-HER trials), and three trials compared 6-month to the 12-month duration of trastuzumab (the Hellenic trial, PHARE, and PERSEPHONE).

In the FinHer study, 1010 women with axillary node-positive or high-risk node-negative BC were randomized to receive 3 cycles of docetaxel or vinorelbine, followed in both groups by 3 cycles of fluorouracil (F), epirubicin (E), and cyclophosphamide (C). 232 patients with HER 2 positive BC were further treated with trastuzumab or no additional therapy. Even with the shorter duration of trastuzumab after a median follow-up of 8 years, distant DFS (83.3% versus 73%) and OS (91.3% versus 82.3%) favored the trastuzumab arm.

In the SOLD trial, 2176 patients with early-stage HER2-positive BC were randomized (1:1) to the 9-week trastuzumab arm or the 12-month trastuzumab arm. Patients in both arms received three cycles of docetaxel (80 mg/m2 or 100 mg/m2) and trastuzumab three times a week, followed by three cycles of chemotherapy. Patients in the 9-week arm received no further treatment, whereas those in the 12-month arm received trastuzumab every 3 weeks for 14 cycles. The trial failed to establish that 9 weeks of adjuvant trastuzumab were not inferior to the standard 12 months in terms of DFS. The 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).

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**Table 4: HER2-directed ADCs in clinical development.**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Anti-HER2 Mab/payload (target)</th>
<th>Drug to antibody ratio</th>
<th>Linker drug</th>
<th>Phase of development</th>
<th>ORR in HER2-positive</th>
<th>ORR in HER2 low (IHC1+/2+/3+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab-DM1 (T-DM1)49</td>
<td>Trastuzumab/DM1 (anti-tubulin)</td>
<td>3.5</td>
<td>Non-cleavable</td>
<td>US FDA Approved</td>
<td>43.6%</td>
<td>-</td>
</tr>
<tr>
<td>Trastuzumab duruxtecan (DS-8201a)59</td>
<td>Trastuzumab/exatecan derivative (topoisomerase I inhibitor)</td>
<td>8</td>
<td>Cleavable</td>
<td>II/III NCT03248492 NCT03529110 NCT03523585</td>
<td>54.5%</td>
<td>50%</td>
</tr>
<tr>
<td>SYD98560</td>
<td>Duocarmycin derivative (alkylating agent)</td>
<td>2.8</td>
<td>Cleavable</td>
<td>III NCT03262935</td>
<td>33%</td>
<td>HR + 27% HR ~ 40%</td>
</tr>
<tr>
<td>XMT-152261</td>
<td>XMT-1519/monomethyl auristatin (anti-tubulin)</td>
<td>12</td>
<td>Cleavable</td>
<td>I NCT02952729</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

ADC, antibody-drug conjugate; HR+, hormone receptor-positive; HR−, hormone receptor-negative; IHC, immunohistochemistry; ISH, In Situ Hybridization; Mab, monoclonal antibody; NCT, ClinicalTrials.gov identifier; ORR, overall response rate; US FDA, United States Food and Drug Administration.

In the Short-HER study 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 endpoints were DFS and OS. Secondary endpoints included failure rate at 2 years and the incidence of cardiac events. The 5-year DFS was not non-inferior (87.5% versus 85.4% in the long and short groups, respectively, hazard ratio [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 to 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

Table 5: New anti HER 2 agents and combinations.62

<table>
<thead>
<tr>
<th>Novel HER2 antibodies</th>
<th>Mechanism of action</th>
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</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td><strong>Mechanism of action</strong></td>
</tr>
<tr>
<td>Margetuximab (MGAH22)</td>
<td>Optimized Fc domain for enhanced binding to HER2 and HER3 receptors</td>
</tr>
<tr>
<td>MCLA-128</td>
<td>IgG1 bispecific antibody with enhanced ADCC activity targeting both HER2 and HER3 receptors</td>
</tr>
<tr>
<td>ZW-25</td>
<td>The bispecific antibody directed against two distinct epitopes of HER2</td>
</tr>
</tbody>
</table>

**Antibody-Drug Conjugates (ADC)**

<table>
<thead>
<tr>
<th>SYD 985</th>
<th>Trastuzumab with an alkylant prodrug DUBA (Duocarmicin derivate) payload</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS-8201</td>
<td>HER2 antibody attached to topoisomerase I inhibitor (DXd) payload</td>
</tr>
</tbody>
</table>

**Tyrosine Kynase Inhibitors (TKIs)**

| Neratinib | Oral TKI that irreversibly inhibits HER1, HER2 and HER 4 |
| Tucatinib | Oral TKI, ATP competitive, selectively inhibits HER2 relative to EGFR |
| Poziotinib | Irreversible oral TKI, pan-HER kinase inhibitor |
| Pyrotinib | Irreversible oral, TKI pan-HER kinase inhibitor |

**Immune approaches**

| Atezolizumab | Anti-PD-L1 antibody |
| Pembroliumab | Anti-PD-L1 antibody |
| CDK4/6 inhibitor | 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 |

ADCC. Antibody-dependent cell-mediated cytotoxicity, CBR. Clinical benefit rate, ORR. Overall response rate, NR. Not reported, DCR. Disease control rate, TKI. Tyrosine Kynase Inhibitor. T. Trastuzumab. CDK. Cyclin dependent kinase, PI3K. Phosphatidylinositol-3-kinase.

Persephone was a randomized phase III non-inferiority trial comparing 6 months of trastuzumab to the standard 12 months in 4,088 patients enrolled from 152 sites in the United Kingdom between 2007 and 2015.68,69 Patients received standard chemotherapy regimens as per institutional practice as either adjuvant chemotherapy or neoadjuvant chemotherapy, and either concurrently with or sequentially to trastuzumab, and trastuzumab for either 6 or 12 months based on random allocation. Randomization occurred before the 10th cycle of trastuzumab. At a median follow-up of 5 years, the researchers found near-identical results between the 2 treatment arms: DFS was 89.4% among women in the 6-month arm and 89.8% among women in the 12-month arm.68,69

Seven-year follow-up analysis of adjuvant Paclitaxel and Trastuzumab trial

The first report from the adjuvant Paclitaxel and Trastuzumab trial, after a median follow-up of 4 years, showed a 3-year invasive DFS of 98.7%. A secondary analysis was planned to report longer-term outcomes and characterize the biology of small HER2-positive tumors and genetic factors that may predispose to paclitaxel-induced peripheral neuropathy (TIPN).70 In this phase II study, patients with HER2-positive BC with tumors 3 cm or smaller and negative nodes received paclitaxel (80 mg/m2) with trastuzumab for 12 weeks, followed by trastuzumab for 9 months.70 The primary endpoint was DFS. Recurrence-free interval (RFI), breast cancer-specific survival, and overall survival (OS) were also analyzed, 410 patients were enrolled from October 2007 to September 2010. The 7-year DFS of 93.3% included 94.6% in patients with HR-positive tumors and 90.7% in the HR-negative subgroup. Key secondary outcomes at 7 years included: relapse-free interval: 97.5%, Breast cancer-specific survival: 98.6%, OS: 95.70 This long-term data support the use of adjuvant paclitaxel and trastuzumab as a treatment option for patients with stage I, HER 2-positive breast cancer. This regimen represents an important step forward in de-escalating therapy to preserve the quality of life while achieving excellent outcomes for patients with HER2-positive breast cancer.70

Adjuvant ado-Trastuzumab Emtansine versus Trastuzumab in early-stage HER2-Positive breast cancer

The phase III KATHERINE clinical trial compared the use of ado-trastuzumab emtansine (T-DM1) vs trastuzumab as adjuvant therapy in patients with HER2-positive early-stage BC with residual invasive disease after receiving neoadjuvant chemotherapy and trastuzumab.43 1,486 patients from 273 sites in 28 countries were randomly assigned between April 2013 and December 2015 to receive adjuvant T-DM1 3.6 mg/kg intravenously (IV) every 3 weeks (n=743) or trastuzumab 6 mg/kg IV every 3 weeks (n=743) for 14 cycles. T-DM1 reduced the risk of developing an invasive recurrence of the BC or death by 50%, corresponding to an absolute improvement of 3-year invasive disease-free survival rate by 11.3 percentage points (77% with trastuzumab and 88.3% with T-DM1).43 Secondary efficacy endpoints of disease-free survival and
distant recurrence-free interval also demonstrated clinically meaningful improvements with T-DMI.  

**Extended duration of anti-HER2 therapy**

Food and Drug Administration (FDA) approved neratinib in 2017 for the extended adjuvant treatment of adult patients with early-stage HER 2+ breast cancer, to follow adjuvant trastuzumab. Till now, the overall strategy has escalated the treatment by combining more HER 2 targeted agents. But, the treatment escalation is encumbered by high cost and significant toxicity, and in some cases might be an overtreatment. Thus, redesigning the current treatment strategies is crucial and de-escalation is a research priority to diminish adverse effects without compromising patient outcomes.

**CHALLENGES AND FUTURE DIRECTIONS**

**Targeting HER2/ER crosstalk**

Although HER2 inhibition is highly effective in improving outcomes in HER2-positive BC patients, but tumors expressing estrogen receptor (ER) have poorer responses to targeted therapy and are more likely to relapse. Current theories have revealed that a key mechanism of trastuzumab resistance in patients with HER2-positive/ER-positive tumors could be crosstalk between HER2 and ER, most likely via PI3K. Significant crosstalk exists between the HER2 and ER pathways. 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.

PI3K is a main member 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. Pre-clinical 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. In a few studies, the combination of HER2 and ER inhibition improved outcomes over inhibition of either pathway alone. In the neoadjuvant setting, targeting both pathways simultaneously did not impact on response.

**CONCLUSION**

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

Trastuzumab is a breakthrough drug for anti-HER2 treatment. One-year treatment with trastuzumab is a standard for adjuvant therapy. Pertuzumab also showed an overall good efficacy in adjuvant therapy. Double-targeted adjuvant therapy can be beneficial in high-recurrence risk groups (positive-lymph nodes or ER/PR negative patients). At present, the standard of first-line care for HER2-positive MBC is dual anti-HER2 blocking with pertuzumab and trastuzumab plus chemotherapy. The T-DMI is recommended as the second-line treatment and small-molecule TKI as the third-line.

Though trastuzumab, pertuzumab, lapatinib, and neratinib are greatly 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 therapy or regimen, careful attention must be given to the risks versus benefits of therapy.

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**REFERENCES**


Cancer: Results From the Randomized Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial. J Clin Oncol. 2016;34:1034-42.
38. Moreno-Aspitia A, Holmes E, Jackisch C, de Azambuja E, Boyle F, Hillman DW, et al. Updated results from the phase III ALTTO trial (BIG NCCTG/Alliance N063D) comparing one year of anti-Her2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T → L) or their combination (L + T) in the adjuvant treatment of HER2-positive early breast cancer. J Clin Oncol. 2017;35(suppl):2-06.


78. Rimawi MF, Mayer IA, Forero A, Nanda R, Goetz MP, Rodriguez AA et al. Multicenter phase II study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with human epidermal growth factor receptor 2-


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