

# Advances in the Treatment of Early-Stage HER2-Positive Breast Cancer

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**Abstract:** The management of early-stage human epidermal growth factor receptor 2–positive (HER2+) breast cancer has evolved in recent years, with the current standard being to tailor the intensity of adjuvant treatment to individual risk. Risk-adapted approaches to systemic therapy have been facilitated both by the recent introduction of multiple novel HER2-targeted therapies and by the development of clinical and pathologic surrogates to enable better prediction of disease behavior. These approaches have been successful at both ends of the disease spectrum. Patients with low-risk tumors now experience excellent long-term outcomes and reduced toxicity after de-escalated adjuvant therapy, and patients with high-risk residual disease after neoadjuvant systemic therapy have had a significant decrease in the risk for disease recurrence with the escalation of adjuvant therapy, including the use of trastuzumab emtansine (also known as T-DM1). We review here key developments in neoadjuvant and adjuvant systemic therapy for early-stage HER2+ breast cancer and provide an overview of the current standards of management, incorporating recent advances in escalation and de-escalation approaches for higher- and lower-risk disease, respectively. We also discuss areas of ongoing clinical uncertainty, including how disease heterogeneity and hormone receptor status affect the selection of treatments and the selection of patients for chemotherapy-free approaches. Finally, we review ongoing areas of active investigation and unmet clinical needs in this patient population.

## Introduction

Breast cancers that overexpress human epidermal growth factor receptor 2 (HER2+) account for approximately 20% of all breast cancer diagnoses. Before the development of HER2-targeted therapies, HER2+ breast cancer represented an aggressive subtype of breast cancer with poor outcomes.<sup>1</sup> Since the introduction of anti-HER2 therapies in the 1990s, outcomes have improved dramatically. The emphasis is now increasingly on tailoring systemic therapy according to recurrence risk, with escalation of systemic therapy for patients with high-risk disease and de-escalation for those with low-risk disease.

## Keywords

Adjuvant, breast cancer, HER2, pertuzumab, T-DM1, trastuzumab

### **Definition of HER2+ Breast Cancer**

Current guidelines from the American Society of Clinical Oncology and the College of American Pathologists define HER2 positivity as follows: (1) immunohistochemistry (IHC) score of 3+; (2) dual-probe in situ hybridization with a HER2/CEP17 ratio of at least 2 and a HER2 copy number of at least 4 per cell; or (3) a HER2 copy number of at least 6 per cell and an IHC score of 2+ if the HER2/CEP17 ratio is less than 2.<sup>2</sup> If an initial biopsy is HER2– but grade 3, repeat HER2 testing of the surgical specimen should be considered. Notably, the NSABP B-47 trial from the National Surgical Adjuvant Breast and Bowel Project found no benefit of adjuvant trastuzumab for HER2-low patients.<sup>3</sup> Even within disease that is clinically HER2+, biological heterogeneity likely contributes to variability in recurrence risk and treatment response. Approximately 50% to 70% of HER2+ breast cancers are hormone receptor–positive (HR+),<sup>4,5</sup> and patients with HER2+/HR+ early-stage disease have a lower risk for recurrence in the first 5 years than patients with HER2+/HR– disease, but a higher risk for late recurrence.<sup>6</sup> An analysis of 500 tumors in The Cancer Genome Atlas demonstrated that 50% of the HER2+ tumors had a luminal rather than a HER2-enriched gene expression signature on the PAM50 assay (now known as Prosigna, NanoString), and that not all of those with a luminal signature were clinically HR+.<sup>7</sup> Although it is not prospectively validated for clinical use, retrospective data have identified an association between PAM50 intrinsic subtype and clinical response to HER2-targeted therapies.<sup>8</sup> A high degree of intratumoral heterogeneity has also been associated with worse outcomes.<sup>9</sup> These findings highlight an important source of biological heterogeneity not captured in the design of the major trials for HER2+ early-stage breast cancer.

### **Adjuvant Trastuzumab**

The first targeted therapy to be developed was trastuzumab, a humanized monoclonal antibody against the HER2 extracellular domain. The addition of 1 year of adjuvant trastuzumab to cytotoxic chemotherapy markedly improved the outcomes of patients with HER2+ early breast cancer in 4 pivotal randomized phase 3 trials. In the joint NSABP B-31 and North Central Cancer Treatment Group (NCCTG) N9831 trials, 4046 women with operable HER2+ breast cancer received doxorubicin and cyclophosphamide followed by paclitaxel (AC-T) with or without 1 year of adjuvant trastuzumab (AC-TH). At the final analysis, with a median of 8.4 years of follow-up, the addition of trastuzumab significantly improved both disease-free survival (DFS) and overall survival (OS), with an increase in the 10-year DFS rate from 62.2% to 73.7% (hazard ratio, 0.60; 95% CI, 0.53-0.78) and in the 10-year OS rate from 75.2% to 84% (hazard ratio,

0.63; 95% CI, 0.54-0.73).<sup>10</sup> N9831 found a statistically nonsignificant trend toward improved outcomes for concurrent taxane and trastuzumab vs trastuzumab sequential to chemotherapy.<sup>11</sup>

The HERA study compared observation with 1 or 2 years of adjuvant trastuzumab after at least 4 cycles of chemotherapy in women with operable HER2+ breast cancer. After a median of 8 years of follow-up, a significant benefit was demonstrated for 1 year of trastuzumab, with a statistically significant hazard ratio of 0.76 for both DFS and OS despite the fact that 52% of patients crossed over to the trastuzumab arm after the first interim analysis demonstrated benefit.<sup>12</sup> No additional benefit was observed with 2 years of trastuzumab.

The chemotherapy regimens in these 3 trials were anthracycline-based, and all 3 noted excess cardiac toxicity in the trastuzumab arms even without the concurrent administration of trastuzumab and doxorubicin, which is not recommended. Notably, trastuzumab can be given concurrently with epirubicin.<sup>13,14</sup> Despite early cardiac toxicity, the 8-year analysis of these trials demonstrated a reassuringly low cumulative incidence of class III/IV heart failure and of death from cardiac causes with trastuzumab, at less than 1% each.<sup>10,12</sup>

Given the cardiac toxicity noted with anthracyclines, the BCIRG 006 trial from the Breast Cancer International Research Group compared a non-anthracycline-containing regimen (docetaxel, carboplatin, and trastuzumab; TCH) vs doxorubicin and cyclophosphamide followed by docetaxel (AC-T) alone or AC-TH.<sup>15</sup> For the primary endpoint, AC-T alone was inferior to both trastuzumab-containing regimens, and no difference in efficacy between AC-TH and TCH was observed, although this trial was not designed as a noninferiority comparison. At 10-year follow-up, the hazard ratios for DFS were 0.70 with AC-TH vs AC-T (95% CI, 0.60-0.83) and 0.76 for TCH vs AC-T (95% CI, 0.65-0.90); the hazard ratios for OS were 0.64 (95% CI, 0.52-0.79) and 0.76 (95% CI, 0.62-0.93), respectively.<sup>16</sup> Importantly, fewer cardiac toxicities were seen with the non-anthracycline regimen; the rates of symptomatic systolic heart failure were 0.4% for TCH vs 2% for AC-TH, although no cardiac deaths were observed. A statistically nonsignificant reduction in the number of secondary leukemias was also noted, which occurred in 1 of 1056 patients in the TCH arm vs 7 of 2118 patients in the anthracycline arms.<sup>15</sup>

The activity of trastuzumab in the neoadjuvant setting was demonstrated in the phase 3 NOAH trial, which compared neoadjuvant anthracycline-based chemotherapy plus trastuzumab followed by 1 year of adjuvant trastuzumab vs chemotherapy alone in 235 women with locally advanced or inflammatory HER2+ breast cancer. After a median of 5.4 years of follow-up, the 5-year event-

free survival (EFS) rate was significantly better in the trastuzumab arm than in the chemotherapy-alone arm, at 58% vs 43% (hazard ratio, 0.64; 95% CI, 0.44-0.93;  $P=.016$ ).<sup>17</sup> A strong association was seen between pathologic complete response (pCR) in the breast and axilla and both EFS and OS specifically in the trastuzumab arm, with 5-year EFS and OS rates of 87% and 91%, respectively, for patients who achieved a pCR vs EFS and OS rates of 38% and 61%, respectively, for those who did not have a pCR after neoadjuvant trastuzumab. The prognostic utility of pCR in HER2+ early breast cancer has subsequently been validated as a strong surrogate for EFS across a number of neoadjuvant trials<sup>18</sup> and has become a valuable tool to identify patients who remain at high risk for recurrence and who are now candidates for escalated adjuvant therapy after surgery.

With the data taken together, 1 year of trastuzumab remains a recommended standard component of adjuvant systemic therapy. The decrease in cardiac toxicity with the TCH regimen makes it an attractive chemotherapy backbone choice in most cases, although AC-TH or even docetaxel, cyclophosphamide, and trastuzumab<sup>19</sup> may be preferred in some patients owing to the alternative toxicity profile, or if inconsistent or equivocal HER2 test results suggest that a tumor may not be strongly HER2-driven.

## Escalation of Adjuvant Therapy

### *Dual HER2-Targeted Therapy*

Pertuzumab (Perjeta, Genentech) is a humanized monoclonal antibody that binds to a unique epitope from trastuzumab on the extracellular domain of HER2.<sup>20</sup> Its synergy with trastuzumab is mediated primarily through inhibition of the dimerization of HER2 with other HER receptors, such as HER3 and HER1.<sup>21</sup> The combination of trastuzumab and pertuzumab resulted in enhanced anti-tumor activity in preclinical models,<sup>22</sup> and in the pivotal first-line CLEOPATRA phase 3 trial in metastatic HER2+ breast cancer, the addition of pertuzumab to trastuzumab plus docetaxel improved median OS from 40.8 to 57.1 months (hazard ratio, 0.69; 95% CI, 0.58-0.82).<sup>23</sup>

On the basis of these encouraging findings, the combination of pertuzumab and trastuzumab was studied in the early-stage setting and received accelerated approval from the US Food and Drug Administration (FDA), initially as neoadjuvant therapy with docetaxel for locally advanced or inflammatory HER2+ breast cancer. This approval was based on 2 neoadjuvant studies, NeoSphere<sup>13</sup> and TRYPHAENA,<sup>14</sup> which demonstrated improved pCR rates with the addition of pertuzumab to trastuzumab plus docetaxel given alone or sequentially either with 5-fluorouracil, epirubicin, and cyclophosphamide (FEC)

or with carboplatin (TCH-P). However, the confirmatory phase 3 APHINITY trial of dual anti-HER2 therapy with pertuzumab in the adjuvant setting has shown benefit only in node-positive disease. APHINITY compared the addition of pertuzumab or placebo to standard chemotherapy plus 1 year of trastuzumab.<sup>24</sup> Patients with node-positive or high-risk node-negative HER2+ breast cancer were eligible. Initial results demonstrated 3-year invasive DFS rates of 94.1% with pertuzumab vs 93.2% with placebo (hazard ratio, 0.81; 95% CI, 0.66-1.00;  $P=.045$ ) in the whole cohort and invasive DFS rates of 92.0% vs 90.2% in the node-positive subset ( $P=.02$ ). Although longer-term follow-up of the whole cohort at a median of 74.1 months demonstrated continued invasive DFS benefit with pertuzumab, at 90.6% vs 87.8% (hazard ratio, 0.76; 95% CI, 0.64-0.91), no difference was found in 6-year OS (94.8% vs 93.9%; hazard ratio, 0.85; 95% CI, 0.67-1.07),<sup>25</sup> and only the node-positive subset demonstrated improved invasive DFS (87.9% vs 83.4%).

Pertuzumab has been well-tolerated in these trials. The long-term follow-up from APHINITY demonstrated a 0.8% risk for significant cardiac events, including death or New York Heart Association class III or IV heart failure with decreased left ventricular ejection fraction (LVEF), and a 2.7% risk for asymptomatic or mildly symptomatic LVEF decrease. Diarrhea and rash are other common side effects of pertuzumab. In summary, although pertuzumab is FDA-approved for neoadjuvant or adjuvant therapy, the absolute benefit of pertuzumab when given in combination with multi-agent chemotherapy and trastuzumab does appear to be small. It is reasonable to consider omitting pertuzumab, especially for patients with node-negative HER2+ breast cancers.

Lapatinib (Tykerb, Novartis) is an oral, reversible tyrosine kinase inhibitor that targets epidermal growth factor receptor (EGFR/HER1) and HER2. It initially received FDA approval in 2007 in combination with capecitabine for the treatment of patients with HER2+ metastatic breast cancer whose disease had progressed on trastuzumab-based chemotherapy.<sup>21</sup> Despite the results of the neoadjuvant NeoALTTO trial, which demonstrated that dual HER2 targeting with trastuzumab and lapatinib improved pCR rates,<sup>26</sup> ultimately the combination did not improve EFS or OS.<sup>27</sup> The adjuvant randomized phase 3 ALTTO study also demonstrated no improvement with the combination in the primary endpoint of 4-year DFS.<sup>28</sup> Therefore, lapatinib is not currently used as a standard agent in early-stage HER2+ breast cancer.

### *Trastuzumab Emtansine*

The antibody-drug conjugate trastuzumab emtansine (T-DM1; Kadcyla, Genentech) consists of trastuzumab

covalently linked to the cytotoxic microtubule poison DM1. Clinical activity for this agent in HER2+ breast cancer was first demonstrated in advanced disease. In the phase 3 EMILIA trial, T-DM1 improved overall survival compared with capecitabine and lapatinib in metastatic HER2+ breast cancer after prior trastuzumab therapy (30.9 vs 25.1 months; hazard ratio, 0.68; 95% CI, 0.55-0.85).<sup>29</sup> In early-stage HER2+ disease, the landmark phase 3 KATHERINE trial evaluated the role of T-DM1 specifically in the higher-risk population with residual disease after standard neoadjuvant therapy. In KATHERINE, patients who had received at least 6 cycles of neoadjuvant chemotherapy including a taxane as well as a minimum of 9 weeks of trastuzumab without achieving a pCR were randomly assigned to receive 14 cycles of T-DM1 or to complete 14 cycles of trastuzumab.<sup>30</sup>

The trial met its primary endpoint at the first interim analysis, with the 3-year invasive DFS rate improving from 77% in the trastuzumab arm to 88% in the T-DM1 arm (hazard ratio, 0.50; 95% CI, 0.39-0.64).<sup>30</sup> A numeric improvement in the 3-year OS rate was also observed at this early time point, from 92.5% to 94.3%. About 70% of the population had HR+ disease, and no difference in efficacy was seen between the HR+ and HR- subgroups. However, the 20% of patients with no more than 1 cm of residual disease in the breast and no residual disease in the nodes had a smaller magnitude of benefit, with an improvement in the 3-year invasive DFS rate—from 85.3% to 90%—that did not reach significance (hazard ratio, 0.60; 95% CI, 0.33-1.12). This likely reflects the lower baseline risk for recurrence in these patients, and for them, the added toxicity of T-DM1 should be considered along with its likely relatively small benefit in deciding whether to transition to T-DM1.

The T-DM1 toxicity profile in KATHERINE was similar to that seen in the metastatic setting, with a modest increase in the rates of adverse events vs trastuzumab. In the T-DM1 group, 10% of the patients required dose modification for toxicity. A total of 18% of patients in the T-DM1 group discontinued this agent early; most of these patients subsequently received trastuzumab. The rates of all-grade neuropathy were 18.6% for T-DM1 vs 6.9% for trastuzumab, although the rates of grade 3 or higher neuropathy remained low, at 1.4% and 0%, respectively. Notably, T-DM1 was continued per trial protocol during adjuvant radiation without any concerning toxicity signal.

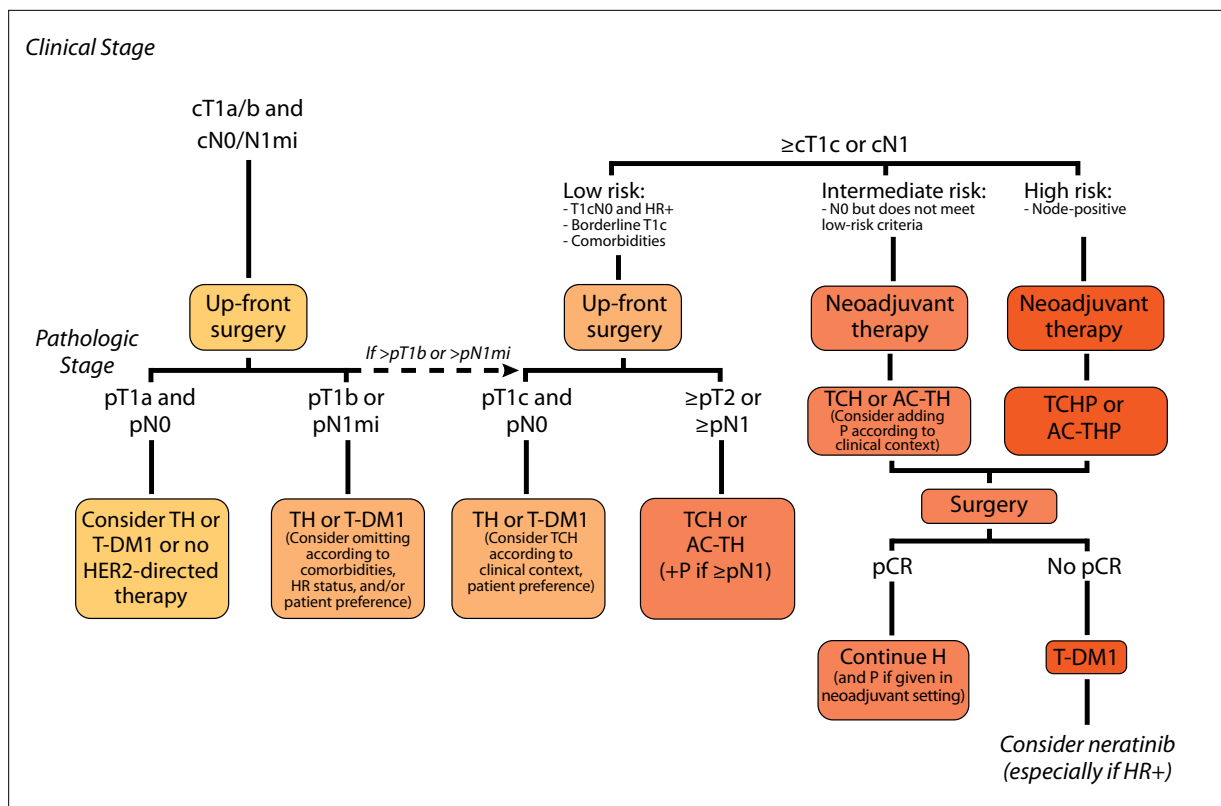
Because KATHERINE enrolled most of its patients before the approval of pertuzumab in the adjuvant/neoadjuvant setting, only 18% of patients received neoadjuvant pertuzumab, and it was not continued after surgery in either arm. However, the benefit of T-DM1 did seem to be preserved in these patients despite the small subgroup size. Given the quite significant improvement in invasive DFS

rates in the KATHERINE trial, T-DM1 has now become the standard of care in the adjuvant setting for patients with significant residual disease after neoadjuvant therapy.

In contrast, T-DM1 has not been shown to be superior to chemotherapy plus trastuzumab and pertuzumab (HP) in the neoadjuvant or adjuvant setting, consistent with results of the phase 3 MARIANNE trial in advanced disease.<sup>31</sup> The phase 3 KRISTINE trial compared neoadjuvant T-DM1 plus pertuzumab (T-DM1/P) with docetaxel, carboplatin, trastuzumab, and pertuzumab (TCH-P) in stage II/III HER2+ breast cancer, with continuation of adjuvant T-DM1/P or HP, respectively, after surgery. Rates of the primary endpoint of pCR were significantly lower, at 44.4%, for T-DM1/P than for TCH-P, at 55.7%, and the risk for EFS events was higher, primarily owing to progression before surgery (hazard ratio, 2.61; 95% CI, 1.36-4.96).<sup>32</sup> The phase 3 KAITLIN trial compared adjuvant T-DM1/P vs taxane/HP, both after 3 to 4 cycles of anthracycline-based chemotherapy, in patients with stage II/III HER2+ breast cancer who had not received neoadjuvant systemic therapy. Again, T-DM1 did not improve invasive DFS in either the node-positive (hazard ratio, 0.97; 95% CI, 0.71-1.32) or intention-to-treat (hazard ratio, 0.98; 95% CI, 0.72-1.32) populations, the co-primary endpoints of the study.<sup>33</sup>

#### ***Extended Therapy With Neratinib***

Neratinib (Nerlynx, Puma Biotechnology) is an oral, irreversible tyrosine kinase inhibitor of EGFR (HER1), HER2, and HER4 that initially demonstrated clinical activity in HER2+ metastatic breast cancer. The phase 3 ExteNET trial compared a year of adjuvant neratinib vs placebo for women with early-stage HER2+ breast cancer who had already completed standard neoadjuvant/adjuvant therapy, including 1 year of trastuzumab.<sup>34</sup> A modest but significant improvement in the primary outcome of 2-year invasive DFS, from 91.6% in the placebo group to 93.9% in the neratinib group (hazard ratio, 0.67; 95% CI, 0.50-0.91), was noted.<sup>34</sup> This improvement persisted at 5-year follow-up, with 5-year invasive DFS rates of 87.7% in the placebo group vs 90.2% in the neratinib group (hazard ratio, 0.73; 95% CI, 0.57-0.92)<sup>35</sup>; the OS analysis was not mature at that time. Grade 3 or higher diarrhea occurred in 40% of patients in the neratinib arm vs 2% of those in the placebo arm, although this was without mandatory diarrhea prophylaxis, which has subsequently been shown to significantly decrease rates of neratinib-induced diarrhea.<sup>36</sup> The rates of serious adverse events were similar, at 7% in the neratinib arm and 6% in the placebo arm, and no deaths were attributed to study treatment. Disease in the trial population was primarily node-positive (75%), with 30% having at least 3 positive nodes, and was HR+ in 60%. In the exploratory subgroup analysis of 5-year



**Figure.** Approach to HER2+ early-stage breast cancer.

AC, doxorubicin and cyclophosphamide; AC-T, doxorubicin and cyclophosphamide followed by a taxane (paclitaxel or docetaxel); AC-TH, AC-T with trastuzumab; AC-THP, AC-T with trastuzumab and pertuzumab; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mi, microscopic; pCR, pathologic complete response; T-DM1, trastuzumab emtansine; TCH, docetaxel, carboplatin, and trastuzumab; TCH-P, docetaxel, carboplatin, trastuzumab, and pertuzumab; TH, paclitaxel and trastuzumab.

invasive DFS, benefit was confined to patients with node-positive disease. Interestingly, the benefit was significant in the HR+ subgroup, with an invasive DFS rate of 91.2% vs 86.8% (hazard ratio, 0.60; 95% CI, 0.43-0.83), but no benefit was seen in the HR- subgroup, with an invasive DFS rate of 88.9% vs 88.8% (hazard ratio, 0.95; 95% CI, 0.65-1.35).<sup>35</sup> Taken together, the data indicate a distinct improvement in invasive DFS with the additional year of neratinib for higher-risk HR+ patients, and likely a modest benefit for node-positive patients regardless of HR status, after 1 year of trastuzumab. However, because the trial was conducted before the availability of other escalated HER2 strategies including pertuzumab and T-DM1, it is unknown to what extent this benefit is preserved in patients who have already received some form of escalated anti-HER2 therapy.

Escalation of neoadjuvant and adjuvant therapy with novel HER2-targeted agents has improved outcomes for patients with early-stage HER2+ breast cancer. However, several clinical challenges have emerged with these new approaches. The significant benefit with

T-DM1 in KATHERINE provides a strong rationale to consider neoadjuvant therapy for most patients, but this must be balanced against the risk of overtreating the lowest-risk patients, who have excellent outcomes with up-front surgery followed by de-escalated therapy, as described in the next section. We favor neoadjuvant therapy for patients with clinically node-positive disease and for those with tumors that are 2 cm or greater, as well as for those with 1- to 2-cm node-negative tumors who have higher-risk features, including younger age and HR negativity, and larger size (Figure). The benefit of neoadjuvant pertuzumab in clinically node-negative disease does remain somewhat unclear, according to APHINITY subgroup analysis. It is reasonable to consider omitting pertuzumab for smaller, clinically node-negative tumors. These areas of uncertainty highlight another important challenge—namely, the limitations of clinical staging with examination and imaging to assess risk before neoadjuvant therapy as up-front sentinel node biopsy has become less common. Finally, many of these studies were reported concurrently, so the role of

adjuvant T-DM1 after neoadjuvant pertuzumab, and the role of neratinib after T-DM1 or pertuzumab, remain unknown. Thus, individualized decision making based on patient preference should play an important role in the consideration of each of these therapies. Ultimately, it is remarkable to see the overall excellent outcomes in early-stage HER2+ breast cancer. This success also sets a high bar in terms of demonstrating clinical benefit with any further escalation of therapy in an unselected population.

## De-escalation of Adjuvant Therapy

### *Lower-Intensity Chemotherapy*

As outcomes have improved with HER2-directed therapy, a key clinical question has been when treatment can be de-escalated. One major de-escalation approach that has been studied for low-risk HER2+ early-stage breast cancer has been to limit the chemotherapy backbone or use T-DM1 instead of traditional chemotherapy.

The APT trial of adjuvant paclitaxel and trastuzumab was a single-arm study of weekly paclitaxel at 80 mg/m<sup>2</sup> for 12 weeks with concurrent trastuzumab, then completion of a total of 12 months of trastuzumab.<sup>37</sup> It was designed for patients who had lower-risk HER2+ breast cancer, with tumors that measured up to 3 cm and node-negative disease or 1 node with micrometastatic disease. A total of 406 patients were enrolled, the majority of whom had T1 tumors (49.4% microscopic T1 [T1mi] to T1b; 41.6% T1c) and HR+ disease (67%); only 1.5% had micrometastatic nodal involvement. The primary endpoint was invasive DFS, with a 3-year invasive DFS rate of 9.2% or higher deemed unacceptable and a rate of 5% or lower considered successful. The trial met its primary endpoint, with a 3-year invasive DFS rate of 98.7% (95% CI, 97.6%-99.8%).<sup>37</sup> Updated 7-year follow-up demonstrated an ongoing excellent prognosis in this cohort, with a 7-year invasive DFS rate of 93% (95% CI, 90.4%-96.2%).<sup>38</sup> However, there does appear to be a potential for worse outcomes among patients who have HR- tumors, with a 7-year invasive DFS rate of 94.6% for the HR+ subgroup vs 90.7% for those with HR- disease.

The ATEMPT trial for stage I HER2+ breast cancer recently reported results.<sup>39</sup> This was a 3:1 randomized phase 2 study of adjuvant T-DM1 vs paclitaxel plus trastuzumab, both to 17 total doses of HER2-directed therapy. The co-primary endpoints were 3-year DFS in the T-DM1 arm and a comparison of clinically relevant toxicities, which were defined as neurotoxicity of at least grade 2, nonhematologic toxicity of at least grade 3, hematologic toxicity of at least grade 4, febrile neutropenia, or any toxicity requiring a dose delay or discontinuation of protocol therapy. Of the 497

patients, the majority (75%) had HR+ disease; 11% had T1a, 32% had T1b, and 57% had T1c disease. In the T-DM1 arm, the 3-year DFS rate was 97.7%, meeting the first co-primary endpoint. However, the incidence of clinically relevant toxicities was identical in the 2 arms, not meeting the co-primary endpoint of a 40% decrease in toxicities with T-DM1. The patients receiving paclitaxel had a higher rate of neurotoxicity, but more of those receiving T-DM1 required early discontinuation; 17% did not complete all 17 cycles.

The APT or ATEMPT approaches should be standard if chemotherapy is being given for T1a or T1b HER2+ breast cancers. For clinical T1cN0 breast cancers, as discussed previously, the challenge is whether to treat with a neoadjuvant approach to allow post-neoadjuvant T-DM1 if residual disease is found, or to perform surgery up front to allow definitive pathologic staging for deciding between the APT/ATEMPT regimens vs more-intensive chemotherapy. Our approach is shown in the Figure.

### *Omitting Chemotherapy*

The use of HP without chemotherapy had a pCR rate of 17% in NeoSphere,<sup>13</sup> and the HP-only arm of the West German Study Group's WSG-ADAPT neoadjuvant trial in HER2+/HR- early-stage breast cancer had a pCR rate of 36%.<sup>40</sup> Although in both trials the pCR rates were markedly higher with the addition of chemotherapy, these findings nevertheless suggest that there is a subset of patients with tumors highly sensitive to HER2-directed therapy for whom chemotherapy might be omitted. A robust body of preclinical and clinical evidence has demonstrated crosstalk between the HR and HER2 pathways,<sup>41</sup> and a subset of patients with HER2+/HR+ disease responds well to the combination of dual anti-HER2 therapy plus endocrine therapy without chemotherapy in the metastatic setting.<sup>42</sup> This crosstalk was further seen in the neoadjuvant setting, when patients with HER2+/HR+ disease in the HP-only arm of NeoSphere, without endocrine therapy, had a pCR rate of only 6%<sup>13</sup>, whereas the trastuzumab and endocrine therapy arm of the WSG-ADAPT trial in HER2+/HR+ early-stage breast cancer had a pCR rate of 15%.<sup>43</sup> The phase 2 PerELISA trial refined this approach by utilizing the initial Ki67 response to letrozole as a molecular biomarker to guide a chemotherapy-free approach to neoadjuvant therapy for HER2+/HR+ disease.<sup>44</sup> Patients who demonstrated at least a 20% reduction in Ki67 positivity after a 2-week letrozole run-in received neoadjuvant HP plus letrozole without chemotherapy. The chemotherapy-free approach in the molecular responders had a pCR rate of 20.5%, which was modestly higher than that of the WSG-ADAPT trial; in addition, a low residual cancer burden (RCB-I) was observed in an

**Table 1.** Trials of Shorter-Course Trastuzumab

Study Name (N)	Design	Regimens	Primary Outcome
PHARE <sup>46,50</sup> (3384)	Noninferiority: HR margin of 1.15	Chemotherapy + H × 12 mo Chemotherapy + H × 6 mo	Median follow-up 7.5 y DFS 79.6% vs 78.8% HR 1.08 (0.93-1.25); <i>P</i> =.39 <b>Noninferiority not demonstrated</b>
Short-HER <sup>49</sup> (1254)	Noninferiority: HR margin of 1.29	AC/EC × 4 → taxane + H × 4 → H (to complete 12 mo) Docetaxel + weekly H (9 wk) → FEC × 3	Median follow-up 6 y 5-year DFS 88% vs 85% HR 1.13 (0.89-1.42) <b>Noninferiority not demonstrated</b>
SOLD <sup>48</sup> (2174)	Noninferiority: HR margin of 1.3	Docetaxel + H (9 wk) → FEC × 3 → H (total 12 mo) Docetaxel + H (9 wk) → FEC × 3	Median follow-up 5.2 y DFS 90.5% vs 88% HR 1.39 (1.12-1.72) <b>Noninferiority not demonstrated</b>
PERSEPHONE <sup>45</sup> (4089)	Noninferiority: ≤3% absolute difference	Chemotherapy + H × 12 mo Chemotherapy + H × 6 mo	Median follow-up 4 y 4-year DFS 89.8% vs 89.4% HR 1.07 (0.93-1.24); <i>P</i> =.011 <b>Noninferiority demonstrated</b>
Hellenic Oncology Research Group Trial <sup>54</sup> (481)	Noninferiority: HR margin of 1.53	dd FEC × 4 → dd docetaxel + H → H (total 12 mo) dd FEC × 4 → dd docetaxel + H → H (total 6 mo)	Median follow-up 4 y 3-year DFS 95.7% vs 93.3% HR 1.57 (0.86-2.10); <i>P</i> =.137 <b>Noninferiority not demonstrated</b>

AC, doxorubicin and cyclophosphamide; dd, dose-dense; DFS, disease-free survival; EC, epirubicin and cyclophosphamide; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; HR, hazard ratio; mo, months; wk, weeks; y, years.

additional 25%. However, this rate was still much lower than that of the molecular nonresponders, who went on to standard neoadjuvant therapy with paclitaxel plus HP and had a pCR rate of 80%. Although this remains an area of active investigation, the lack of adequate clinical or molecular biomarkers for successful patient selection at present precludes any recommendation for the use of chemotherapy-free regimens outside an investigational setting.

### Shorter Courses of Trastuzumab

Finally, although the landmark adjuvant trastuzumab studies established 1 year as the standard duration for this therapy, 5 large, randomized phase 3 studies have evaluated shorter durations of trastuzumab, ranging from 9 weeks to 6 months (Table 1). All were designed as noninferiority studies. Only 1 study (PERSEPHONE) met the primary endpoint for noninferiority.<sup>45</sup> Notably, this study utilized an absolute difference in 4-year DFS of less than 3% for noninferiority design, whereas the other trials were based on the upper end of the hazard ratio not exceeding a specific margin, which ranged from 1.15 to 1.53. If PERSEPHONE had used the same statistical design as the other trials, this would correspond to a hazard

ratio margin for noninferiority of 1.171.<sup>46,47</sup> In addition, the confidence intervals varied (95% in PHARE, 90% in PERSEPHONE). Thus, it is possible that variations in study design influenced the primary outcomes of these studies. DFS outcomes were very good across these studies, and absolute differences in DFS between arms were small. However, the majority of patients enrolled in the trials had node-negative, HR+ breast cancer, and subgroup analyses from SOLD and PERSEPHONE suggest that those patients with HR- or node-positive disease may have benefited most from the 12-month duration.<sup>45,48</sup> In terms of toxicity, both PERSEPHONE and Short-HER2 did demonstrate a significant reduction in risk for cardiac events in the shorter-duration treatment arms,<sup>45,49</sup> although long-term follow-up from PHARE identified no differences in late cardiac safety.<sup>50</sup>

Overall, although the noninferiority of courses shorter than 12 months has not been definitively demonstrated and 12 months remains the standard recommendation, it would be reasonable to consider shorter courses of trastuzumab in the case of treatment toxicity or in resource-limited settings, at least for low-risk (HR+, node-negative) patients. It also remains unclear at this time whether patients who have a pCR

**Table 2.** Selected Ongoing Trials in Early-Stage HER2+ Breast Cancer

NCT Identifier (Name)	Design	Setting	Regimen	Primary Outcome	Status
<i>De-escalation</i>					
NCT04266249 (CompassHER2-pCR)	Nonrandomized phase 2	Neoadjuvant	Taxane/H/P × 4 → surgery; if pCR: HP × 13; if no pCR: T-DM1 × 14	RFS	Recruiting
NCT02907918 (PALTAN)	Nonrandomized phase 2	Neoadjuvant HER2+/HR+	H, letrozole (plus OFS if premenopausal), and palbociclib for 16 wk	pCR	Recruiting
NCT03644186 (TOUCH)	Randomized phase 2	Neoadjuvant HER2+/HR+ Age >65 y	Paclitaxel/H/P vs palbociclib/letrozole/H/P	pCR	Recruiting
<i>Novel HER2 therapies</i>					
NCT01042379 (I-SPY 2)	Adaptively randomized phase 2	Neoadjuvant	AC-paclitaxel/H/P with or without tucatinib	pCR	Recruiting
<i>Vaccines</i>					
NCT03387553	Phase 1	Neoadjuvant	HER2-sensitized dendritic cell vaccine with standard neoadjuvant therapy	Immune response and pCR	Recruiting
NCT03384914	Randomized phase 2	Residual disease after standard neoadjuvant therapy	Dendritic cell vaccine vs WOKVAC vaccine	Immune response (DFS as secondary outcome)	Recruiting
NCT04197687	Randomized phase 2	Residual disease after standard neoadjuvant therapy	HER2 vaccine (TPIV100) vs placebo with T-DM1 and sargramostim	DFS	Recruiting
<i>Checkpoint inhibitors</i>					
NCT03747120 (neoHIP)	Randomized phase 2	Neoadjuvant	Paclitaxel/H × 12 wk plus P, vs P and pembrolizumab, vs pembrolizumab	pCR	Recruiting
NCT03742986	Nonrandomized phase 2	Neoadjuvant (inflammatory only)	AC-paclitaxel/H/P plus nivolumab	pCR	Recruiting
NCT03894007	Randomized phase 2	Neoadjuvant	TCH-P × 4 → EC × 3 with atezolizumab or placebo → surgery; if pCR, H × 14; if no pCR, T-DM1 × 14	pCR	Recruiting
NCT03620201	Phase 1	Neoadjuvant	Two doses of M7824 (anti-PD-L1/TGFβRII fusion) before standard neoadjuvant therapy	Change in TILs before/after M7824 (pCR as secondary outcome)	Recruiting

AC, doxorubicin and cyclophosphamide; DFS, disease-free survival; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; HER2, human epidermal growth factor receptor 2; HP, trastuzumab and pertuzumab; HR, hormone receptor; OFS, ovarian function suppression; P, pertuzumab; pCR, pathologic complete response; PD-L1, programmed death ligand 1; RFS, recurrence-free survival; TCH-P, docetaxel, carboplatin, trastuzumab, and pertuzumab; T-DM1, trastuzumab emtansine; TGFβRII, transforming growth factor β receptor II; TIL, tumor-infiltrating lymphocyte; wk, weeks; WOKVAC, “wings of Karen” vaccine.



after neoadjuvant chemotherapy with trastuzumab alone or trastuzumab plus pertuzumab need to continue anti-HER2 therapy for a full year, or whether a shorter course of therapy would be sufficient.

## Future Directions

The shift toward neoadjuvant systemic therapy has made possible the selective escalation of targeted therapy in patients who do not have a pCR after neoadjuvant therapy. Even with escalated anti-HER2 therapy, however, this population remains at increased risk for metastatic relapse. The poorer outcomes in patients with significant residual disease may also partly reflect the proportion of HER2+ tumors that are not biologically HER2-driven or that have a high degree of intratumoral heterogeneity,<sup>6-9</sup> and the development of biomarkers predictive of HER2-driven disease remains an area of active investigation. In addition to approaches based on gene expression signature, recent intriguing work has demonstrated the feasibility of microscale phosphoproteomic techniques that permit the quantitation of HER2 pathway protein expression and phosphorylation in core biopsy specimens, which in a pilot study correlated with the response to neoadjuvant anti-HER2-directed therapies.<sup>51</sup> As soon as such predictive biomarkers become more robustly validated, they will facilitate the development of novel approaches in clinically HER2+ but gene/protein expression signature non-HER2-driven disease.

HER2+ breast cancer is associated with an increased risk for central nervous system (CNS) metastases. Current adjuvant HER2-targeted therapies have minimal CNS penetrance, so CNS relapse remains a significant problem. Although lapatinib has not demonstrated much benefit in the adjuvant setting, later-generation small-molecule HER2 inhibitors with CNS penetrance and higher efficacy rates may hold more promise. Tucatinib (Tukysa, Seattle Genetics) was recently approved in the metastatic setting after demonstrating remarkable efficacy, including CNS activity, in the HER2CLIMB trial.<sup>52</sup> Tucatinib is now being investigated in the neoadjuvant setting via the I-SPY2 trial platform (Table 2).

On the basis of preclinical and clinical data demonstrating a role for tumor immune response in HER+ breast cancer, other novel strategies under investigation in the neoadjuvant and adjuvant settings include immunomodulatory therapies such as HER2 vaccines and the addition of checkpoint inhibitors (Table 2).

Conversely, in low-risk disease, ongoing investigation has focused on expanding de-escalation strategies to minimize toxicity while maintaining clinical benefit in a population with overall excellent outcomes. One exciting approach involves decreasing the intensity of neoadjuvant

therapy to identify patients with treatment-sensitive disease and then tailoring additional therapy according to response at the time of surgery. In the EA1181 CompassHER2-pCR trial (Table 2), patients receive just 4 cycles of a taxane plus HP before surgery, followed by 13 cycles of HP if they achieve a pCR or T-DM1 (with an investigational agent) if they do not achieve a pCR. Improved patient selection for chemotherapy-free approaches remains another area of active investigation, especially for patients with HER2+/HR+ disease. The addition of novel HER2 and other targeted therapies is also being studied as a way to increase the efficacy of chemotherapy-free regimens—for example, the addition of CDK4/6 inhibitors to chemotherapy-free approaches for HER2+/HR+ early-stage breast cancer. The phase 2 NA-PHER2 trial demonstrated a pCR rate of 27% with neoadjuvant trastuzumab, pertuzumab, letrozole, and palbociclib (Ibrance, Pfizer) in this population,<sup>53</sup> which is better than the pCR rates observed in previous trials with the combination of dual anti-HER2 therapy plus endocrine therapy. Several similar trials are ongoing (Table 2).

## Conclusion

The landscape of HER2+ early-stage breast cancer has changed dramatically in the past 2 decades since landmark studies demonstrated clear improvement in breast cancer survival with the addition of adjuvant trastuzumab. Risk-adapted approaches are now standard. Patients who have low-risk disease receive lower-intensity regimens, such as the APT regimen, and patients who have higher-risk disease receive dual anti-HER2 therapy with trastuzumab and pertuzumab plus chemotherapy, followed by T-DM1 in those without a pCR, as well as consideration of adjuvant neratinib. Ongoing studies are evaluating improved biomarkers, further de-escalation strategies with chemotherapy-light or chemotherapy-free regimens, and escalation strategies for those at highest risk. This evolution in care has resulted in a significantly improved prognosis for patients with early-stage HER2+ breast cancer.

## Disclosures

*Dr Wisinski is an advisory board member for Genomic Health, AstraZeneca, Pfizer, and Eisai. She has conducted contracted research for AstraZeneca, Novartis, Pfizer, Sanofi, and Eli Lilly and investigator-initiated research for Pfizer. Dr Sharifi has no disclosures.*

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