HER2-Positive Breast Cancer

Sara M. Tolaney, MD, Nancy U. Lin, MD, and Eric P. Winer, MD

Abstract

• **Objective:** To review the diagnosis and management of HER2-positive breast cancer.
• **Methods:** Qualitative review of the literature.
• **Results:** Amplification of HER2 occurs in 20% to 25% of breast cancers and is associated with high-grade tumors that are poorly differentiated and have higher rates of recurrence. Trastuzumab, a recombinant humanized monoclonal antibody against the extracellular domain of HER2, has dramatically changed the treatment of HER2-positive breast cancer. Clinical studies demonstrate that trastuzumab can significantly improve disease-free survival and overall survival in patients with HER2-positive disease in both the adjuvant and advanced settings. Trastuzumab is generally well-tolerated but can result in cardiac toxicity in about 2% to 4% of patients receiving an anthracycline-based regimen.
• **Conclusion:** Trastuzumab is now established as standard treatment for this subtype of breast cancer. Further work is needed to elucidate the mechanism of trastuzumab and trastuzumab resistance.

Breast cancer is the most common malignancy in women, with approximately 214,000 new cases and 41,000 deaths predicted to occur in 2006 [1]. With advances in our understanding of the underlying molecular biology of the disease, breast cancer is now recognized as not being a single disease but rather a group of several different tumor subtypes, each requiring a somewhat different treatment approach [2]. One unique subtype is defined by overexpression of the HER2/neu gene. HER2/neu belongs to a family of transmembrane tyrosine kinases, including the epidermal growth factor receptor (EGFR), HER2, HER3, and HER4. These receptors regulate cell growth, differentiation, and survival [3]. Overexpression of the HER2/neu gene occurs in 20% to 25% of breast cancer and is associated with poorly differentiated, high-grade tumors with a high rate of recurrence in visceral sites, including the lung, liver, and brain [4,5].

Trastuzumab, a monoclonal antibody against the extracellular domain of HER2/neu, has revolutionized the treatment of HER2-positive breast cancer. This antibody was created by inserting a portion of the antigen-binding site of a mouse monoclonal antibody against HER2/neu into a human monoclonal antibody [6]. Clinical studies revealed that inhibition of cell growth by trastuzumab is limited to HER2-positive cancers, and testing for the overexpression of HER2 has become important in selecting patients for treatment. Recent randomized clinical trials have shown that adjuvant treatment with trastuzumab in women with HER2-positive operable breast cancer can improve disease-free and overall survival. Efforts are underway to identify which women will derive the most benefit from trastuzumab and which women will have disease recurrence despite treatment with trastuzumab. Moving forward, a number of HER2-targeted agents are in varying stages of clinical development for women with trastuzumab-refractory disease.

**Trastuzumab: Mechanism of Action**

While the mechanism by which trastuzumab works in humans remains unclear, many possible explanations have been proposed. There is no natural ligand for HER2, but activation of HER2 can occur when there is dimerization with another HER2 family receptor. It is also thought that phosphorylation of HER2 can occur by ligand-bound EGFR or HER4. HER2 then activates multiple cellular signaling pathways, including the phophatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase cascades [7]. By binding to HER2, it is thought that trastuzumab reduces signaling via these pathways and promotes cell cycle arrest and apoptosis. There is also some thought that decreased receptor signaling might be due to trastuzumab-mediated internalization and degradation of the receptor. Other potential mechanisms include immune mechanisms such as antibody-dependent cell-mediated cytotoxicity, inhibition of angiogenesis, and inhibition of DNA repair [8–10].

**Determining HER-2 Status**

Accurate HER2 testing is essential for selecting patients for trastuzumab therapy, and all primary breast tumors should be evaluated for HER-2 status. There are 2 current methods of testing that are approved by the U.S. Food and Drug Administration (FDA): immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). IHC measures...
HER2-POSITIVE BREAST CANCER

Table 1. Concordance Between Outside Laboratory Immunohistochemistry Results and Fluorescence In Situ Hybridization (FISH) Results from a Central Laboratory

<table>
<thead>
<tr>
<th>Concordance</th>
<th>Outside Laboratory</th>
<th>Central Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunohistochemistry</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>Fluorescence In Situ Hybridization</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fluorescence In Situ Hybridization</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>Fluorescence In Situ Hybridization</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>Fluorescence In Situ Hybridization</td>
<td>3+</td>
<td>3+</td>
</tr>
</tbody>
</table>

Permission to electronically reproduce this table not granted by copyright holder.


HER2 protein levels on the cell surface using a HER2-specific antibody. IHC scoring is performed by a pathologist on a subjective basis. HER2 immunostaining is graded as 0, 1+, 2+, or 3+ based on the percentage of malignant cells stained and the degree of membrane staining present in these malignant cells [11]. The 2 IHC tests approved by the FDA are HerceptTest (Dako, Carpinteria, CA) and PATHWAY (Ventana Medical Systems, Tucson, AZ).

More recently, FISH has been developed to identify patients with HER2-positive tumors. This test directly measures HER2 gene amplification and is more specific and sensitive than IHC [12]. In comparing FISH with IHC, the IHC 2+ category was found to be most likely discordant with FISH HER2 status (Table 1), and therefore FISH should be routinely performed on all patients with tumors that are IHC 2+. Patients with tumors that are IHC 2+ but FISH nonamplified do not appear to benefit from treatment with trastuzumab [13]. The National Comprehensive Cancer Network Task Force developed recommendations for HER2 testing and determined that either IHC or FISH methods may be used [14]. A tumor with an IHC score of 0 or 1+ or a FISH ratio of less than 1.8 is considered to be HER2 negative. A tumor with an IHC score of 3+ or a FISH ratio greater than 2.2 is considered to be HER2 positive. A tumor with an IHC score of 2+ should be further tested using FISH, with HER2 status determined by the FISH result. A tumor with a FISH ratio of 1.8 to 2.2 is considered to be borderline.

Trastuzumab in the Metastatic Setting

Trastuzumab was first employed for the treatment of metastatic breast cancer. The pivotal randomized phase 3 trial revealed that trastuzumab significantly enhanced the clinical benefit of chemotherapy compared with chemotherapy alone [13]. In this trial, 469 HER2-positive women with previously untreated metastatic breast cancer were enrolled. Women who had received adjuvant anthracyclines (n = 188) were randomly assigned to receive paclitaxel with or without trastuzumab, while those who were anthracycline-naive (n = 281) were randomly assigned to an anthracycline plus cyclophosphamide with or without trastuzumab. The addition of trastuzumab to paclitaxel or to an anthracycline plus cyclophosphamide improved with disease-free survival at a median follow-up of 30 months. The overall survival was 25.1 months in the chemotherapy plus trastuzumab arm compared with 20.3 months in the chemotherapy alone arm. A cardiac event was seen in 28% of those receiving an anthracycline plus cyclophosphamide and trastuzumab compared with 9.6% of those receiving an anthracycline plus cyclophosphamide alone. Due to this finding, the combination of trastuzumab with an anthracycline is generally not administered outside of a clinical trial.

In an attempt to overcome the cardiotoxicity observed with trastuzumab and anthracycline therapy in the phase 3 pivotal trial, other combinations of trastuzumab with chemotherapeutic agents have been assessed. Studies of trastuzumab in combination with taxanes, vinorelbine, gemcitabine, and capcitabine have demonstrated added activity [15–18]. The use of trastuzumab in the metastatic setting has changed the natural history of the disease and has made the prognosis similar, if not better, than that with HER2-negative disease. The combination of trastuzumab with chemotherapy is now the standard first-line treatment for women with HER-positive metastatic breast cancer.

The continued use of trastuzumab beyond the time of disease progression remains controversial. There are no published results from randomized trials to help answer this question, and it is unlikely that a trial will ever answer the question. The clinical evidence that continuation of trastuzumab after progression is equivocal. An extension of the phase 3 pivotal trial was performed in which patients were given the opportunity to continue on trastuzumab at the time of progression, either alone or with chemotherapy [19]. The reported response rate of 11% for those women who had been on trastuzumab and continued on a trastuzumab-based regimen is somewhat disappointing, although among those patients who did respond, the response duration was 6.7 months. Safety data revealed who longer duration of trastuzumab therapy did not appear to significantly increase the risk of cardiac dysfunction. There have also been several retrospective studies looking at the efficacy of continued trastuzumab therapy. Taken as a whole, these studies provide weak evidence that continuation of trastuzumab beyond progression may be a beneficial strategy in some patients, although this approach remains unproven and should not be considered the standard of care [20–22].

Another approach to treating those who progress on trastuzumab would be to utilize other HER2-targeted agents. A number of small molecule inhibitors of the HER2 kinase domain are in clinical development, including lapatinib, BIBW2992, and HKI-272 [23]. Of these, lapatinib is furthest in development. Lapatinib is an oral small molecule dual kinase
inhibitor of EGFR and HER2. In vitro data suggests that lapatinib inhibits the growth of HER2 overexpressing cells lines and has activity against cells with resistance to trastuzumab [24]. Lapatinib has demonstrated activity as a single agent in HER2-positive metastatic breast cancer in phase 2 trials [25], and recent evidence from a phase 3 study demonstrates that lapatinib in combination with capecitabine is active in patients who progressed on prior trastuzumab-containing regimens [26]. This phase 3 study enrolled women with HER2-positive locally advanced or metastatic breast cancer who had evidence of disease progression after treatment with trastuzumab. Patients were randomized to capecitabine alone or to capecitabine in combination with lapatinib. The trial was closed early by the independent monitoring committee after a planned interim analysis demonstrated a clinically meaningful advantage in the lapatinib arm that crossed the pre-specified stopping rules. Data were available for 324 of the 392 participants. The addition of lapatinib significantly improved median time to progression (8.4 months vs. 4.4 months; \( P = 0.10 \)) compared with capecitabine alone. Median overall survival was not yet reached in either arm, and with short follow-up, no difference was seen between arms. Even with longer follow-up, an overall survival difference is unlikely, as patients in the capecitabine alone arm were offered crossover to combined treatment with lapatinib. Furthermore, fewer patients receiving lapatinib had disease recurrence in the brain (4 vs. 11 patients), although the difference did not reach statistical significance \( (P = 0.10) \). In terms of toxicity, treatment-related cardiac events were rare, seen only in 4 patients in the combination arm; all patients were asymptomatic, and cardiac events were reversible. Based on this study, the FDA approved lapatinib/capecitabine in patients with HER2-positive metastatic breast cancer who have previously received treatment with an anthracycline, a taxane, and trastuzumab. These findings suggest that lapatinib is useful in the treatment of breast cancer that has progressed on a trastuzumab-containing regimen. Ongoing trials are evaluating lapatinib in combination with other agents.

Lapatinib has also been studied in the treatment of HER2-positive brain metastases. Approximately one third of women with HER2-positive metastatic breast cancer develop brain metastases [27–29], and there is evidence of a numeric increase in central nervous system (CNS) disease as the first site of recurrence in the adjuvant trials [30,31]. Trastuzumab does not cross the blood–brain barrier [32], and CNS progression is emerging as a clinical problem in this patient population. Results from a recent phase 2 study of lapatinib patients with HER2-positive breast cancer with brain metastases that developed on trastuzumab appears promising [33]. Two partial responses by RECIST criteria were observed among 39 patients enrolled. In an exploratory analysis, 4 patients achieved greater than 30% volumetric decline in CNS lesions. These results suggest that lapatinib is able to penetrate the blood–tumor barrier and may be a potential way to treat HER2-positive patients with brain metastases. Further studies of lapatinib in HER2-positive CNS disease are ongoing.

### Trastuzumab in the Adjuvant Setting

There have been 5 important trials validating the use of trastuzumab in the adjuvant treatment of breast cancer: the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 [30], North Central Cancer Treatment Group (NCCTG) N9831 [30], Breast International Herceptin Adjuvant (HERA) [31], Breast Cancer International Research Group (BCIRG)-006 [34], and the Finnish FinHer trial (Table 2) [35]. The NSABP B-31 and NCCTG N9831 trials compared adjuvant chemotherapy with or without concurrent trastuzumab in women with surgically resected HER2-positive breast cancer [30]. Both trials enrolled patients with node-positive disease. NCCTG N9831 also enrolled patients with high-risk node-negative disease, defined as estrogen-receptor (ER)– or progesterone-receptor (PR)–positive with tumor size greater than 2 cm or ER- and PR-negative with tumor size greater than 1 cm. Due to similar eligibility and treatment protocols, the decision was made to perform a

---

**Table 2. Summary of Adjuvant Trastuzumab Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Arm</th>
<th>Control Arm</th>
<th>Total # of Patients</th>
<th>Median Follow-up</th>
<th>Hazard Ratio for DFS</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-31/N9831 [30]</td>
<td>AC → TH</td>
<td>AC → T</td>
<td>3351</td>
<td>2 yr</td>
<td>0.48</td>
<td>2 × 10⁻¹²</td>
</tr>
<tr>
<td>HERA [31]</td>
<td>Chemotherapy → H</td>
<td>Chemotherapy</td>
<td>3387</td>
<td>1 yr</td>
<td>0.54</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>BCIRG-006 [34]</td>
<td>AC → DH</td>
<td>AC → D</td>
<td>3222</td>
<td>2 yr</td>
<td>0.49</td>
<td>4.8 × 10⁻²</td>
</tr>
<tr>
<td>FinHer [35]</td>
<td>DH → CEF</td>
<td>T → CEF</td>
<td>232</td>
<td>3 yr</td>
<td>0.61</td>
<td>0.00015</td>
</tr>
</tbody>
</table>

AC = doxorubicin and cyclophosphamide; CEF = cyclophosphamide, epirubicin, and 5-fluorouracil; D = docetaxel; DCH = docetaxel, carboplatin, and trastuzumab; DFS = disease-free survival; H = trastuzumab; T = paclitaxel; V = vinorelbine. (Adapted with permission from Gonzalez-Angulo AM, Hortobagyi GN, Esteva FJ. Adjuvant therapy with trastuzumab for HER-2/neu positive breast cancer. The Oncologist 2006;11:859.)
combined analysis. The NSABP B-31 compared doxorubicin 60 mg/m², cyclophosphamide 600 mg/m² every 3 cycles for 4 cycles followed by paclitaxel 175 mg/m² every 3 weeks for 4 cycles with the same regimen plus 52 weeks of weekly trastuzumab. The N9831 compared 3 arms: doxorubicin and cyclophosphamide every 3 weeks for 4 cycles followed by weekly paclitaxel for 12 cycles, the same regimen followed by 52 weeks of trastuzumab, and the same regimen plus 52 weeks of trastuzumab initiated concurrently with paclitaxel. Because trastuzumab was not given concurrently in the second arm, this arm was not included in the overall analysis. Overall, there were 1736 patients in the NSABP B-31 trial and 1615 patients in N9831, and at the time of the combined analysis, the median follow-up was 2 years. Compared with the control arm, the trastuzumab arm showed a statistically significant increase in 3-year disease-free survival (5.4% vs. 87.1%, respectively) and a significant increase in overall survival (91.7% vs. 94.3%).

The HERA trial had a somewhat different design and focused on a different set of questions [31]. Patients were randomized to 1 of 3 arms: observation, trastuzumab every 3 weeks for 1 year, or trastuzumab every 3 weeks for 2 years. Patients had either node-negative disease if their tumor size was greater than 1 cm (32.1%) or node-positive disease; all patients had HER2-positive tumors. At a median follow-up of 1 year from randomization (which occurred after women had completed all chemotherapy and/or radiation), the addition of trastuzumab to neoadjuvant and adjuvant chemotherapy resulted in a statistically significant reduction in recurrence (85.8% vs. 77.4%). An overall survival benefit was not seen in the initial publication but was seen in an updated analysis presented at the American Society of Clinical Oncology meeting in 2006. Further analysis is expected to determine if 2 years is superior to 1 year of treatment.

The BCIRG-006 trial aimed at maximizing the efficacy of trastuzumab while minimizing cardiac toxicity. The trial enrolled 3222 patients with node-positive or high-risk lymph node–negative HER2-positive tumors to 1 of 3 arms: doxorubicin-cyclophosphamide every 3 weeks for 4 cycles followed by docetaxel every 3 weeks for 4 cycles (ACD); or the same regimen plus 52 weeks of trastuzumab, weekly during chemotherapy then every 3 weeks during follow-up (ACDH); or docetaxel-carboplatin every 3 weeks for 6 cycles plus 52 weeks of trastuzumab (DCH) with the same schedule as given in arm 2. A recent update of this trial reported 4-year disease-free survival rates of 77% in the ACD arm, 83% in the ACDH arm, and 82% in the DCH arm, with no statistical difference between the trastuzumab-containing arms [34]. There was also no significant difference in overall survival between the 2 trastuzumab-containing arms. Cardiac events were more common in the ACDH regimen as opposed to the DCH regimen (20 events vs. 4 events; \( P = 0.0015 \)). Of note, this study does not have the power to compare the 2 trastuzumab-containing arms directly to each other right now. Therefore, despite the decreased risk of cardiotoxicity with DCH, for the average patient with high-risk, HER2-positive early-stage breast cancer, an anthracycline-based regimen remains the preferred choice for patients treated outside of a clinical trial.

The FinHer trial involved 1010 patients randomized to docetaxel every 3 weeks for 3 doses versus 9 weeks of vinorelbine followed in both groups by 3 cycles of cyclophosphamide, epirubicin, and fluorouracil (CEF) [35]. The 232 patients found to be HER2-positive were randomized to receive weekly trastuzumab for 9 weeks with docetaxel or vinorelbine. This trial enrolled women with axillary node-negative disease or women with node-negative breast cancer with tumors greater than 2 cm and PR-negative. After a median follow-up of 3 years, they found that recurrence was less frequent amongst women receiving docetaxel/CEF with 42/502 recurrences compared with 71/307 recurrences in the vinorelbine/CEF arm at 3 years. More importantly, they found that the administration of trastuzumab for 9 weeks was effective in preventing breast cancer recurrence, with 12/115 events in the trastuzumab arm compared with 27/116 events in the arm without trastuzumab (\( P = 0.01 \)).

Data from these trials suggest that the addition of trastuzumab to adjuvant chemotherapy in women with HER2-positive breast cancer results in an approximate 50% reduction in the risk of recurrence. To date, the improvement in survival has been small in absolute terms, but the follow-up remains quite limited and it is likely that the survival advantage will increase over time. Since virtually all women who developed recurrences would have been expected to receive trastuzumab in the metastatic setting, the survival benefit indicates that the earlier administration of trastuzumab is of benefit. While the 4 large randomized trials establish a 1-year treatment course with trastuzumab as the current standard, findings from the FinHER trial are provocative and suggest that perhaps treatment with a shorter duration of trastuzumab may yield similar benefit. If the HERA trial fails to demonstrate a benefit of 2 years of trastuzumab compared with 1 year, it will be important to study shorter durations of adjuvant trastuzumab therapy.

**Safety of Trastuzumab**

Trastuzumab therapy is generally well tolerated. The most worrisome toxicity is congestive heart failure and cardiomyopathy, which develops in 2% to 4% of patients receiving adjuvant trastuzumab and anthracyclines (Table 3). Limited clinical experience suggests a lower risk of cardiomyopathy for patients receiving nonanthracycline chemotherapy and trastuzumab. While anthracycline-related cardiac toxicity is related to the cumulative dose of the agent, trastuzumab-induced
cardiac damage does not appear to be dose-dependent and is generally thought to be reversible [36].

The mechanism by which trastuzumab induces cardiac toxicity is unclear. There is preclinical data which suggest that HER2 is critical in cardiac development [37]. Furthermore, HER2 signaling is thought to be essential for the prevention of dilated cardiomyopathy [38]. There is also some concern that trastuzumab may result in immune-mediated destruction of cardiomyocytes [39,40].

Because of the risk of cardiac toxicity, relative contraindications for trastuzumab therapy include abnormal cardiac function, high levels of prior anthracycline exposure, and preexisting cardiac disease. Cardiac function should be evaluated prior to initiating therapy and should be monitored during treatment with history, physical examination, and noninvasive imaging of ventricular function, either by echocardiography or nuclear cardiac scanning. The adjuvant trials generally assessed cardiac function prior to treatment, after completion of anthracycline therapy, after 12 weeks of trastuzumab therapy, and at 6, 9, and 18 months. While there is currently no standard recommendation for monitoring, most clinicians assess cardiac function prior to treatment, after anthracycline therapy, and on a regular basis during the course of adjuvant therapy.

There has been an attempt to predict which patients may develop cardiac dysfunction with trastuzumab therapy. The NSABP B-31/N9831 analysis of adjuvant patients found that age and hypertension were risk factors for cardiac dysfunction [30]. In a retrospective analysis in patients with metastatic disease, preexisting diabetes, coronary artery disease, and valvular dysfunction were also associated with apparent higher rates of trastuzumab-related cardiac events; however, hypertension and age were not [41].

Several strategies have been considered in order to minimize cardiac toxicity. Besides eliminating concurrent trastuzumab and anthracycline, some have proposed shortening the duration of trastuzumab, as done in the FinHer study with just 9 weeks of trastuzumab. However, this strategy is still investigational, and is not recommended for current clinical care.

Potential Predictive Markers of Trastuzumab Efficacy

While HER2 overexpression defines a unique subset of breast cancer that might benefit from trastuzumab therapy, it will be important to further define which patients may receive the most benefit, especially when weighing the potential cardiac toxicity of the medication.

Overexpression of topoisomerase IIα (TOP2A) and HER2 has been shown to be associated with poor survival in a number of retrospective studies [42]. While there is evidence that anthracycline-based chemotherapy is particularly effective for HER2-positive breast tumors [43,44], there is also in vitro data suggesting that overexpression of TOP2A is associated with increased susceptibility to anthracyclines. Overexpression of the TOP2A protein is thought to provide more target for topoisomerase II inhibitor drugs, such as anthracyclines [45]. The gene for TOP2A is located on chromosome 17q12, very close to the gene for HER2. TOP2A amplification is thought to occur in the presence of HER2 amplification in most patients [46]. Tanner et al [47] reported TOP2A was amplified in 37% of HER2-positive tumors compared with 1.7% to 10.9% of HER2-negative tumors. In an initial analysis of the BCIRG-006 study, those patients with TOP2A overexpression had a trend towards better disease-free survival after adjuvant therapy with trastuzumab and an anthracycline-containing combination than those in the nonanthracycline arm [48]. In the updated analysis, however, there was no significant difference between the 3 arms [34]. At this point, TOP2A testing should not be used to determine whether or not to give anthracycline-based therapy to certain patients.

Overexpression of c-MYC is found in 6% to 32% of breast carcinomas and is found more frequently in breast tumors that are poorly differentiated [49]. In a meta-analysis, amplification of the c-MYC gene was associated with poor prognostic features, such as high tumor grade, lymph node invasion, and trastuzumab; V = vinorelbine.

Table 3. Summary of Cardiac Safety with Trastuzumab in Adjuvant Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Class III or IV Congestive Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-31 [30]</td>
<td>0.8%</td>
</tr>
<tr>
<td>AC → T</td>
<td>4.1%</td>
</tr>
<tr>
<td>AC → TH</td>
<td>0.3%</td>
</tr>
<tr>
<td>HERA [31]</td>
<td>2.5%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.06%</td>
</tr>
<tr>
<td>Chemotherapy + trastuzumab × 1 year</td>
<td>1.7%</td>
</tr>
<tr>
<td>BCIRG-006 [34]</td>
<td>0.29%</td>
</tr>
<tr>
<td>AC → D</td>
<td>1.59%</td>
</tr>
<tr>
<td>AC → DH</td>
<td>0.38%</td>
</tr>
<tr>
<td>DCH</td>
<td>2.59%</td>
</tr>
<tr>
<td>D or V + FEC</td>
<td>0.27%</td>
</tr>
</tbody>
</table>

AC = doxorubicin and cyclophosphamide; D = docetaxel; DH = docetaxel and trastuzumab; DCH = docetaxel, carboplatin, and trastuzumab; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; H = trastuzumab; T = paclitaxel; TH = paclitaxel and trastuzumab; V = vinorelbine.
metastasis, and negative PR status [50]. In 1900 patients with node-positive breast cancer in the NSABP B-28 trial, a multivariate analysis suggested 3 amplons were independently linked to poor prognosis: HER2, HTPAP, and cMYC. Coamplification of HER2 and HTPAP was rare, but coamplification of HER2 and cMYC was more common and was associated with a worse outcome than when each one was amplified alone [51]. In NSABP B-31, cMYC FISH screening results were available for 1549 individuals, and cMYC was amplified in 30% of cases. Patients with coamplification of cMYC and HER2 had worse outcome when treated with chemotherapy alone; however, the addition of trastuzumab reversed this trend, resulting in a decrease in recurrence from 21.8% to 5.5% [51]. The authors concluded that perhaps the prosapoptotic function of dysregulated cMYC requires an antiapoptotic signal from another activated oncogene to counteract it, and amplified HER2 may serve as such an antiapoptotic signal. If the activity of HER2 is blocked by trastuzumab, apoptosis can occur. This suggests that c-MYC amplification appears to increase sensitivity to HER2-targeted therapy.

While the results of these retrospective analyses are interesting, further investigation is needed before TOP2A can be considered a marker for anthracycline sensitivity or c-MYC amplification can be considered a predictive marker of response to trastuzumab.

Remaining Questions
There remain many unanswered questions. The exact biological mechanism of action of trastuzumab is unknown, and a better understanding would help determine whether trastuzumab is best given concurrently with chemotherapy, or whether sequential therapy may be adequate. Based on the available data, most clinicians would favor concurrent therapy if a taxane is included in the adjuvant treatment. Concurrent treatment with an anthracycline is contraindicated outside of a clinical trial. The optimal duration of therapy in the adjuvant setting is unknown, and the role of trastuzumab therapy beyond tumor progression in the metastatic setting is not well defined. Furthermore, understanding the molecular mechanisms that contribute to trastuzumab resistance are unknown, and a better understanding of the underlying molecular biology will be of major importance as new anti-HER2 therapies are developed. Several mechanisms have been proposed for the development of trastuzumab resistance, including altered receptor-antibody interaction, alternative growth factor pathways, loss of PTEN, and activating mutations in PI3K [7]. Potential treatment approaches to trastuzumab resistance are being investigated, including novel tyrosine kinase inhibitor, inhibitors of insulin-like growth factor, heat shock protein 90 inhibitors, and mTOR (mammalian target of rapamycin) inhibitors.

Summary
HER2-positive breast cancers represent a unique subtype of breast cancer associated with poorly differentiated, high-grade tumors that have with a worse prognosis than HER2-negative breast cancers. The introduction of trastuzumab, however, has changed the natural history of HER2-positive disease and is now established as standard treatment for this subtype of breast cancer. Adequate assessment of HER2 status is critical for determining who will benefit from trastuzumab therapy, and careful cardiac monitoring is warranted. While there remain many unanswered questions, clinical trials are ongoing and will help further define the sequence and length of trastuzumab therapy.

Case Examples
Case Study 1
A 40-year-old premenopausal woman palpated a lump in her right breast approximately 2 months ago. She followed up with her primary care physician who palpated a lump in the 3 o’clock position and also noted an enlarged right axillary node. A mammogram showed a spirulated density corresponding to the mass, and an ultrasound-guided biopsy revealed a grade 2 invasive ductal carcinoma. She underwent a lumpectomy and an axillary node dissection and pathology revealed a 2.9-cm grade 2 invasive ductal carcinoma with negative margins. The tumor was ER-positive, PR-positive, and HER2 2+ by IHC. Axillary node dissection revealed the presence of carcinoma in 4 of 11 lymph nodes.

• What other tests should be performed?

Since about 20% of patients with an IHC result of 2+ will have a positive FISH test, it is important to check a FISH in order to see if the tumor truly overexpresses HER2. Only patients who are found to overexpress HER2 will benefit from trastuzumab therapy. In addition to FISH testing, further imaging tests should be performed in order to rule out the presence of metastatic disease since she has evidence of axillary node involvement. Standard imaging tests that should be performed include a computed tomography scan of the chest, abdomen, and pelvis, as well as a bone scan. Moreover, if the patient is expected to receive either anthracycline-based chemotherapy or trastuzumab, cardiac imaging, with either an echocardiogram or nuclear scanning, should be performed in order to evaluate her ejection fraction.

Results of Testing
The results of the above tests reveal that the patient’s tumor is HER2 amplified with a ratio of 5.1. Staging studies show
that there is no evidence of metastatic disease, and an echocardiogram reveals a normal ejection fraction of 64%.

- **What would be standard treatment recommendations for adjuvant chemotherapy?**

Based on the results of the large randomized trials with trastuzumab therapy, most clinicians would recommend treatment with 4 cycles of adriamycin and cyclophosphamide given every 3 weeks, followed by paclitaxel and trastuzumab given weekly for 12 weeks, and completed by trastuzumab monotherapy given every 3 weeks to complete a total of 52 weeks of trastuzumab therapy. Furthermore, she will require radiotherapy since she had a lumpectomy, and has evidence of involved multiple axillary nodes. Also, given that she is hormone receptor–positive, she would benefit from adjuvant hormonal therapy. Since she is premenopausal, a 5-year course of tamoxifen remains the standard endocrine treatment. Ongoing clinical trials are evaluating other approaches to adjuvant endocrine therapy.

- **How often should cardiac monitoring be performed during therapy?**

Based on the monitoring done in the large randomized trials, noninvasive cardiac monitoring with echocardiogram or nuclear scans should be done prior to initiating chemotherapy, at completion of anthracycline therapy, after paclitaxel and trastuzumab therapy, at 6 months, 9 months, and after completion of trastuzumab.

**Follow-up**

After completion of paclitaxel and trastuzumab, her ejection fraction is stable, and she is initiated on trastuzumab monotherapy every 3 weeks in conjunction with radiotherapy, and hormonal therapy with tamoxifen. An echocardiogram performed at 6 months reveals an ejection fraction of 48%.

- **Would you continue trastuzumab therapy?**

Given that her ejection fraction decreased by greater than 10% and is now below the lower limit of normal, trastuzumab therapy should be held and a repeat echocardiogram should be obtained after 4 weeks. If this repeat ejection fraction is improved and is within 10% of the original ejection fraction, trastuzumab can be reinitiated.

**Further Follow-up**

Trastuzumab is reinitiated. A repeat echocardiogram at 9 months and after completion of therapy reveals a normal ejection fraction. She continues on tamoxifen therapy and is tolerating treatment well.

- **How should this patient be followed?**

The American Society of Clinical Oncology has formulated guidelines for following patients with breast cancer. The guidelines recommend a history and physical examination be performed every 3 to 6 months for the first 3 years after treatment, and every 6 to 12 months for years 4 and 5, and every year thereafter. A mammogram should be performed 1 year after the first mammogram but no earlier than 6 months after radiotherapy. She should visit her gynecologist regularly, especially since she is on tamoxifen therapy, and report any vaginal bleeding. Routine imaging studies to screen for occult metastatic disease are not recommended in follow-up because they have not been shown to lengthen survival.

**Case Study 2**

Three years ago, a 58-year-old postmenopausal woman was diagnosed with a 2-cm, node-negative, ER-negative, PR-negative, and HER2-positive invasive ductal carcinoma of her left breast. She was treated with a mastectomy followed by doxorubicin and cyclophosphamide given every 3 weeks for 4 cycles. She now presents with right upper quadrant pain, and imaging studies reveal 3 liver lesions. A liver biopsy is consistent with malignant cells that are ER-negative, PR-negative, and HER2 overexpression is confirmed by FISH.

- **What type of treatment would you recommend?**

This patient has HER2-positive, hormone receptor–negative liver metastases. First-line treatment would involve a trastuzumab-based chemotherapy regimen. Possible options would include a combination of paclitaxel with trastuzumab, navelbine and trastuzumab, docetaxel and trastuzumab, or carboplatin in combination with trastuzumab and docetaxel [52].

An echocardiogram was obtained and revealed normal cardiac function. The patient initiated therapy with weekly paclitaxel and trastuzumab and tolerated treatment well. Reimaging studies performed after 3 months demonstrated a good response; however, after 9 months of therapy, imaging studies revealed that liver metastases had grown and
there were several new lung nodules that were suspicious for metastases.

- What are your recommendations for therapy now?

Since she has evidence of disease progression, paclitaxel and trastuzumab should be discontinued. Recent evidence suggests that the combination of lapatinib and capecitabine is active in patients with HER2-positive metastatic breast cancer that has progressed on trastuzumab-containing regimens and results in improved time to progression and progression-free survival.

Corresponding author: Sara M. Tolianey, MD. Dana-Farber Cancer Institute, 44 Binney St., Mayer 2, Boston, MA 02445, stolane@partners.org.

Financial disclosures: Dr. Lin has received consulting fees from GlaxoSmithKline.

References

www.turner-white.com


