Neoadjuvant and Adjuvant Therapy for HER2 Positive Disease

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OVERVIEW

Since the initial description of the HER2 proto-oncogene as a poor prognostic factor in breast cancer in 1987, to the first randomized trial of a monoclonal antibody directed against HER2 in combination with chemotherapy for the treatment of metastatic HER2-positive breast cancer published in 2001, to the American Society of Clinical Oncology (ASCO) 2005 Annual Meeting in which we saw the unprecedented collective presentations demonstrating the dramatic benefit of trastuzumab in the adjuvant setting—the clinical landscape of HER2-overexpressing breast cancer has forever changed. More recently, there has been increasing use of preoperative chemotherapy and anti-HER2 targeted therapies in primary operable HER2 disease in the research domain and in clinical practice. In the next few years, we will see if dual adjuvant anti-HER2 antibody inhibition produces clinically significant improvements in outcome; understand if there is a role of small molecule inhibitors of the HER family of receptors either in combination or sequential to trastuzumab; further refine the relationship between pathologic complete response (pCR) and long-term clinical outcomes; and find predictive biomarkers to identify cohorts of patients that may need differential combinations and/or durations of anti-HER2 therapies.

From the original description of the human epidermal growth factor receptor 2 (HER2) as a proto-oncogene, to being a prognostic marker, to then being a therapeutic target has revolutionized the categorization, risk assessment, and treatment of breast cancer. Though this subtype of breast cancer represents less than 25% of incident breast cancers, many lessons can be learned from the development of anti-HER2 therapies in early-stage disease. In particular, much work has recently been put forth in neoadjuvant trials assessing combinations of anti-HER2 therapies. This review will touch on the landmark studies in both the adjuvant and neoadjuvant settings and comment on some of the controversies that still remain today in both clinical care and as research questions.

LANDMARK RANDOMIZED TRIALS OF ADJUVANT TRASTUZUMAB

Current clinical guidelines clearly state that standard of care in 2015 recommends the use of the monoclonal anti-HER2 antibody trastuzumab in combination with or after adjuvant chemotherapy in medically fit patients diagnosed with stage I to III HER2-positive breast cancer.1,2 The four landmark randomized trials investigating the benefit of adjuvant trastuzumab (National Surgical Adjuvant Breast and Bowel Project [NSABP] B-31, North Central Cancer Treatment Group [NCCTG] N9831, HERA, and Breast Cancer International Research Group [BCIRG] 006) in their initial analysis reported outcomes with median follow-ups of 24 to 36 months.3-5 The range in benefit in disease-free survival (DFS) in favor of trastuzumab was with hazard ratios (HRs) between 0.48 and 0.67 (p < 0.0001), and the range in benefit in overall survival (OS) was between 0.59 and 0.67 (p = NS to p = 0.015). Absolute improvements in DFS ranged from 6% to 11%, with corresponding absolute differences in OS of 1% to 2.5% (Table 1).

With longer follow-up from these trials (now 8-year median follow-up from HERA and from the combined analyses of NSABP B-31 and NCCTG N9831), there continues to be statistically and clinically significant improvements in DFS and OS.6-8 Though the magnitude of benefit, as measured by HRs, appears to have lessened slightly over time as more events (both relapses and deaths) occur, absolute gains in overall survival are larger now than in earlier analyses (Table 2). The selective crossover of some of the patients initially randomly assigned to the no trastuzumab arm across the trials will have mitigated some of the initial differences seen in the studies. However, relapses unfortunately continue to occur at a relatively constant rate over time in the trastuzumab-treated arm(s)—with an estimated 10-year DFS of 73.7% from the combined analyses of NSABP B-31 and NCCTG N9831.6 What is encouraging, however, is that with longer follow-up, the cumulative incidence of cardiac adverse events plateaus, with cardiac events rarely occurring following completion of trastuzumab treatment.7 In the HERA study, at 8-years follow-up, only 4.1% of patients experienced...
New York Head and Neck Service class I or class II cardiac dysfunction with a left ventricular ejection fraction (LVEF) drop of 10% or more below baseline and to an absolute LVEF of 50% or less. Furthermore, it is felt that the majority of cardiac events secondary to trastuzumab are reversible in nature.

Perhaps the remaining limited questions at hand specific to clinical practice in relation to these landmark trials are (1) treatment of HER2-positive T1a-bN0 breast cancers, (2) an anthracycline or no anthracycline-based regimen, and (3) concurrent compared with sequential trastuzumab therapy. A small minority of patients in these four pivotal trials had T1a-bN0 breast cancers. Several retrospective prognostic studies demonstrate a significantly worse prognosis in HER2-positive T1a-bN0 breast cancers compared with HER2-negative T1a-bN0 breast cancers.9,10 In a recent analysis from the National Comprehensive Cancer Network (NCCN) database examining this exact question, 4,113 patients with T1a-bN0 breast cancers treated between 2000 and 2009 were assessed especially for hormone receptor–positive/HER2-positive breast cancer, the risks and inconvenience of treatment may potentially outweigh the benefit of therapy—especially for hormone receptor–positive/HER2-positive T1N0 breast cancers.

In the same vein, the selection of adjuvant chemotherapy regimen in combination with trastuzumab varies. Based on the risk/benefit ratio, consideration should be made for a limited nonanthracycline-based regimen in stage I disease. Though not studied within a randomized trial, the regimens of weekly paclitaxel (80 mg/m² weekly for 12 weeks) concurrent with trastuzumab (for 1 year) or four cycles of docetaxel and cyclophosphamide (75 mg/m² and 600 mg/m², respectively) every 3 weeks for four cycles concurrent with trastuzumab (for 1 year) both demonstrate a generally low toxicity profile with very favorable clinical outcomes.12,13 In the recently published phase II study of 406 women with primarily stage I HER2-positive disease (>90%), the 3-year IDFS was 98.7% with weekly paclitaxel for 12 weeks concurrent with trastuzumab.12 There was a reported 0.5% rate of symptomatic congestive heart failure and a 3.2% rate of asymptomatic declines in LVEF. Likewise, in the phase II single-arm, open-label study of docetaxel and cyclophosphamide (four cycles) concurrent with trastuzumab, the reported 2-year DFS of 97.8% was quite favorable as well. Otherwise, for stage II to III disease, consideration should be given for the regimens studied in the landmark pivotal trials, the vast majority of which contained an anthracycline (four cycles) sequentially followed by a taxane (four cycles), except for the six cycles of docetaxel, carboplatin, and trastuzumab arm in BCIRG 006.9

Lastly, it would seem both practical and potentially more efficacious to deliver the trastuzumab concurrent with the

**TABLE 1. Initial Reports from the Large Adjuvant Trastuzumab Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trastuzumab Duration</th>
<th>Median Follow-up (Months)</th>
<th>Treatment Arms</th>
<th>No. of Patients</th>
<th>HR for DFS (95% CI) 2-3 yr DFS</th>
<th>HR for OS (95% CI) 2-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA4</td>
<td>1 yr</td>
<td>24</td>
<td>Chemotherapy</td>
<td>1,698</td>
<td>0.64 (0.54-0.76) 85.8%</td>
<td>0.66 (0.47-0.91) 96.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemotherapy → H</td>
<td>1,703</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP B-33</td>
<td>1 yr</td>
<td>24</td>
<td>AC → P</td>
<td>1,679</td>
<td>75.4%</td>
<td>91.1%</td>
</tr>
<tr>
<td>NCTCG N9831</td>
<td>1 yr</td>
<td>36</td>
<td>AC → P → H</td>
<td>1,672</td>
<td>0.48 (0.39-0.59) 87.1%</td>
<td>0.67 (0.48-0.93) 94.3%</td>
</tr>
<tr>
<td>BCIRG 0065</td>
<td>1 yr</td>
<td>36</td>
<td>AC → T</td>
<td>1,073</td>
<td>81%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TcarboH</td>
<td>1,075</td>
<td>0.61 (0.48-0.76) 88%</td>
<td>0.59 (0.42-0.85) N/A</td>
</tr>
</tbody>
</table>

**KEY POINTS**

- The treatment of HER2-positive early-stage breast cancer should incorporate 12 months of adjuvant trastuzumab, preferably concurrent with a taxane backbone.
- Neoadjuvant systemic therapies are now routinely delivered in both primary operable and locally advanced breast cancer in the research domain and in clinical practice.
- The combination of lapatinib and trastuzumab inconsistently improved pathologic complete response (pCR) rates across its neoadjuvant trials and ultimately did not improve disease-free survival (DFS) in the large adjuvant ALTTO trial.
- In a large pooled analysis, pCR (with or without the presence of in situ disease) in the breast and nodes most closely correlates with DFS and overall survival.
- Well-designed, randomized, neoadjuvant trials with tissue acquisition are essential to more precisely plan adjuvant trials, assess for predictive biomarkers, and accelerate drug development for early-stage disease.

Abbreviations: HR, hazard ratio; DFS, disease-free survival; OS, overall survival; H, trastuzumab; NSABP, National Surgical Adjuvant Breast and Bowel Project; A, doxorubicin; C, cyclophosphamide; P, paclitaxel; NCTCG, National Central Cancer Treatment Group; BCIRG, Breast Cancer International Research Group; T, docetaxel; carbo, carboplatin.
taxane. In the NCCTG N9831 study, one arm delivered paclitaxel (weekly) concurrent with trastuzumab (arm C), whereas in another arm, the trastuzumab was delivered sequential (arm B). Although there was a numerical increase in DFS in favor of the concurrent arm (84.4% vs. 80.1%), it did not meet statistical significance based on the interim analysis criteria (arm C/arm B HR 0.77; 95% CI, 0.53 to 1.11). However, as there was no difference in toxicity between these two arms, and for convenience and earlier completion of therapy, it would be overall advantageous to deliver the trastuzumab concurrent with the taxane.

**LANDMARK RANDOMIZED TRIALS OF NEOADJUVANT HER2-TARGETED THERAPIES**

The standard clinical use of neoadjuvant chemotherapy today can be categorized into two populations of patients: the locally advanced breast cancers (LABC) and the primary operable breast cancers (POBC). The defined purpose for the use of neoadjuvant chemotherapy for LABC is to convert a baseline inoperable condition to an operable state. Whereas in POBC, the standard clinical utility of neoadjuvant chemotherapy has the potential to downstage a tumor and thus convert a baseline mastectomy candidate into a breast-conservation candidate. However, as individual trials and the Early Breast Cancer Trialists Collaborative Group overview of neoadjuvant trials demonstrated that standard chemotherapy regimens (anthracyclines ± taxanes) whether given preoperatively or postoperatively (adjuvant) provided the same long-term clinical outcomes, one can now potentially deliver standard systemic treatment in either the neoadjuvant or adjuvant setting with similar confidence. The same holds true, if not even more so, for HER2-positive breast cancers. The additional advantages of delivery in the neoadjuvant setting include the ability to study new agents with the utility of a surrogate endpoint for outcome; the ability to obtain tumor tissue for pharmacodynamic assessment, understanding of biology and discovery of predictive biomarkers; earlier initiation of systemic therapies; and the ability to monitor response (which is clearly not possible in the adjuvant setting).

The first landmark trial investigating the benefit of neoadjuvant trastuzumab in the LABC setting was the NOAH trial. NOAH randomly selected 228 patients with HER2-positive disease to receive a neoadjuvant regimen consisting of doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) with or without concurrent trastuzumab (throughout the entire chemotherapeutic regimen). This is the largest randomized trial of a true locally advanced and inflammatory population to date. The trastuzumab-treated cohort demonstrated a significantly superior rate of pCR in breast and nodes (total pCR [tpCR]; 38% vs. 19%; p = 0.001), which ultimately translated to an improved 3-year event-free survival (EFS; 71% vs. 56%, HR 0.59; 95% CI, 0.38 to 0.90). Not only was a doubling of the tpCR rate impressive, but also the magnitude of improvement in EFS of a similar degree (HR 0.59) as the landmark adjuvant trastuzumab trials is an interesting observation. Although the use of the specific chemotherapy regimen from NOAH is not likely to be common, the concept of neoadjuvant trastuzumab concurrent with chemotherapy now is.

**Lapatinib-Based Neoadjuvant Trials**

Lapatinib is a small molecule tyrosine kinase inhibitor (TKI) of the HER1 and HER2 receptors. Despite the lack of a head-to-head trial with trastuzumab in the metastatic setting, several randomized neoadjuvant trials were initiated. All these trials included both POBC and HER2-positive LABC. The GeparQuinto study compared trastuzumab (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks given concurrently with chemotherapy during the preoperative period) with lapatinib (1,250 mg/day continuously for 12 weeks) added to a backbone of four cycles of epirubicin (90 mg/m²) and cyclophosphamide (600 mg/m²) followed by four of docetaxel (100 mg/m²) in 615 patients with HER2-positive disease. A significantly higher tpCR rate (breasts and nodes) was seen in the trastuzumab arm (30.3% vs. 22.7%; odds ratio 0.68; 95% CI, 0.47 to 0.97; p = 0.04). Furthermore, in this study, dose reductions were required in nearly one-third of patients receiving lapatinib, prompting a protocol amendment reducing the lapatinib dose to 1,000 mg/m².

The smaller CHER-LOB study was conducted using a chemotherapy backbone of weekly paclitaxel (80 mg/m²) for 12 weeks followed by three-weekly 5-fluorouracil, epirubicin, cyclophosphamide (FEC; 500/75/500 mg/m², respectively)
with either weekly trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly) or lapatinib (1,250 mg daily) given concurrently with chemotherapy. This study also examined the efficacy of a trastuzumab-lapatinib doublet with dose-adjusted lapatinib (750 mg/day). Dual HER2 targeting substantially improved pCR (breast and nodes) over either trastuzumab or lapatinib alone. pCR rates were 46% (90% CI, 34.4% to 58.9%), 25% (90% CI, 13.1% to 36.9%), and 26.3% (90% CI, 14.5% to 38.1%), respectively. As was seen in the GeparQuinto trial, gastrointestinal toxicity with lapatinib was a significant adverse event. More than 50% of those receiving lapatinib experienced diarrhea of grade 1 or higher, even after a protocol amendment directing a dose reduction from 1,500 mg/day to 1,250 mg/day in the single-agent arm, and from 1,000 mg/day to 750 mg/day in the doublet arm.

The NeoAdjuvant Lapatinib and/or Trastuzumab Optimization (NeoALTTO) trial was a three-armed study addressing the comparative efficacy of single compared with dual HER2 blockade using trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly), lapatinib (1,500 mg daily), or a combination (trastuzumab standard dose and lapatinib 1,000 mg daily), alongside weekly paclitaxel (80 mg/m²) chemotherapy. This trial scheduled a 6-week lead in period of targeted therapy alone before introduction of paclitaxel for a further 12 weeks of therapy. Dual HER2 targeting induced tpCR (breast and nodes) rates in 46.8% of patients compared with 27.6% in the trastuzumab alone arm (p = 0.0007). There was no statistically significant difference in pCR rates between the trastuzumab alone and lapatinib alone arms (27.6% and 20%; p = 0.13).

In a fourth trial, the NSABP B-41 study randomly selected 529 patients with HER2-positive disease to receive doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) every 3 weeks for four cycles, followed by weekly paclitaxel (80 mg/m²) for a further 12 weeks with either concurrent weekly trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly), 1,250 mg of lapatinib daily, or weekly trastuzumab plus lapatinib (750 mg/day). pCR was achieved for 62% of patients receiving combination HER2 targeting compared with 52.5% in the trastuzumab arm (p = 0.095). There was no significant difference between the trastuzumab and lapatinib alone arms (52.5% vs. 53.2%; p = 0.990).

Lastly, the Cancer and Leukemia Group B 40601, a neoadjuvant phase III trial of weekly paclitaxel (T) and trastuzumab (H) with and without lapatinib (L) in HER2-positive breast cancer, was presented at the 2013 ASCO Annual Meeting. This trial randomly selected 305 patients, of which two-thirds had clinical stage II disease. The pCR rates in the breast alone were 51% (42% to 60%) THL, 40% (32% to 49%) TH, 32% (22% to 44%) TL. The combination arm of THL was not significantly different from the standard arm of trastuzumab and paclitaxel (p = 0.11; Table 3).

### TABLE 3. Neoadjuvant Trials of Dual HER2 Targeted Therapies

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Treatment Arms</th>
<th>pCR (Breast and Nodes)</th>
<th>p</th>
<th>3-yr EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeparQuinto17</td>
<td>309</td>
<td>ECH → TH</td>
<td>31.3%</td>
<td>p &lt; 0.05</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>311</td>
<td>ECL → TL</td>
<td>21.7%</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>NeoALTTO19</td>
<td>149</td>
<td>H → HP</td>
<td>27.6%</td>
<td></td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td>154</td>
<td>L → LP</td>
<td>20.0%</td>
<td>p = 0.13</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>152</td>
<td>HL → HLP</td>
<td>46.9%</td>
<td>p = 0.001</td>
<td>84%</td>
</tr>
<tr>
<td>CHER-LOB18</td>
<td>36</td>
<td>HP → FECH</td>
<td>25%</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>LP → FECL</td>
<td>26.3%</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>HLP → FECHL</td>
<td>46.7%</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>NSABP B-41</td>
<td>177</td>
<td>AC → HP</td>
<td>52.5% (breast)</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>171</td>
<td>AC → LP</td>
<td>53.2% (breast)</td>
<td>p = 0.9852</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>171</td>
<td>AC → HLP</td>
<td>62.0% (breast)</td>
<td>p = 0.095</td>
<td>N/A</td>
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<tr>
<td>CALGB 40601</td>
<td>120</td>
<td>HP</td>
<td>40% (breast)</td>
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<tr>
<td></td>
<td>67</td>
<td>LP</td>
<td>32% (breast)</td>
<td></td>
<td>N/A</td>
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<tr>
<td></td>
<td>118</td>
<td>HLP</td>
<td>59% (breast)</td>
<td>p = 0.11</td>
<td>N/A</td>
</tr>
<tr>
<td>NeoSphere22</td>
<td>107</td>
<td>TH</td>
<td>29.0% (breast)</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>PerHT</td>
<td>45.8% (breast)</td>
<td>p = 0.0141</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>PerH</td>
<td>24.0% (breast)</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>PerT</td>
<td>16.8% (breast)</td>
<td></td>
<td>N/A</td>
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<tr>
<td>TRYPHENA23</td>
<td>73</td>
<td>PerHFECH → PerTH</td>
<td>61.6% (breast)</td>
<td></td>
<td>N/A</td>
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<tr>
<td></td>
<td>75</td>
<td>FEC → PerTH</td>
<td>57.3% (breast)</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>TcarboPer</td>
<td>66.2% (breast)</td>
<td></td>
<td>N/A</td>
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</table>

Abbreviations: pCR, pathologic complete response; EFS, event-free survival; E, epirubicin; C, cyclophosphamide; H, trastuzumab; T, docetaxel; L, lapatinib; P, paclitaxel; F, 5-fluorouracil; NSABP, National Surgical Adjuvant Breast and Bowel Project; A, doxorubicin; CALGB, Cancer and Leukemia Group B; Per, pertuzumab; carbo, carboplatin.
Pertuzumab-Based Neoadjuvant Trials

Pertuzumab, a humanized monoclonal antibody that inhibits dimerization of HER2 with other HER receptors, has been evaluated in two randomized phase II studies. In the NeoSphere trial, 417 women with HER2-positive POBC/LABC disease were randomly selected to receive either four cycles of neoadjuvant trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks), docetaxel (75 mg/m² escalating to 100 mg/m² as tolerated) and pertuzumab (loading dose 840 mg, followed by 420 mg every 3 weeks), or trastuzumab plus docetaxel, or pertuzumab and trastuzumab without chemotherapy, or pertuzumab plus docetaxel. The combination of dual HER2 targeting and docetaxel induced a pCR (breast) for 45.8% (95% CI, 36.1 to 55.7) compared with 29% of those randomly assigned to trastuzumab and docetaxel (95% CI, 20.6 to 38.5; p = 0.0141). After surgery, all patients received three cycles of FEC and the remainder of 1 year of trastuzumab. pCR was achieved for 24.0% of those receiving pertuzumab and docetaxel and 16.8% of women who were treated with dual HER2 targeted therapy in the absence of chemotherapy. Neither short- nor long-term clinical outcomes (EFS and OS) have been reported yet from NeoSphere.

TRYPHENA was a phase II trial with cardiac safety as the primary endpoint. All 225 participants received dual HER2 targeting with trastuzumab and pertuzumab. The three study arms were randomly assigned to 500 mg 5-fluorouracil, 100 mg epirubicin, and 500 mg/m² cyclophosphamide (FEC100) for three cycles, followed by docetaxel (75 mg/m²) with concurrent with trastuzumab and pertuzumab; FEC for three cycles followed by docetaxel with trastuzumab and pertuzumab given only alongside docetaxel; or six cycles of docetaxel, carboplatin, trastuzumab, and pertuzumab. In this trial, pCR (breast) was a secondary endpoint, with rates ranging between 57.3% and 66.2%, in keeping with results seen elsewhere. The lack of an arm without pertuzumab limits the extrapolation of these results to other studies and to standard clinical practice.

On September 30, 2013, the U.S. Food and Drug Administration (FDA) granted accelerated approval to pertuzumab in combination with trastuzumab and chemotherapy as a neoadjuvant treatment regimen in patients with HER2-positive locally advanced, inflammatory, or early-stage disease (tumor size > 2 cm or with positive lymph nodes). This was a landmark ruling as pertuzumab is the first FDA- approved agent for use in the neoadjuvant setting. The allowance of use in clinical care and guidelines (NCCN2) does provide a window of opportunity to potentially prevent relapses in higher-risk cohorts while awaiting results from the confirmatory adjuvant trial (APHINITY). Not only is this of potential benefit to patients today, but it also excites the drug development world about an accelerated path to drug approval in the much larger cohort of early-stage disease.

Areas of Ongoing Controversy

Despite the breadth of the trials and the consistency of results across them, a number of questions remain regarding the op-
trend was seen, there was no significant difference in EFS between the combination arm and the trastuzumab arm (HR 0.78; 95% CI, 0.47 to 1.28; p = 0.33). The ALTTTO trial randomly assigned 8,381 patients, of whom 40% had node-negative disease and 57% had hormone receptor–positive disease. The four arms of the study were trastuzumab for 12 months (T), lapatinib for 12 months (L), trastuzumab for 12 weeks followed sequentially by lapatinib for 34 weeks (T → L), and the combination of trastuzumab and lapatinib for 12 months (TL). Although the study was powered for 850 DFS events, the study was analyzed at 4.5 years (median) of follow-up as per protocol stipulation but with only 555 DFS events. At the first efficacy interim analysis, the comparison of L to T crossed the futility boundary, and as such, the L arm was crossed over to a recommended course of trastuzumab for 12 months. At the time of reporting of the efficacy of the primary endpoint at the 2014 ASCO Annual Meeting, the 4-year DFS for the T, T→L, and TL arms were 86%, 87%, and 88%, respectively. The HR comparing TL and T was 0.84 (0.70–1.02; p = 0.048), which was not significant, for a p ≤ 0.025 was required for statistical significance. The interaction test for hormone receptor status and for schedule of anti-HER2 therapy was not significant. However, numerically, the sequential administration of anti-HER2 therapy arms had some difference (T vs. TL 4-year DFS of 83% vs. 86%, respectively), whereas the combination arms did not (T vs. TL 4-year DFS of 90% vs. 90%, respectively). Lapatinib was also associated with a greater rate of adverse events, which subsequently led to only 60% to 78% of patients in the lapatinib treatment arms receiving at least 85% of the intended dose intensity of L. These factors, in addition to a time-driven analysis (rather than the initial powering of the study for an event-driven analysis) may have affected the true efficacy of the dual anti-HER2 combination arm.

Neratinib has been studied in a neoadjuvant manner as part of the I-SPY 2 program, as well as in an extended manner in a placebo-controlled trial in a population of patients following 1 year of standard adjuvant trastuzumab-based therapy. In the I-SPY 2 trial, neratinib was given in combination with weekly paclitaxel (80 mg/m² for 12 weeks) in both the HER2-positive and HER2-negative cohorts. All patients subsequently received sequential doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) for four cycles without neratinib or trastuzumab before proceeding to definitive surgery. In the HER2-positive signature cohort, the pCR rate was 39% in the neratinib plus paclitaxel arm, compared to 23% in the trastuzumab plus paclitaxel arm. The magnitude of improvement in pCR was similar regardless of the hormone receptor status in the HER2-positive cohort. No significant difference in pCR rates was seen in the HER2-negative signature cohort. A significant rate of grade 2–3 diarrhea was seen, however, in the neratinib arms resulting in dose reductions/holds in 65% of cases for neratinib (vs. 15% in the control arm).

ExeNET is a double-blind phase III trial of neratinib (240 mg orally once daily) versus placebo in 2,821 women with early-stage HER2-positive (local confirmation) breast cancer after adjuvant treatment with trastuzumab. The primary endpoint of the study was DFS. The results of the study have not yet been presented in a peer review forum, but a press release from July 22, 2014, stated, “The results of the trial demonstrated that treatment with neratinib resulted in a 33% improvement in disease-free survival versus placebo. The hazard ratio was determined to be 0.67, which was statistically significant with a p value of 0.0046. The secondary endpoint of the trial was disease-free survival including ductal carcinoma in situ (DFS-DCIS). The results of the trial demonstrated that treatment with neratinib resulted in a 37% improvement in disease-free survival including ductal carcinoma in situ versus placebo. The hazard ratio was determined to be 0.63, which was statistically significant with a p value of 0.0009.” Results from this potential practice-changing trial are expected to be presented at the 2015 ASCO Annual Meeting as we await the details of the absolute improvements in DFS and other clinical endpoints as well as the associated toxicities on trial.

Correlation of pCR and Long-Term Clinical Outcomes
There remains an ongoing debate regarding the correlation of pCR status and long-term clinical outcomes such as DFS, EFS, and OS. The attractiveness of an early surrogate marker of efficacy in early-stage disease allows for the use of the neoadjuvant space to test new drugs for efficacy (and toxicity) to expedite development and approval of new therapies in early-stage disease. Multiple studies have repeatedly demonstrated a prognostic effect for the cohort of patients achieving a pCR—particularly those achieving a pCR in breast and lymph nodes (tpCR). Recently, a pooled analysis of 12 large trials of 11,955 patients treated with preoperative chemotherapy with available data on pCR and at least 3-year follow-up data on EFS and OS was performed by the FDA (CTNeoBC pooled analysis). The analysis concluded several points. First, the definition of eradication of tumor in breast and lymph nodes, with or without presence of in situ disease (ypT0/is ypN0) was most closely associated with improved EFS (0.48; 95% CI, 0.43 to 0.54) and OS (HR 0.36; 95% CI, 0.31 to 0.42). Moving forward this should be the consistent and standard definition used as the primary endpoint in neoadjuvant trials. Second, the association between pCR and long-term outcomes was strongest in triple-negative breast cancer and HER2-positive/estrogen receptor–negative breast cancers treated with trastuzumab. Last, in their analysis, they found little association between the degree of increase in pCR response and EFS. The German Breast Group performed a similar analysis with seven of their trials involving 6,366 patients. These patients were also included in the CTNeoBC pooled analysis. Their overall conclusions were similar to the FDA analysis but with some slight differing results. They found that no invasive and no in situ disease in breast and nodes (ypT0ypN0) was the greatest discriminator with long-term outcome. They also concluded that pCR was perhaps not a suitable surrogate endpoint for hormone receptor–positive/HER2-positive breast cancer.
CONCLUSION
In conclusion, in the post-adjuvant trastuzumab era, the outcome of HER2-positive breast cancer has now evolved from a subtype with the worse prognosis to one with arguably the best long-term outcomes. Current standard of care should incorporate 12 months of adjuvant trastuzumab and preferably be concurrent with a taxane backbone. Moving forward we must continue embracing the neoadjuvant model as both standard of care and an important strategy to test new therapeutic agents and accelerate drug development. Well-designed, randomized, neoadjuvant studies importantly allow us to more intelligently guide and support the trial design of adjuvant studies and, by doing so, will minimize overall timelines for drug development in early-stage disease. Although an adequate signal from preoperative trials may not necessarily predict the outcome in a confirmatory adjuvant trial, the lack of a signal should halt further development in a more resource-intensive adjuvant trial.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Institutional relationships are marked “Inst.” Relationships marked “U” are uncompensated.


References


28. Piccart-Gebhart M, Holmes AP, Baselga J, et al. First results from the phase III ALTTO trial (BIG 02-06; NCCTG 063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T 224 L) or their combination (L + T) in the adjuvant treatment of HER2-positive early breast cancer (EBC). 50th ASCO Annual Meeting, June 2014. Chicago, IL.


