How Long is Enough – Optimal Timing of Anti-HER2/neu Therapy in the Adjuvant Setting in Early Breast Cancer

Ana Catarina Pintoa,b Evandro de Azambuja a,b Martine Piccart-Gebhart a

© Medicine Department, Institut Jules Bordet, Université libre de Bruxelles,
Br.E.A.S.T. Data Centre, Institut Jules Bordet, Brussels, Belgium

Keywords
Early breast cancer · Adjuvant · HER2/neu-positive · Trastuzumab

Summary
Trastuzumab administered in combination with various chemotherapy regimens has led to outstanding improvements in both disease-free survival and overall survival. So far, thousands of patients have been treated in this way which has proven to be reasonably safe, with cardiac events being the predominant recognisable toxicity requiring surveillance. Notwithstanding the large cumulative experience of the oncology community in treating early HER2/neu-positive breast cancer with trastuzumab, some uncertainties remain, with key issues being the ideal time of chemotherapy administration and the optimal duration of trastuzumab therapy. This paper discusses these issues in the light of the recent updates of some of the pivotal clinical trials in the adjuvant context.

Introduction
Trastuzumab is a humanised monoclonal antibody that, when added to chemotherapy, has markedly improved the disease-free survival (DFS) and overall survival (OS) of patients with human epidermal growth factor receptor 2 (HER2/neu)-positive breast cancer, first in the metastatic [1] and subsequently in the adjuvant setting [2, 3]. Despite the fact that trastuzumab is considered to be the standard-of-care treatment for patients with HER2/neu-positive early breast cancer (EBC), some controversial issues prevail: When should trastuzumab and chemotherapy be administered? How long should the treatment last? Should trastuzumab be used for T1a,bN0 breast cancers? How can the treatment be tailored to subgroups of patients (e.g. according to nodal status, hormonal receptor status, topoisomerase II alpha (TOP2A) amplification)? In addition, the risk of cardiac dysfunction, manifested as either congestive heart failure (CHF) or drops in left ventricular ejection fraction (LVEF), continues to raise some concern, although most studies have reported reversibility of this effect [4–7]. This article will spotlight the question of timing and duration of adjuvant trastuzumab administration.
Efficacy Data of the Pivotal Adjuvant Trials in HER2/neu-Positive EBC

Nowadays, we have results from 7 large randomised, multicentre, controlled trials that have accrued, in total, over 17,000 patients, evaluating the combination of trastuzumab at different moments, for different periods of time, and with several chemotherapeutic regimens (fig. 1, table 1). These trials include the Herceptin Adjuvant (HERA) trial [2, 8–10], the National Surgical Adjuvant Breast and Bowel Project B-31 (NSABP B-31) trial [3, 11–13], the North Central Cancer Treatment Group N9831 (NCCTG N9831) trial [11, 12, 14], the Breast Cancer International Research Group (BCIRG 006) trial [15, 16], the Protocol for Herceptin as Adjuvant therapy with Reduced Exposure (PHARE) [17, 18], the Finland Herceptin (FinHer) trial [19], and the Protocol Adjuvant dans le Cancer du Sein (PACS-04) [20]. As shown in table 1, HERA, the combined analysis (henceforth ‘Joint Analysis’) of the NSABP-B31 and NCCTG N9831 trials, NCCTG N9831, and BCIRG 006 were positive for their primary endpoint, demonstrating a statistically significant improvement in DFS. Improvements in OS have been reported for HERA, the Joint Analysis, and BCIRG-006.

The HERA Trial

HERA [2, 8] is an international, multicentre, randomised, open-label phase III trial comparing trastuzumab for 1 or 2 years with observation after standard neoadjuvant/adjuvant chemotherapy in women with HER2/neu-positive EBC. This study included 5,102 women with centrally confirmed HER2/neu-positive EBC, who had completed locoregional therapy (surgery with or without radiotherapy) and received neoadjuvant and/or adjuvant chemotherapy (at least 4 cycles); LVEF of 55% or more at study entry was required (either assessed by multigated acquisition scan (MUGA) or echocardiography). Results for the comparison of 1 year versus observation were published in 2005 [2], leading to trastuzumab being established as standard-of-care in the adjuvant setting and resulting in the protocol amendment that allowed patients in the observation arm to selectively cross over to treatment with the antibody.

At the 2012 European Society of Medical Oncology (ESMO) [9] congress in Vienna, followed soon after by the 2012 San Antonio Breast Cancer Symposium (SABCS) [10], the long-awaited landmark results of the 2-year versus 1-year comparison were presented at 8 years of median follow-up.

Fig 1. Trial designs of the pivotal adjuvant trials in HER2/neu-positive early breast cancer.
(mFU). As detailed in table 1, they show no benefit for the longer trastuzumab administration given as sequential treatment following chemotherapy. Also, patients in the 2-year arm experienced more cardotoxic events (increase in secondary cardiac adverse events, although no significant difference in CHF New York Heart Association (NYHA) class III or IV). HERA results at 8 years of mFU show sustained and statistically significant DFS and OS benefit for 1 year trastuzumab versus observation in an intention-to-treat (ITT) analysis, despite an elevated crossover rate (52.1%) and previous ITT results published at 4 years of mFU [8] suggesting an attenuation of the trastuzumab benefit.

**Joint Analysis of NSABP B-31 and NCCTG N9831 Trials**

NCCTG N9831 [12] and NSABP B-31 [3] were both multicentre, randomised, open-label phase III trials run in the United States (US). They were similarly designed, with both assessing the efficacy and safety of adding 52 weeks of trastuzumab to a doxorubicin-paclitaxel (AC→P) chemotherapy backbone in women with operable HER2/neu-positive EBC, with trastuzumab initiated simultaneously with the first dose of paclitaxel, versus chemotherapy alone. The NCCTG N9831 also included a treatment arm B with the same schema, but initiating trastuzumab after completion of cytotoxic chemotherapy (hence, in a sequential manner). This arm B was not included in the combined analysis approved by the National Cancer Institute (NCI) and the Food and Drug Administration (FDA), but data of its comparison to the concurrent arm C of NCCTG N9831 were later published (see below). Efficacy results with an mFU of 3.9 years [11] as well as safety results have been previously published, albeit separately [13, 14]. Updated results from the combined analysis presented at SABCS 2012 show an 11.5% gain in DFS and an 8.8% gain in OS at an mFU of 8.4 years for patients treated with trastuzumab. The crossover rate in B-31/N9831 was 20.4%, and it is important to mention that 5% of patients assigned to the trastuzumab treatment arm never received the antibody because of decreases in LVEF.

**Table 1. Overview and updated efficacy results of the pivotal adjuvant trials in HER2/neu-positive early breast cancer**

<table>
<thead>
<tr>
<th>Study [ref.]</th>
<th>Treatment regimen</th>
<th>H duration, weeks</th>
<th>Patients, n</th>
<th>Median follow-up, months</th>
<th>OS, 5% CI p value</th>
<th>DFS, 5% CI p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA [2, 8–10]</td>
<td>CT – H</td>
<td>52 sequential</td>
<td>1,698</td>
<td>96</td>
<td>0.76 / 0.66–0.87 &lt; 0.0001</td>
<td>0.76 / 0.65–0.88 0.0005</td>
</tr>
<tr>
<td>Joint Analysis [11, 12]</td>
<td>AC→P→H</td>
<td>52 sequential</td>
<td>2,018</td>
<td>100.8</td>
<td>0.99 / 0.85–1.14 0.86</td>
<td>0.60* / 0.53–0.68 &lt; 0.0001</td>
</tr>
<tr>
<td>NSABP-B31</td>
<td>AC→H</td>
<td>104 concurrent</td>
<td>8,325</td>
<td>72</td>
<td>0.67* / 0.54–0.81 &lt; 0.001</td>
<td>0.88 / 0.75–1.05 0.022</td>
</tr>
<tr>
<td>NCCTG N9831</td>
<td>AC→H</td>
<td>52 concurrent</td>
<td>1,087</td>
<td>72</td>
<td>0.99 / 0.85–1.14 0.26</td>
<td>0.60 / 0.47–0.75 &lt; 0.001</td>
</tr>
<tr>
<td>Joint Analysis [11, 12]</td>
<td>AC→D→H</td>
<td>52 concurrent</td>
<td>1,097</td>
<td>994</td>
<td>0.77* / 0.64* 0.64* / 0.53–0.78 &lt; 0.001</td>
<td>0.88 / 0.75–1.05 0.022</td>
</tr>
<tr>
<td>NSABP-B31</td>
<td>AC→D</td>
<td>52 concurrent</td>
<td>1,097</td>
<td>994</td>
<td>0.77* / 0.64* 0.64* / 0.53–0.78 &lt; 0.001</td>
<td>0.88 / 0.75–1.05 0.022</td>
</tr>
<tr>
<td>NCCTG N9831</td>
<td>AC→H</td>
<td>52 concurrent</td>
<td>949</td>
<td>0.77 / 0.64–1.11 0.022</td>
<td>1.05 / 0.86–1.28 0.022</td>
<td></td>
</tr>
<tr>
<td>BCIRG 006 [15, 16]</td>
<td>AC→H</td>
<td>52 concurrent</td>
<td>1,073</td>
<td>65</td>
<td>0.64 / 0.53–0.78 &lt; 0.001</td>
<td>0.88 / 0.75–1.05 0.022</td>
</tr>
<tr>
<td>PHARE [17, 18]</td>
<td>CT + H</td>
<td>26 concurrent/sequential</td>
<td>1,690</td>
<td>42.5</td>
<td>1.28 / 1.05–1.56 0.29</td>
<td>1.47 / 1.28–1.70 0.04</td>
</tr>
<tr>
<td>CT + H</td>
<td>52</td>
<td>1,690</td>
<td>42.5</td>
<td>1.28 / 1.05–1.56 0.29</td>
<td>1.47 / 1.28–1.70 0.04</td>
<td></td>
</tr>
<tr>
<td>FinHer [19]</td>
<td>D/V→H</td>
<td>9 concurrent</td>
<td>115</td>
<td>82</td>
<td>0.65 / 0.38–1.12 0.12</td>
<td>0.55 / 0.27–1.11 0.094</td>
</tr>
<tr>
<td>PACS-04 [20]</td>
<td>FEC/ED→H</td>
<td>52 sequential</td>
<td>268</td>
<td>47</td>
<td>0.86 / 0.61–1.22 0.17</td>
<td>1.27 / 1.04–1.55 0.02</td>
</tr>
</tbody>
</table>

Regarding chemotherapy backbone and trastuzumab, Radiotherapy and/or hormonal therapy were started after the end of the cytotoxic chemotherapy (hence, in a sequential manner). Radiotherapy and/or hormonal therapy were started after the end of the cytotoxic chemotherapy, if indicated. Radiotherapy and/or hormonal therapy were started after the end of the cytotoxic chemotherapy, if indicated.

**H = Trastuzumab; CI = confidence interval; HR = hazard ratio; CT = chemotherapy; A = doxorubicin; C = cyclophosphamide; P = paclitaxel; D = docetaxel; Carbo = carboplatin; V = vinorelbine; F = fluorouracil; E = epirubicin; NR = not reported; HERA = Herceptin Adjuvant trial; NSABP B-31 = National Surgical Adjuvant Breast and Bowel Project B-31 trial; NCCTG N9831 = North Central Cancer Treatment Group N9831 trial; BCIRG 006 = Breast Cancer International Research Group trial; PHARE = Protocol for Herceptin as Adjuvant therapy with Reduced Exposure trial; FinHer = Finland Herceptin trial; PACS-04 = Protocol Adjuvant dans le Cancer du Sein trial.**
Breast Care 2013;8:264–269

Anti-HER2/neu Therapy in the Adjuvant Setting in Early Breast Cancer

The PHARE Trial

PHARE is a French multicentre, non-inferiority phase III trial, randomising 3,380 women to stop treatment at 6 months or continue it up to 12 months. Randomisation took place after having completed 6 months of trastuzumab given concomitantly or sequentially to a chemotherapy regimen of at least 4 cycles (almost 75% received an anthracycline-taxane based backbone). The primary endpoint was DFS, and OS was a secondary endpoint. The statistical plan foresaw a 2% variation in terms of absolute difference in recurrence rates and that the 95% confidence interval (CI) margins should not cross the 1.15 boundary. PHARE’s first results [17, 18], presented at ESMO 2012 (table 1), failed to prove the non-inferiority of the 6-month trastuzumab regimen in terms of DFS; however, they showed a significant difference in cardiac events in favour of the shorter duration of the antibody. The OS data are not sufficiently mature, and translational studies are still ongoing [17].

The NCCTG N9831 Trial

The results of DFS, OS, and toxicity regarding N9831 have also been presented separately [14], since this was a 3-arm trial that, besides the comparison previously mentioned and included in the Joint Analysis, was also planned to compare the sequential and the concurrent administration of trastuzumab (arms B and C, respectively). The latter revealed an increase in DFS with the concurrent modality relative to the sequential one (table 1), but the p value of 0.022 did not cross the prespecified statistical boundary defined for the interim analysis; there was no statistically significant difference in OS (table 1). Although more mature data are still awaited, the authors [14] recommend the incorporation of trastuzumab into a concurrent regimen with taxanes based on the risk-benefit ratio (trend for superior efficacy and similar toxicity profiles, except slightly increased CHF events and asymptomatic LVEF drops in arm C).

The BCIRG 006 Trial

The BCIRG 006 trial [15] is an international, multicentre, open-label phase III trial randomising 3,222 women with EBC to 3 treatment arms: the control one included 4 cycles of 3-weekly AC followed by 4 cycles of docetaxel, the second arm was the same with the concurrent addition of trastuzumab starting at the same time of the first docetaxel administration and given for 52 weeks, and the third arm was innovative since it was a non-anthracycline containing arm with trastuzumab (docetaxel + carboplatin + trastuzumab), also concurrently given with chemotherapy for a total duration of 52 weeks. At an mFU of 65 months [16], the DFS rates were 75% for AC-D, 84% for AC-DH, and 81% for DCH; the OS rates were 87, 92, and 91%, respectively. The risk-benefit ratio favoured the DCH over the AC-DH arm, although the study was not powered to directly compare these 2 arms.

The FinHer Trial

FinHer was a small substudy of a national trial conducted in Finland [19] that assigned 232 women with HER2/neu-positive EBC to receive 3 cycles of docetaxel or vinorelbine with or without trastuzumab given concomitantly during 9 weeks followed by 3 cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC). The primary endpoint, after an amendment, was distant disease-free survival (DDFS), and OS was a secondary endpoint. The results at 62 months of mFU [19] showed that adjuvant trastuzumab tended to improve DDFS, yet only when given in combination with docetaxel, although no statistically significant benefit was seen in OS. The cardiotoxicity rate in this trial was very low, with only 1 subject presenting symptomatic heart failure in the trastuzumab group.

The PACS-04 Trial

This was a French multicentre phase III trial [20] evaluating the benefits of adjuvant chemotherapy consisting of 6 cycles of epirubicin/docetaxel (ED) or FEC (first randomisation) followed or not by the addition of 1 year of trastuzumab (second randomisation) in patients with node-positive EBC. This study was unable to demonstrate a statistically significant advantage for the trastuzumab-containing arm in terms of DFS (primary endpoint). OS has not been reported so far (secondary endpoint).

Optimal Duration of Trastuzumab

Presently, the large phase III randomised trials, including a total of about 12,000 patients, support the standard use of 1 year of adjuvant trastuzumab, independent of the associated chemotherapy backbone. All regimens are globally safe, presenting cardiotoxicity as the chief safety concern. Nevertheless, this side effect is reversible most of the time, as long as it is identified in a timely manner and adequately managed.

Trastuzumab Duration Longer than 1 Year

HERA was the only trial testing upfront a longer duration of trastuzumab (2 years versus 1 year). There was the assumption that prolonged blockade of the HER2/neu receptor would translate into better outcomes (DFS and OS), similar...
to what has been documented for adjuvant hormonal therapy. As stated previously, the 2012 HERA results failed to substantiate this hypothesis (table 1). There was no improvement in either DFS or OS with the extension of trastuzumab for 2 years. Moreover, the secondary cardiac events (LVEF < 50% and ≥ 10% below baseline confirmed by repeat assessment, excluding patients with cardiac death or CHF NYHA class III and IV) were more frequently reported in the 2-year arm than in the 1-year arm (7.2 versus 4.1%, respectively).

Trastuzumab Duration Less than 1 Year

In view of FinHer’s interesting results, and given the risk of cardiac dysfunction coupled with the high cost of 1 year of adjuvant trastuzumab, several trials were launched after 2005 in order to test shorter durations of adjuvant trastuzumab (9 weeks, 3 months, and 6 months).

Regarding the 9-week trastuzumab administration, there is an international phase III randomised controlled trial called Synergism Or Long Duration (SOLD), comparing weekly or 3-weekly trastuzumab plus 3-weekly docetaxel (3 cycles) followed by 3-weekly FEC (3 cycles) to the same regimen with the addition of trastuzumab to complete 1 year, thus comparing 9 weeks to 1 year of the targeted agent. Primary objective is DFS, and recruitment is ongoing.

As far as the 3-month duration is concerned, the ShortHER trial is a phase III, randomized, non-inferiority study comparing (arm A, long) 4 courses of AC or EC followed by docetaxel or paclitaxel in combination with trastuzumab, followed by 14 additional courses of the antibody (total of 18 3-weekly administrations) to (arm B, short) 3 courses of 3-weekly docetaxel in combination with weekly trastuzumab (total of 9 weekly administrations) followed by 3 courses of FEC. The study’s primary objective is DFS and recruitment is reaching completion.

The recently released results from the PHARE trial failed to show that 6 months of trastuzumab is non-inferior to 12 months. Nevertheless, the cardiac safety profile was more favourable for the shorter modality. 2 additional studies are testing this trastuzumab duration: the Persephone and the Hellenic Oncology Research Group trials. The former is a non-inferiority phase III randomised controlled trial whose primary endpoint is DFS, and recruitment is ongoing.

Optimal Timing of Trastuzumab Administration: Concurrent or Sequential to Cytotoxic Chemotherapy

The aggregate data from the aforementioned pivotal trials (table 1) demonstrate the benefit of combining trastuzumab with chemotherapy in the adjuvant setting of HER2/neu-positive EBC, whether given concomitantly with the taxane element of the regimen (Joint Analysis and BCIRG 006) or sequentially after chemotherapy completion (HERA and arm B of N9831). Moreover, benefit has also been proven when trastuzumab is administered concurrently with an anthracycline-free regimen (BCIRG 006), keeping in mind that comparisons across trials should be made with caution, however, the magnitude of the beneficial effect seems to be greater in the concurrent regimens than in the sequential ones (cf. Joint Analysis: HR = 0.60; 95% CI = (0.53; 0.68), p < 0.0001 and OS = 0.63; 95% CI = (0.54; 0.73), p < 0.0001; HERA DFS: HR = 0.76; 95% CI = (0.66; 0.87), p < 0.0001 and OS = 0.85; 95% CI = (0.70; 1.01), p = 0.1087). Similarly, the PACS-04 trial (sequential) did not show a statistically significant improvement in DFS or OS, although it was a relatively small trial (n = 528). In the NCCTG N9831 study, although there is benefit of the sequential approach (AC→P→H better than AC→P), the comparison of the sequential (AC→P→H) versus the concomitant (AC→PH→H) arm tended to favour the latter but did not reach statistical significance (table 1).

Of note, the Persephone trial formerly mentioned will also test the sequential versus the concurrent administration, besides examining the duration of trastuzumab, but the trial will be underpowered given its relatively small size. Thus, for the time being, treatment with trastuzumab should be tailored to the individual patient, their comorbidities, and the disease at hand, bearing in mind that concurrent regimens should be favoured if feasible.

Conclusion

The year of 2012 has been particularly fruitful in bringing mature OS results for several important trials which all confirm that 1 year of adjuvant trastuzumab should be considered as part of the standard-of-care treatment for patients with HER2/neu-positive EBC. However, challenges for the future remain, such as i) the lack of biomarkers to identify those patients more likely to be resistant to trastuzumab and for whom different treatments should be developed; ii) determining whether the use of a dual HER2/neu blockade (i.e. trastuzumab in combination with lapatinib or pertuzumab) will further improve patient survival; iii) identifying the patients who can benefit from anti-HER2/neu-positive drugs alone and thereby avoid chemotherapy and its side effects; and iv) introducing the routine use of cardiac biomarkers (or other technologies) to identify those patients most likely to experi-
ence cardiac toxicity. While these issues are yet unresolved, the reaction caused by adjuvant trastuzumab in the management of patients with EBC remains a landmark in the history of medical oncology.

Disclosure Statement

M. P.-G. received consulting fees and honoraria from Astra-Zeneca, Sanofi-Aventis, Amgen, Bayer, Roche-Genentech, and PharmaMar and honoraria from Novartis. E.D.A. received honoraria and travel grant from Roche and research and travel grants from GSK. A.C.P. has no disclosures to make.

References


5 Perez EA, Suman VJ, Davidson NE, Gralow JR, Kaufman PA, Visscher DW, Chen B, Ingle JN, Dakhil SR, M. P.-G. received consulting fees and honoraria from Astra-Zeneca, Sanofi-Aventis, Amgen, Bayer, Roche-Genentech, and PharmaMar and honoraria from Novartis. E.D.A. received honoraria and travel grant from Roche and research and travel grants from GSK. A.C.P. has no disclosures to make.

269

Anti-HER2/neu Therapy in the Adjuvant Setting in Early Breast Cancer

Breast Care 2013;8:264–269

Disclosure Statement

M. P.-G. received consulting fees and honoraria from Astra-Zeneca, Sanofi-Aventis, Amgen, Bayer, Roche-Genentech, and PharmaMar and honoraria from Novartis. E.D.A. received honoraria and travel grant from Roche and research and travel grants from GSK. A.C.P. has no disclosures to make.

References


5 Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA, Martinez D, Slamon DJ, Kaufman PA, Visscher DW, Chen B, Ingle JN, Dakhil SR, M. P.-G. received consulting fees and honoraria from Astra-Zeneca, Sanofi-Aventis, Amgen, Bayer, Roche-Genentech, and PharmaMar and honoraria from Novartis. E.D.A. received honoraria and travel grant from Roche and research and travel grants from GSK. A.C.P. has no disclosures to make.

269

Anti-HER2/neu Therapy in the Adjuvant Setting in Early Breast Cancer

Breast Care 2013;8:264–269

Disclosure Statement

M. P.-G. received consulting fees and honoraria from Astra-Zeneca, Sanofi-Aventis, Amgen, Bayer, Roche-Genentech, and PharmaMar and honoraria from Novartis. E.D.A. received honoraria and travel grant from Roche and research and travel grants from GSK. A.C.P. has no disclosures to make.