Adjuvant Trastuzumab: A Milestone in the Treatment of HER-2-Positive Early Breast Cancer

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Key Words. Adjuvant • Early breast cancer • Trastuzumab • HER-2 positive • Clinical trial

ABSTRACT
Up to one fourth of women diagnosed with early breast cancer (EBC) have tumors that are human epidermal growth factor receptor 2 (HER-2) positive. This is associated with a high risk of relapse and death from metastatic disease. Trastuzumab, a monoclonal antibody directed against the extracellular domain of HER-2, improves survival and quality of life in women with HER-2-positive metastatic breast cancer receiving chemotherapy. Four major adjuvant trials—Herceptin® Adjuvant (HERA), National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, North Central Cancer Treatment Group (NCCTG) N9831, and Breast Cancer International Research Group (BCIRG) 006—including between them >13,000 women with HER-2-positive EBC, have investigated different adjuvant treatment approaches with trastuzumab. These trials have shown that trastuzumab reduces the 3-year risk of recurrence by about half in this population. The benefit was similar across the trials despite differences in patient populations, chemotherapy regimens, and sequencing of treatment. At a 2-year follow-up, interim results from the combined analysis of the NSABP B-31 and NCCTG N9831 trials showed a one third lower mortality for trastuzumab, and there was a trend toward an overall survival benefit in the HERA and BCIRG trials. A small Finnish trial, FinHer, investigating another regimen of trastuzumab, has also shown similarly positive results. Further follow-up of the major adjuvant trials will clarify the survival benefit for women receiving trastuzumab, as well as the optimal treatment duration (1 or 2 years). Notably, cardiac events in the trastuzumab-containing arms of these trials have remained within acceptable levels, with a slightly higher (0.6%–3.3%) incidence of congestive heart failure that mostly responded to treatment. Further follow-up will provide information on long-term cardiac safety. Overall, results from clinical trials are sufficiently compelling to consider 1 year of adjuvant trastuzumab treatment for women with HER-2-positive EBC based on the risk:benefit ratio demonstrated in these studies. The Oncologist 2006;11(suppl 1):4–12

INTRODUCTION
Up to 25% of women with early breast cancer (EBC) have human epidermal growth factor receptor 2 (HER-2)-positive disease, which is associated with aggressive disease, a higher likelihood of recurrence after initial treatment, and a poor prognosis [1, 2]. Trastuzumab (Herceptin®; F. Hoffmann-La Roche Ltd., Basel, Switzerland), a monoclonal antibody directed against HER-2, improves survival and quality of life when given in combination with taxanes as first-line therapy in women with metastatic breast cancer [3–5] and has shown efficacy as monotherapy [6, 7].

Motivated by the proven benefits of trastuzumab therapy in metastatic breast cancer, four major international studies of adjuvant trastuzumab with a planned enrollment of >13,000 women with HER-2-positive EBC were initiated in 2000–2001: the Herceptin® Adjuvant (HERA) trial, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial, the North Central Cancer Treatment...
Group (NCCTG) N9831 trial, and the Breast Cancer International Research Group (BCIRG) 006 trial. In 2005, the initial results from these adjuvant trials, in addition to data from a subgroup in a smaller Finnish study, FinHer, became available [8–11].

Importantly, each of these trials looked at treatment with trastuzumab from a different perspective, which in the longer term will offer clinicians valuable insights into a variety of questions regarding the use of adjuvant trastuzumab. In this article, we review the key efficacy and safety data from these adjuvant trials and evaluate the implications for clinical practice.

PATIENT ELIGIBILITY

All the trastuzumab adjuvant trials enrolled patients with HER-2-positive (immunohistochemistry 3+/fluorescence in situ hybridization positive or chromogenic in situ hybridization positive for FinHer) invasive breast cancer resected by lumpectomy or mastectomy. Patients could have node-positive (all trials) or high-risk, node-negative (N9831, HERA, BCIRG 006, FinHer) disease, and all patients were to receive adjuvant chemotherapy and appropriate radiotherapy and hormonal therapy. In addition, patients were required to have no locally advanced or distant disease and no previous or current cardiac disease.

Cardiac eligibility criteria differed between the trials. The HERA trial required patients to have a normal left ventricular ejection fraction (LVEF) ≥55% (as measured by echocardiography or multiple-gated acquisition [MUGA] scan) after completion of chemotherapy and radiotherapy, while in the B-31 and N9831 trials, baseline LVEF was required to be ≥50% after completion of chemotherapy. In the BCIRG 006 trial, baseline LVEF was required to be ≥50% after surgery. Additional cardiac exclusion criteria included a history of myocardial infarction, congestive heart failure (CHF), coronary artery disease, angina pectoris requiring medication, uncontrolled hypertension, clinically significant valvular disease, or unstable arrhythmias.

STUDY DESIGNS

The designs of all four major adjuvant trastuzumab trials and the smaller FinHer study are summarized in Figure 1 [8–11]. Chemotherapy regimens and the timing of trastuzumab administration varied among the trials. The cardiac function of patients was carefully monitored in all trials: regular LVEF assessments took place, although the timing of assessments differed between the studies. All the large trials included stopping rules with regard to the difference in cardiotoxicity between the trastuzumab-containing arms and the nonexperimental arms (>4% difference).

HERA

The HERA trial is an ongoing, international (non-U.S.), multicenter, randomized, three-arm trial in patients with HER-2-positive invasive EBC who have completed at least four cycles of (neo)adjuvant chemotherapy, with or without radiotherapy [8]. All chemotherapy (selected from an approved list of standard regimens) and radiotherapy treatments were completed before the initiation of trastuzumab. Patients were randomized to observation only, 1 year of trastuzumab, or 2 years of trastuzumab, given on a 3-weekly schedule [8].

The primary efficacy end point for HERA was disease-free survival (DFS), defined as time from randomization to the first occurrence of any of the following events: local/ regional/distant recurrence, contralateral breast disease (including ductal carcinoma in situ), secondary nonbreast malignancy, and death without evidence of recurrence [8]. Secondary end points included time to recurrence, time to distant recurrence, and overall survival [8].

Combined Analysis of NSABP B-31 and NCCTG N9831

Romond et al. [9] reported combined results from the North American, multicenter, randomized NSABP B-31 and NCCTG N9831 trials investigating treatment with the standard adjuvant chemotherapy regimen of doxorubicin plus cyclophosphamide (AC) followed by paclitaxel and 1 year with or without concurrent trastuzumab therapy in women with operable HER-2-positive breast cancer. The combined analysis of data from these two treatment arms was approved by the National Cancer Institute (NCI) [9]. A third arm of the N9831 study, in which patients received sequential trastuzumab after AC and paclitaxel, was not included in the combined analysis, but interim data comparing this sequential arm with the control and concurrent trastuzumab–paclitaxel arms were presented in 2005 [12]. The primary efficacy end point for the combined analysis was DFS, and secondary end points included overall survival and time to distant recurrence [9].

BCIRG 006

In the global, multicenter, randomized BCIRG 006 trial, treatment with AC followed by docetaxel was compared with AC followed by docetaxel plus trastuzumab, and with docetaxel in combination with carboplatin and trastuzumab [10]. The docetaxel–carboplatin–trastuzumab arm is of interest, as it investigates an anthracycline-free regimen to minimize the risk of cardiac toxicity seen when trastuzumab is used with or after anthracycline-based regimens [10]. The primary end point of the BCIRG trial was DFS; secondary end points
included overall survival, toxicity, and evaluation of pathologic and molecular markers for predicting efficacy in these patients.

FinHer

Patients enrolled in the smaller FinHer trial were randomized to three cycles of docetaxel or vinorelbine followed by three cycles of fluorouracil, epirubicin, and cyclophosphamide [11]. The primary aim of that trial was to compare treatment using docetaxel with treatment using vinorelbine. The subset of women with HER-2-positive tumors (n = 232) was further randomized to either receive or not receive trastuzumab for 9 weeks together with the first three cycles of docetaxel or vinorelbine [11]. The primary end point of FinHer was recurrence-free survival; secondary end points included adverse events (AEs), the effect of treatment on LVEF, time to distant recurrence, and overall survival [11].

Efficacy

HERA

At a 1-year median follow-up, patients treated with trastuzumab in the HERA trial experienced a 46% lower risk of a first event (hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.43–0.67; \( p < .0001 \)) than patients under observation (Fig. 2) [8]. This corresponded to an absolute DFS benefit favoring trastuzumab of 8.4% at 2 years (95% CI, 2.1–14.8). As expected in an HER-2-positive patient population, the majority of first events were distant metastases, the incidence of which was significantly lower with trastuzumab (HR, 0.49; \( p < .0001 \)) (Fig. 3) [8]. Despite the short follow-up of this study, there is already a trend toward longer overall survival, and survival data with longer follow-up are eagerly awaited. Although the HERA interim analysis was not powered for subgroup analyses and HRs varied depending on the chemotherapy received, all subgroups with sufficient patient numbers showed a statistically significant treatment effect.

Combined Analysis of NSABP B-31 and NCCTG N9831

At a 2-year median follow-up, patients treated with trastuzumab in the combined analysis of NSABP B-31 and NCCTG N9831 experienced a significantly longer DFS time than patients in the control group, with a 52% lower risk of a DFS event (HR, 0.48; 95% CI, 0.39–0.59;
(Fig. 2) and an absolute difference in DFS between groups of 12% at 3 years [9]. Furthermore, the risk of distant recurrence was 53% lower (95% CI, 0.37–0.61; \( p < .0001 \)) in those patients who received trastuzumab concurrently with paclitaxel following AC. At a 2-year median follow-up, there was also a significant effect on overall survival (HR, 0.67; 95% CI, 0.48–0.93; \( p = .015 \)) [9]. Data from the N9831 trial evaluating the timing of the introduction of trastuzumab indicate a strong trend for better DFS for those patients receiving concurrent versus sequential trastuzumab relative to chemotherapy [12].

**BCIRG 006**
The BCIRG 006 trial further confirmed the efficacy of trastuzumab in EBC. At a 2-year median follow-up, both experimental trastuzumab-containing arms showed significantly longer DFS compared with the nontrastuzumab control arm (AC followed by docetaxel) (Fig. 2). Patients who received trastuzumab concurrently with docetaxel following treatment with AC experienced a 51% lower risk of relapse than those receiving docetaxel alone (\( p < .0001 \)) [10]. Patients receiving docetaxel in combination with carboplatin and trastuzumab experienced a 39% lower risk of relapse (\( p = .0002 \)) [10]. Further follow-up is needed to
determine whether efficacy differs significantly between the two trastuzumab arms.

The BCIRG trial protocol also included an exploratory subset analysis of patients with coamplification of the topoisomerase-IIα gene, which is in the same chromosomal region as the her-2 gene (17q 21). As anthracyclines target topoisomerase-IIα, it was of interest to compare the efficacy of anthracycline- and nonanthracycline-containing regimens according to topoisomerase-II amplification. Of the 2,120 patients whose tumors were available for this exploratory analysis in the BCIRG trial, 744 (35%) had coamplification of the topoisomerase-II region.

The main finding from this translational analysis of the BCIRG trial showed that it was only those tumors that were coamplified for both topoisomerase-II and HER-2 that appeared to have a poorer outcome when treated with the docetaxel–carboplatin–trastuzumab regimen, compared with those treated with AC followed by docetaxel with trastuzumab. Further follow-up, with a more complete analysis and exploration of the role of topoisomerase-II status (amplification, deletion, normal), is required, but these results suggest that it may be possible to omit adjuvant anthracyclines in some women with HER-2-positive breast cancer without loss of efficacy.

**FinHer**

Of 1,010 women who were randomized in the FinHer trial, 232 were HER-2 positive, and these women were further randomized to either receive (n = 116) or not receive (n = 116) trastuzumab [11]. At a 3-year median follow-up, recurrence-free survival was significantly improved, with 12 patients in the trastuzumab group having had a recurrence of breast cancer or dying without recurrence, compared with 27 in the control group (HR, 0.42; 95% CI, 0.21–0.83; p = .01) (Fig. 2) [11]. However, there has been no statistically significant survival benefit yet demonstrated.

**OVERALL SAFETY**

In the HERA trial, 7.0% of patients in the trastuzumab arm experienced one or more serious AEs, compared with 4.7% of patients in the control arm. Moreover, 7.9% of patients who received trastuzumab experienced one or more NCI Common Toxicity Criteria grade 3 or 4 AEs, compared with 4.4% in the control arm [8]. There was little difference between treatment groups in the incidence of any AEs in the combined analysis of B-31 and N9831, with the exception of rare cases of interstitial pneumonitis (four and five cases in the trastuzumab arms of B-31 and N9831, respectively) [9]. In BCIRG 006, there were no significant differences in grade 3 or 4 hematologic or nonhematologic AEs among the three treatment arms [10], although there were eight (0.8%) treatment-related deaths in the docetaxel–carboplatin–trastuzumab arm. In the FinHer trial, there was no significant difference in AEs with or without trastuzumab in the respective combinations with vinorelbine or docetaxel [11].

**CARDIAC SAFETY**

**HERA**

In the HERA trial, LVEF was evaluated at baseline and at 3, 6, 12, 18, 24, 30, 36, and 60 months after randomization with either MUGA or echocardiography scan. Three cardiac safety analyses were performed after 300, 600, and 900 patients were enrolled and treated for 6 months [8]. An absolute difference of >4% in the incidence of severe CHF or cardiac death between the trastuzumab and observation arms would have triggered a trial suspension [8].

The incidence of New York Heart Association class III/IV CHF in the HERA trial was low: 0.6% in the trastuzumab arm and 0% in the observation arm (Table 1). At a 1-year follow-up, symptomatic CHF occurred in 1.7% and 0.06% of patients in the trastuzumab and observation arms, respectively [8]. One patient in the nontrastuzumab-containing arm suffered cardiac death. The majority of patients in the HERA trial recovered from trastuzumab-related cardiac events. Of the 10 patients who experienced severe CHF in the trastuzumab arm, nine (90%) are receiving active treatment for CHF. Eight (80%) patients had no symptoms at last assessment, and eight (80%) had an LVEF that recovered or stabilized within 3–6 weeks of the initial decrease (Roche, data on file). Fifty-one patients experienced a confirmed LVEF decrease (defined as an EF decrease of ≥10 points from baseline to an LVEF <50%) in the trastuzumab arm, which recovered or stabilized within 3–6 weeks of initial treatment in 86% of cases (Roche, data on file).

**NSABP B-31/NCTG N9831**

Both the B-31 and N9831 trials assessed the incidence of cardiovascular events in each treatment group, defined as class III/IV CHF or definite or probable cardiac death. A >4% difference between the trastuzumab and control arms of each trial would have triggered a trial suspension. LVEF was evaluated at baseline, 3 months (post-AC), 6 months, 9 months, and 18 months postrandomization with either MUGA (B-31 and N9831) or echocardiography (N9831) scans. If a patient’s post-AC LVEF had dropped >15 points or had dropped ≤15 points and fallen below the lower limit of normal, treatment with trastuzumab was not initiated.
In the B-31 trial, 1,664 patients who initiated trastuzumab therapy after AC were evaluable for the cardiac safety analysis. Thirty-one of 850 patients in the trastuzumab arm had confirmed symptomatic cardiac events (31 CHFs, no cardiac deaths), compared with five of 814 patients in the control arm (four CHFs, one probable cardiac death) (Table 1) [13]. The 3-year cumulative incidence of cardiac events for trastuzumab-treated patients was 4.1%, compared with 0.8% for control patients (Table 1) [13].

At the last assessment, 27 of 31 patients (87%) in the trastuzumab arm of the B-31 trial with CHF were asymptomatic; 18 remained on cardiac medication [13]. The analysis of risk factors in the combination paclitaxel–trastuzumab arm showed that CHF was significantly more frequent in older patients and patients whose post-AC LVEF was only marginally greater than the lower limit of normal [13]. However, there was not a higher incidence of CHF in women receiving radiotherapy (HR, 0.80; \( p = .59 \)) [13].

In the N9831 trial, 39 cardiac events (two cardiac deaths, 37 CHFs) were reported in the three treatment arms over 3 years (Table 1) [14]. The 3-year cumulative incidence of cardiac events in the AC followed by paclitaxel arm was 0.3%, compared with 3.5% in the AC followed by paclitaxel plus trastuzumab arm and 2.5% in the sequential arm [14]. Further analysis of risk factors in that trial showed that concurrent radiotherapy was not associated with a higher incidence of cardiac events [14]. Furthermore, while there was a trend toward more cardiotoxicity with greater patient age (as in the B-31 trial), there was no apparent connection between post-AC LVEF and the development of cardiac events [14].

**BCIRG 006**

Cardiac events in the BCIRG trial were defined as cardiac death, CHF, grade 3 or 4 arrhythmias, or grade 3 or 4 cardiac ischemia/infarction (the latter two definitions were specific to BCIRG 006). Ten (0.95%) patients who received AC followed by docetaxel experienced clinically significant cardiac events compared with 25 (2.3%) who received AC followed by docetaxel and trastuzumab and 14 (1.3%) who received docetaxel in combination with carboplatin and trastuzumab [10]. There were no cardiac deaths in the BCIRG trial in any of the treatment arms (Table 1) [10]. Three (0.3%) patients in the control arm experienced grade 3 or 4 CHF, compared with 17 (1.6%) in the AC followed by docetaxel plus trastuzumab arm and four (0.4%) in the docetaxel–carboplatin–trastuzumab arm (Table 1) [10]. Grade 3 or 4 arrhythmias were experienced by seven (0.7%) patients in the control arm, four (0.4%) in the AC followed by docetaxel plus trastuzumab arm, and nine (0.9%) in the docetaxel–carboplatin–trastuzumab arm [10]. No patients in the control arm experienced grade 3 or 4 cardiac ischemia/infarction compared with four (0.4%) patients in the AC followed by docetaxel plus trastuzumab arm and one (0.1%) in the docetaxel–carboplatin–trastuzumab arm [10]. These data suggest that the docetaxel–carboplatin–trastuzumab regimen is less cardiotoxic, at least acutely, than the AC–docetaxel–trastuzumab combination.

### Table 1. Summary of cardiac safety with trastuzumab in early breast cancer [8, 10, 11, 13, 14]

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arm</th>
<th>Baseline LVEF (%)</th>
<th>CHF (%)</th>
<th>Cardiac death (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA</td>
<td>Nil</td>
<td>≥55</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>H 1 year</td>
<td></td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>NSABP B-31</td>
<td>AC→P</td>
<td>≥50</td>
<td>0.8(^{cum})</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>AC→PH</td>
<td></td>
<td>4.1(^{cum})</td>
<td>0</td>
</tr>
<tr>
<td>NCCTG N9831</td>
<td>AC→P</td>
<td>≥50</td>
<td>0.3(^{cum})</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>AC→P→H</td>
<td></td>
<td>2.5(^{cum})</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>AC→PH</td>
<td></td>
<td>3.5(^{cum})</td>
<td>0</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>AC→D</td>
<td>≥50</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>AC→DH</td>
<td></td>
<td>1.6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>DCarboH</td>
<td></td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>FinHer</td>
<td>No H</td>
<td></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AC, doxorubicin plus cyclophosphamide; BCIRG, Breast Cancer International Research Group; Carbo, carboplatin; CHF, congestive heart failure; cum, cumulative incidence; D, docetaxel; H, trastuzumab; HERA, Herceptin® Adjuvant; LVEF, left ventricular ejection fraction; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; P, paclitaxel.

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**FinHer**

None of the patients who received trastuzumab in the FinHer trial experienced clinically significant cardiac events (Table 1) [11]. One patient in the control group experienced cardiac infarction, and three patients experienced cardiac failure [11]. Furthermore, LVEF was preserved in women receiving trastuzumab: the median LVEFs in women who received either combination containing trastuzumab were slightly better than those of patients who did not receive trastuzumab [11].

**DISCUSSION**

More than 13,000 patients with HER-2-positive EBC have enrolled in trastuzumab adjuvant trials (Table 2). Despite differences in patient populations (e.g., inclusion/exclusion of node-negative disease and age distribution), chemotherapy regimens, the timing of randomization, and median follow-up times, adjuvant therapy with trastuzumab has consistently shown an approximately 50% reduction in the risk of recurrence in this population of women with EBC at high risk of early relapse. Furthermore, there was a significantly longer overall survival time with 1 year of adjuvant trastuzumab in the B-31/N9831 joint analysis and a clear trend in the other studies with shorter follow-up. Together, these data present a variety of effective trastuzumab-based treatment options for clinicians.

In the HERA trial, trastuzumab was given after completion of chemotherapy and radiotherapy. Recognizing the differing chemotherapy regimens used worldwide, the unique design of HERA has resulted in clinical data with general relevance. Longer follow-up will clarify the overall survival benefit for women treated with this sequential regimen and results of the 1- versus 2-year comparison are eagerly awaited. The trastuzumab adjuvant trials have also provided valuable information on the efficacy and safety of combining trastuzumab with specific standard chemotherapy regimens. The NSABP B-31 and NCCTG N9831 trials have shown that trastuzumab can be combined with a standard AC–paclitaxel regimen, and the BCIRG 006 trial has shown that trastuzumab can be combined with a standard AC–docetaxel and a nonanthracycline regimen. Trastuzumab-based nonanthracycline regimens may provide an alternative for clinicians treating women with pre-existing cardiac risk factors and who are thus unsuitable for anthracycline treatment. The exploratory analysis of the coamplified versus noncoamplified topoisomerase-IIα gene in that trial may offer direction for future research to identify which patients will benefit most from anthracyclines. The recent data from Pritchard et al. [15], demonstrating the benefit of anthracyclines as related to HER-2 status in the adjuvant chemotherapy setting, will need to be considered in treatment decisions. At present, it is not possible to conclude which trastuzumab-based regimen is the most effective in EBC patients because, as a result of differences in design (e.g., different patient populations, different timing of randomization), comparisons cannot be drawn between the various adjuvant clinical trials.

Importantly, no new or unexpected AEs were observed in the adjuvant clinical trials, and trastuzumab was generally well tolerated in all the studies. The incidence of cardiac events with trastuzumab in the EBC setting remained at an acceptable level and was similar across the adjuvant trials, with a reported overall incidence that was 0.6%–3.3% higher (Table 1). Furthermore, the majority of patients with symptomatic CHF

### Table 2. Summary of patient characteristics from the trastuzumab adjuvant trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HERA (n = 5,090)</th>
<th>Combined analysis (n = 5,535)</th>
<th>BCIRG 006 (n = 3,222)</th>
<th>FinHer (n = 232)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;50 yrs (%)</td>
<td>51</td>
<td>51</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>Node-negative disease (%)</td>
<td>32b</td>
<td>5.7</td>
<td>29c</td>
<td>16d</td>
</tr>
<tr>
<td>Grade III tumors (%)</td>
<td>60</td>
<td>69</td>
<td>NA</td>
<td>65</td>
</tr>
<tr>
<td>Taxane-based chemotherapy (%)</td>
<td>26</td>
<td>100</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>Planned endocrine therapy (%)</td>
<td>46</td>
<td>52</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>Normal cardiac function (%)</td>
<td>At completion of locoregional therapy and chemotherapy</td>
<td>At completion of AC × 4</td>
<td>After surgery</td>
<td>After surgery</td>
</tr>
</tbody>
</table>

*HER-2-positive subgroup.

bOnly if tumor size >1 cm.

cOnly if other concomitant risk factors.

dOnly if tumor size >2 cm and PgR negative.

Abbreviations: AC, doxorubicin plus cyclophosphamide; BCIRG, Breast Cancer International Research Group; ER, estrogen receptor; HERA, Herceptin® Adjuvant; NA, not available; PgR, progesterone receptor.
improved with treatment. However, definitions of cardiac events, evaluations for cardiac safety, analysis of cardiac end points (e.g., cumulative vs. overall incidence), and duration of follow-up differed among the adjuvant trials and thus make comprehensive cross-trial conclusions difficult. Comparisons regarding cardiac safety should therefore be approached with caution. Analysis of cardiac events with a unified perspective would be useful to clinicians and hopefully provide firm recommendations on how to monitor and make decisions for further therapy with trastuzumab based on risk factors and current cardiac status. For example, it remains unclear if post-AC LVEF should be considered as a risk factor for the development of cardiotoxicity. In addition, it is unknown what the implications are, if any, of a decrease in LVEF during adjuvant administration of trastuzumab in the absence of symptoms. Currently, the cardiac function of all patients who start treatment with trastuzumab should be monitored. With further follow-up, it will become clearer whether sequential or anthracycline-free regimens carry a lower risk of cardiac toxicity with equivalent efficacy.

Overall, data from the trials indicate that clinicians have a variety of potential trastuzumab-based options for treatment of patients with EBC. A number of questions remain unanswered regarding issues such as treatment duration and regimens. The FinHer trial evaluated trastuzumab given over 9 weeks combined with a nonstandard chemotherapy regimen in a small subset of patients with HER-2-positive EBC. At this time, the FinHer results are intriguing and helping to generate hypotheses for future studies. Data comparing the 1- and 2-year trastuzumab arms of HERA will provide information on whether extending treatment beyond 1 year offers additional benefit. Further follow-up on the N9831 trial will provide data on the relative benefits of administering trastuzumab concurrently with or sequentially after paclitaxel in the AC–paclitaxel regimen, and follow-up on the BCIRG 006 trial may help to determine whether trastuzumab is just as effective in combination with an anthracycline- or nonanthracycline-containing chemotherapy regimen. Further follow-up of the adjuvant trials will also increase our knowledge of the nature and reversibility of cardiac events associated with trastuzumab use. Although these data will help clarify the risk:benefit ratios of different trastuzumab-based regimens, it is likely that no one regimen will be optimal in all situations. Clinicians should consider risk:benefit on an individual patient basis.

Longer follow-up will provide further information on the long-term safety and clinical relevance of cardiac events associated with trastuzumab. However, all four of the major adjuvant trastuzumab trials, as well as the smaller FinHer trial, have shown a highly significant and consistently lower risk of recurrence in women with HER-2-positive EBC. In addition, a significant survival benefit was seen with 1 year of trastuzumab in the joint analysis. These efficacy results are sufficiently compelling to consider 1 year of adjuvant trastuzumab treatment in clinical practice for women with HER-2-positive EBC based on its risk:benefit ratio.

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Disclosure of Potential Conflicts of Interest
J. B. and R. B. have acted as consultants for Roche.

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