Multicentric, Randomized Phase III Trial of Two Different Adjuvant Chemotherapy Regimens plus Three Versus Twelve Months of Trastuzumab in Patients with HER2-Positive Breast Cancer (Short-HER Trial; NCT00629278)

Valentina Guarneri,[1] Antonio Frassoldati,[1] Paolo Bruzzi,[2] Roberto D'Amico,[1] Maurizio Belfiglio,[3] Annamaria Molino,[4] Oscar Bertetto,[5] Stefano Cascinu,[6] Francesco Cognetti,[7] Angelo Di Leo,[8] Paolo Pronzato,[9] Lucio Crinó,[10] Biagio Agostara,[11] PierFranco Conte[1]

Abstract

Trastuzumab, a monoclonal antibody against the HER2 receptor, is currently approved as a part of adjuvant therapy for patients with HER2-overexpressing breast tumors. The Short-HER study is a phase III randomized, multicentric Italian trial aimed at testing the optimal duration of adjuvant trastuzumab. In this trial, 2500 patients with HER2-positive breast cancer will be randomized to receive the following: (arm A, long) 4 courses of anthracycline-based chemotherapy (doxorubicin/cyclophosphamide or epidoxorubicin/cyclophosphamide) followed by 4 courses of docetaxel or paclitaxel in combination with trastuzumab, followed by 14 additional courses of trastuzumab administered every 3 weeks (for a total of 18 3-weekly doses of trastuzumab); or (arm B, short) 3 courses of 3-weekly docetaxel in combination with weekly trastuzumab (for a total of 9 weekly doses of trastuzumab) followed by 3 courses of 5-fluorouracil/epirubicin/cyclophosphamide. The primary objective is disease-free survival.

Clinical Breast Cancer, Vol. 8, No. 5, 453-456, 2008; DOI: 10.3816/CBC.2008.n.056
Keywords: Adjuvant therapy, Cardiac toxicity, HER2, Trastuzumab duration

Rationale and Background

About 20% of breast cancer shows HER2 receptor overexpression; trastuzumab, the humanized monoclonal antibody against HER2 receptor, is an essential component of the treatment of patients with HER2-positive breast cancer at all the stages of disease.

In the adjuvant setting, the results of 6 phase III randomized trials have been published or presented so far.[1-6] In these trials, different chemotherapy regimens and different modalities of trastuzumab administration (in combination or sequentially after chemotherapy) have been explored. Overall, these trials have included > 10,000 women with HER2-positive breast cancer; 5 of these trials have demonstrated the superiority of adding trastuzumab to chemotherapy compared with chemotherapy alone (Table 1). The majority of these trials have tested 1 year of trastuzumab therapy; however, a small Finnish study wherein trastuzumab was administered for a very short period concomitantly with chemotherapy (9 weekly administrations) has produced similar results.[4] A single study, the Programmes d'Actions Concertées Sein (PACS) 04 trial, has shown no benefit for adding trastuzumab at the completion of chemotherapy versus control.[6] A similar finding has been reported in the preliminary analysis of the sequential arm (arm B) of the North Central Cancer Treatment Group N9831 trial.[7] These results are not completely unexpected, taking into account the data

[1]Division of Medical Oncology, Department of Oncology and Hematology, University Hospital, Modena
[2]Clinical Epidemiology and Trials, National Cancer Research Institute, Genova
[3]Unit of Clinical Epidemiology of Cancer, Consorzio Mario Negri Sud
[4]Department of Medical Oncology, University of Verona
[5]Division of Medical Oncology, COES, Azienda Ospedaliera San Giovanni Battista, Torino
[6]Department of Medical Oncology, Università Politecnica delle Marche, University Hospital, Ancona
[7]Division of Medical Oncology A, Regina Elena Cancer Institute, Roma
[8]Sandro Pitigliani Medical Oncology Unit, Hospital of Prato
[9]Division of Medical Oncology, National Cancer Research Institute, Genova
[10]Department of Medical Oncology, S. Maria della Misericordia Hospital, Perugia
[11]Department of Medical Oncology, Hospital M. Ascoli, Italy

Submitted: Apr 28, 2008; Accepted: May 9, 2008

Address for correspondence: PierFranco Conte, MD, Department of Oncology and Hematology, University Hospital, via del Pozzo 71, 41100 Modena, Italy
Fax: 39-059-422-4429; e-mail: conte.pierfranco@unimo.it

Table 1 Summary of Adjuvant Trastuzumab Trials

Trials	Number of Patients	HR (95% CI), Recurrence	HR (95% CI), Mortality
Joint Analysis N9831-NSABP-31[1]	3351	0.48 (0.39-0.59)	0.67 (0.48-0.93)
HERA[3,4]	3387	0.63 (0.53-0.75)	0.66 (0.47-0.91)
FinHer[4]	232	0.42 (0.21-0.83)	0.41 (0.16-1.08)
BCIRG[5]	2147	0.61 (0.48-0.76)	0.59 (0.42-0.85)
PACS 04[6]	528	0.86 (0.61-1.22)	1.27 (0.68-2.38)

Abbreviations: BCIRG = Breast Cancer International Research Group; CI = confidence interval; HERA = Herceptin® Adjuvant; HR = hazard ratio; NSABP = National Surgical Adjuvant Breast and Bowel Project; PACS = Programmes d'Actions Concertées Sein

suggesting a synergism of combined trastuzumab and chemotherapy in metastatic and neoadjuvant settings. The HERA (Herceptin® Adjuvant) trial has also tested the sequential approach, with positive results in terms of disease-free survival (DFS) and overall survival (OS).[2,3] Differently from the other 2 sequential studies, patients on the HERA trial were randomized at completion of chemotherapy; moreover, in this study, the patients received a variety of chemotherapy regimens, and only 25% of the patients received anthracycline-taxane combinations. The HERA trial is the only one specifically designed to test prospectively different durations of trastuzumab administration; up to now, the results of the comparison of 1 versus 2 years of treatment are not yet available.

Another relevant clinical issue is the cardiac safety of trastuzumab, particularly when used as adjuvant therapy. In all the adjuvant trastuzumab trials, selective inclusion criteria with particular regard to previous cardiac morbidities as well as close cardiac function monitoring have been applied. However, despite the selection of the optimal patient population, symptomatic congestive heart failure (CHF) occurred in 1.5%-2.5% of the patients treated with sequential trastuzumab (HERA trial, PACS 04, and N9831 arm B) and in a percentage ranging from 0.4 (Breast Cancer International Research Group [BCIRG] 006 arm C, without anthracyclines) to 3.6 of the patients in the trials in which trastuzumab was started concomitantly with chemotherapy (BCIRG 006 arm B, N9831 arm C, National Surgical Adjuvant Breast and Bowel Project [NSABP] B-31).[5,6,8-10] Moreover, a proportion of patients ranging from 8% to 16% did not complete the planned trastuzumab therapy mostly because of cardiac events. In addition, a significant proportion of patients never started trastuzumab because of left ventricular ejection fraction (LVEF) decline at the end of anthracycline-based chemotherapy (1.9% in the PACS 04, 5% in the N9831, and 6.4% in the NSABP B31 trial). The FinHer (Finland Herceptin) trial is the only adjuvant trastuzumab trial without episodes of CHF; however, the limited number of patients included in this trial does not allow concluding that a shorter trastuzumab treatment is less cardiotoxic.[4]

On the basis of these data, a shorter duration of trastuzumab administered concomitantly with chemotherapy might produce comparable efficacy with significantly lower toxicities and costs. To test this hypothesis, we have designed a phase III multicentric, randomized trial. The primary objective is to evaluate if 3 months of trastuzumab (9 weekly administrations) is not inferior to 12 months of trastuzumab (18 3-weekly administrations), when administered in combination with chemotherapy, in terms of DFS.

Study Objectives

This is a phase III multicentric, randomized trial. The study is designed assuming that prolonged trastuzumab administration concomitantly with chemotherapy produces more frequent cardiac events than does shorter trastuzumab treatment and that the onset of this potentially serious toxicity might preclude the benefit of treatment to a significant proportion of patients.

Primary Objectives

- Disease-free survival, calculated as the time interval between randomization and any of the following events, whichever first: local, regional, and distant recurrence; contralateral breast cancer, excluding in situ carcinoma; other second primary cancer; death before recurrence or second primary cancer. Patients who will not experience relapse at the time of the last follow-up will be censored.

- Overall survival will be evaluated as second primary analysis outcome. The survival will be calculated as the time interval between randomization and patient death or last follow-up.

Secondary Objectives

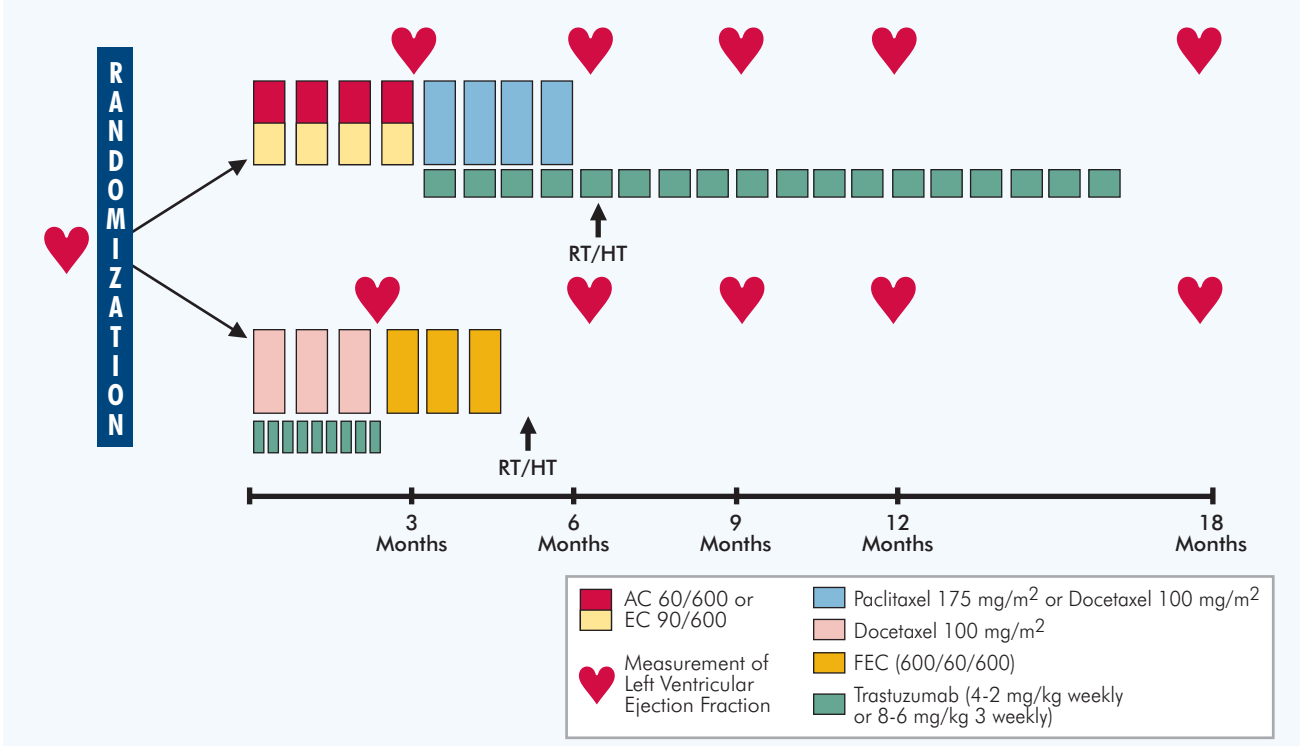
- Failure rate at 2 years, calculated as cumulative incidence of relapse, contralateral breast cancer (excluding in situ carcinoma), death for all causes, treatment withdrawal as a result of toxicity of therapy.
- Incidence of cardiac events, defined as decrease of LVEF > 15% from basal values or decrease > 10% with LVEF absolute value below 50%, symptomatic cardiac failure, or other cardiac side effects grade ≥ 2 according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Eligibility Criteria

Inclusion Criteria

- Surgically resected infiltrating primary breast cancer, HER2-positive tumor (immunohistochemistry 3+ or fluorescence in situ hybridization–positive), suitable for adjuvant chemotherapy.
- Adequate treatment of axillary lymph nodes (sentinel node biopsy or axillary lymph node dissection).
- Node positivity, or if node negativity, with ≥ 1 of the following: tumor > 2 cm, grade 3, presence of lymphovascular invasion, Ki-67 > 20%, age ≤ 35 years, hormone receptor negativity (< 10%).
- Age 18-75 years.
- Eastern Cooperative Oncology Group performance score 0-1.
- Normal liver, renal, and marrow function.

Figure 1 Short-HER: Treatment Plan



Abbreviations: AC = doxorubicin/cyclophosphamide; EC = epirubicin/cyclophosphamide; FEC = 5-FU/epidoxorubicin/cyclophosphamide; HT = hormonal therapy; RT = radiation therapy

- Left ventricular ejection fraction within the institutional range of normal, as measured by echocardiogram or multigated acquisition (MUGA) scan.
- Treatment to be started within 10 weeks from the date of surgery.
- Adequate contraception (women of child-bearing potential).
- Written informed consent.

Exclusion Criteria

- Stage IIIB or IV breast cancer.
- Contraindication to the treatment with anthracycline, cyclophosphamide, 5-fluorouracil (5-FU), paclitaxel, or trastuzumab.
- Previous treatment with chemotherapy, endocrine therapy, or radiation therapy.
- Treatment with any other investigational agents.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic CHF, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements; pregnancy or breastfeeding.

Pathology Review

Eligibility is based on HER2 assessment in the local laboratory. However, a centralized pathology review has been planned for the first 200 randomized patients. On the basis of the concordance between local and central HER2 testing, further action will be discussed.

Sample Size

The analysis will take the form of a noninferiority test. The sample size calculation relates to the study primary outcome, which is the DFS. Hazard ratio (HR) will be the ratio between the hazard rate of events after short treatment and the hazard rate of events after long treatment. Formally, we define the short treatment to be inferior to long treatment if the hypothesis that HR ≥ 1.29 is true (null hypothesis), whereas we define short treatment to be noninferior to long treatment if HR < 1.29 (alternative hypothesis). Setting $\alpha = 0.05$ (one-tail), in order to reject with an 80% power the null hypothesis that HR = 1.29 if indeed the true HR is 1, we need 2332 patients (372 events) to reject the null hypothesis. Moreover, in order to account for approximately 5% of patients lost to follow-up, the sample size will be increased to 2500 patients. All patients will be analyzed according to intent-to-treat and per protocol principle. The HR for DFS and OS will be estimated according to the Cox model, and their relative 90% confidence intervals (CIs) will also be reported. We will also provide estimates and CIs for the crude hazards and cumulative incidence curves in either treatment arm.

Trial Design

Patients will be randomized to 1 of 2 arms:

- Treatment arm A (long): AC (doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2) or EC (epidoxorubicin 90 mg/m^2 plus cyclophosphamide 600 mg/m^2) for 4 courses every 21 days

followed by paclitaxel 175 mg/m^2 or docetaxel 100 mg/m^2 administered concomitantly with trastuzumab intravenously (I.V.; 8-mg/kg loading dose at first cycle and 6 mg/kg thereafter) for 4 courses every 21 days. At completion of the chemotherapy program (4 AC/EC → 4 paclitaxel/docetaxel + trastuzumab), patients will receive trastuzumab alone at 6 mg/kg I.V. infusion every 21 days for 14 additional courses (for a total of 18 trastuzumab 3-weekly doses). At study entry, each center will be asked to state which anthracycline and taxane will be used.

- Treatment arm B (short): docetaxel 100 mg/m^2 I.V. on day 1 every 21 days for 3 courses plus trastuzumab weekly for 9 weeks (4-mg/kg loading dose at first administration only, followed by 2 mg/kg) starting together with the first dose of docetaxel (for a total of 9 weekly doses of trastuzumab). At completion of docetaxel plus trastuzumab, patients will receive 3 courses of FEC (5-FU 600 mg/m^2, epidoxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2), started 21 days after the last docetaxel administration and delivered every 21 days (Figure 1).

Monitoring of Cardiac Safety

Only patients with LVEF within the institutional limits of normal at baseline as measured by echocardiography or MUGA scan are eligible for this protocol. Left ventricular ejection fraction measurements will be repeated in arm A at the end of AC or EC chemotherapy and in arm B at the end of docetaxel/trastuzumab therapy. In both arms, LVEF evaluations will be repeated at 6 months, 9 months, 12 months, and 18 months since randomization and yearly thereafter.

Conclusion

The accrual into this study started as of December 2007. Randomization and data collection is handled by the Trial Office at the Department of Oncology and Hematology, University of Modena and Reggio Emilia, Modena, Italy. At present, 113 Italian institutions have agreed to participate, and study accrual is planned to be completed in 36 months.

Other trials exploring shorter adjuvant trastuzumab duration are recruiting or due to start in Europe; for further details, visit http://www.clinicaltrials.gov.

Acknowledgements

This trial is supported by a research grant from Agenzia Italiana del Farmaco (AIFA).

The EUDRACT number is 2007-004326-25; the NCI ClinicalTrials.gov number is NCT00629278.

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