Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer

Martine J. Piccart-Gebhart, M.D., Ph.D., Marion Procter, M.Sci., Brian Leyland-Jones, M.D., Ph.D., Aron Goldhirsch, M.D.,
Michael Untch, M.D., Ian Smith, M.D., Luca Gianni, M.D., Jose Baselga, M.D., Richard Bell, M.D.,
Christian Jackisch, M.D., David Cameron, M.D., Mitch Dowsett, Ph.D., Carlos H. Barrios, M.D., Günther Steger, M.D.,
Chiun-Shen Huang, M.D., Ph.D., M.P.H., Michael Andersson, M.D., Dr.Med.Sci., Moshe Inbar, M.D.,
Mikhail Lichinitser, M.D., István Láng, M.D., Ulrike Nitz, M.D., Hiroji Iwata, M.D., Christoph Thomssen, M.D.,
Caroline Lohrisch, M.D., Thomas M. Suter, M.D., Josef Rüschoff, M.D., Tamás Sütő, M.D., Ph.D.,
Victoria Greatorex, M.Sc., Carol Ward, M.Sc., Carolyn Straehle, Ph.D., Eleanor McFadden, M.A., M. Stella Dolci,
and Richard D. Gelber, Ph.D., for the Herceptin Adjuvant (HERA) Trial Study Team

ABSTRACT

BACKGROUND

Trastuzumab, a recombinant monoclonal antibody against HER2, has clinical activity in advanced breast cancer that overexpresses HER2. We investigated its efficacy and safety after excision of early-stage breast cancer and completion of chemotherapy.

METHODS

This international, multicenter, randomized trial compared one or two years of trastuzumab given every three weeks with observation in patients with HER2-positive and either node-negative or node-positive breast cancer who had completed locoregional therapy and at least four cycles of neoadjuvant or adjuvant chemotherapy.

RESULTS

Data were available for 1694 women randomly assigned to two years of treatment with trastuzumab, 1694 women assigned to one year of trastuzumab, and 1693 women assigned to observation. We report here the results only of treatment with trastuzumab for one year or observation. At the first planned interim analysis (median follow-up of one year), 347 events (recurrence of breast cancer, contralateral breast cancer, second nonbreast malignant disease, or death) were observed: 127 events in the trastuzumab group and 220 in the observation group. The unadjusted hazard ratio for an event in the trastuzumab group, as compared with the observation group, was 0.54 (95 percent confidence interval, 0.43 to 0.67; P<0.0001 by the log-rank test, crossing the interim analysis boundary), representing an absolute benefit in terms of disease-free survival at two years of 8.4 percentage points. Overall survival in the two groups was not significantly different (29 deaths with trastuzumab vs. 37 with observation). Severe cardiotoxicity developed in 0.5 percent of the women who were treated with trastuzumab.

CONCLUSIONS

One year of treatment with trastuzumab after adjuvant chemotherapy significantly improves disease-free survival among women with HER2-positive breast cancer. (clinicaltrials.gov number, NCT 00045032.)

HER2/*neu* (HEREAFTER REFERRED TO AS HER2) belongs to a family of four transmembrane receptor tyrosine kinases that mediate the growth, differentiation, and survival of cells.[1,2] Overexpression of the HER2 protein, amplification of the *HER2* gene, or both occur in approximately 15 to 25 percent of breast cancers, and are associated with aggressive behavior in the tumor.[3,4]

Trastuzumab (Herceptin, Roche), a humanized monoclonal antibody against the extracellular domain of HER2, has been shown to benefit patients with HER2-positive metastatic breast cancer when administered weekly or every three weeks, alone[5,6] or in combination with chemotherapy.[7,8] Trastuzumab is not associated with the adverse events that typically occur with chemotherapy, such as alopecia, myelosuppression, and severe nausea and vomiting.[9] With the exception of hypersensitivity, which has been seen mainly and occasionally with the first infusion, cardiotoxicity (principally congestive heart failure) is the most important adverse effect of trastuzumab. Cardiotoxicity has been reported in 1.4 percent of women who received the drug as a single agent for metastatic disease.[5,6] The adverse effect of the interaction between trastuzumab and anthracyclines on the heart[7] and the lesser adverse effect of the interaction between trastuzumab and taxanes[7,8] are concerns in the design and conduct of studies of adjuvant therapy, given the established activity and central role of anthracyclines and taxanes in the treatment of breast cancer. For this reason, investigations of trastuzumab in the adjuvant setting require careful cardiac monitoring and stopping rules specified for cardiotoxicity.

Our group investigated whether the administration of trastuzumab was effective as adjuvant treatment for HER2-positive breast cancer if used after completion of the primary treatment (e.g., surgery, radiotherapy, and chemotherapy given preoperatively [neoadjuvant], postoperatively [adjuvant], or both). The administration of trastuzumab after chemotherapy permits the application of our findings to the wide variety of chemotherapy regimens used throughout the world.[10] In our trial, one group of women received trastuzumab for one year and another group received the drug for two years. We included these two groups for three reasons: a major peak in the rate of relapse occurs 18 to 24 months after surgery,[11] effective treatment of HER2-positive breast cancer may require prolonged attenuation of HER2 activity,[12] and tamoxifen, which is an effective targeted therapy for breast cancer, is most beneficial when given for longer than one year.[13] We report a comparison of the results obtained with observation or with one year of trastuzumab after primary treatment of breast cancer.

METHODS

STUDY DESIGN

The Herceptin Adjuvant (HERA) (Breast International Group [BIG] 01-01) Trial is an international, intergroup, open-label, phase 3 randomized trial involving women with HER2-positive (overexpressing or amplified) early-stage invasive breast cancer who completed locoregional therapy (surgery with or without radiotherapy) and a minimum of four courses of chemotherapy (administered as adjuvant treatment postoperatively among 89 percent of the women, or as neoadjuvant treatment preoperatively among 5 percent of the women, or as both adjuvant and neoadjuvant chemotherapy among 6 percent of the women) (Fig. 1). The HER2-positive status of the tumors was centrally confirmed in all cases before randomization. The trial included three groups: women who had observation alone; those treated with trastuzumab, given as adjuvant treatment (at a dose of 8 mg per kilogram of body weight intravenously once, then at a dose of 6 mg per kilogram every three weeks) for two years; and those treated with trastuzumab at the same dose and on the same schedule for one year. Random assignment to one of the three groups was performed within seven weeks from day 1 of the last chemotherapy cycle or six weeks from the end of radiotherapy or definitive surgery, whichever was last. A minimization procedure, according to the methods of Pocock and Simon,[14] was used with stratification according to region of the world, age, nodal status, type of chemotherapy, and hormone-receptor status together with intention to use endocrine therapy (Table 1).

The primary end point was disease-free survival, defined as time from randomization to the first occurrence of any of the following disease-free–survival events: recurrence of breast cancer at any site; the development of ipsilateral or contralateral breast cancer, including ductal carcinoma in situ but not lobular carcinoma in situ; second nonbreast malignant disease other than basal-cell or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix; or death from any cause without documentation of a cancer-related event. Secondary end points included cardiac safety, overall survival, site of first disease-free–survival event, and time to dis-

tant recurrence, defined as the time between randomization and the date of the first distant tumor recurrence, ignoring locoregional recurrences and second breast or nonbreast cancers and taking into account deaths before recurrence of distant breast cancer as censoring events.

The study was conducted under the auspices of the BIG and involved the collaboration of 17 BIG groups, 9 other cooperative groups, 91 independent centers, and the pharmaceutical sponsor, Roche, all of which were represented in the steering committee of the HERA trial. The study was designed by members of the steering committee. The database resided in a system of the sponsor, and access was restricted to data managers of the Breast European Adjuvant Study Team data center and statisticians of Frontier Science (Scotland). The sponsor had no access to the database or the interim analyses. The analyses were presented by the independent statisticians to the independent data monitoring committee without disclosure to the data center, the investigators, or the sponsor. The HERA steering committee was responsible for the decision to publish and for the content of the manuscript. The sponsor provided the drug and financial support.

The institutional review board at each of the 478 participating institutions in 39 countries approved the study protocol. All patients gave written informed consent.

ELIGIBILITY CRITERIA

Eligible patients had histologically confirmed, completely excised invasive breast cancer with HER2 overexpression or *HER2* amplification as assessed in the participating institution and verified in the central laboratory of the trial (Kassel, Germany). A result on immunohistochemical analysis (IHC) at the central laboratory (Herceptest, Dako) of 3+ (IHC 3+), in a range from 0 to 3+ with higher values indicating increased overexpression, was required for confirmation of the status of tumors assessed at the participating institution as IHC 3+, and a positive result on fluorescence in situ hybridization (FISH) for *HER2* amplification (PathVision, Vysis) at the central laboratory was required for tumors that were assessed in the participating institution as IHC 2+ or FISH-positive.

The hormone-receptor status of the tumor was determined and the tumor tissue was accessible for central review. Eligible patients had node-positive disease (irrespective of pathological tumor size) or node-negative disease (including only a negative

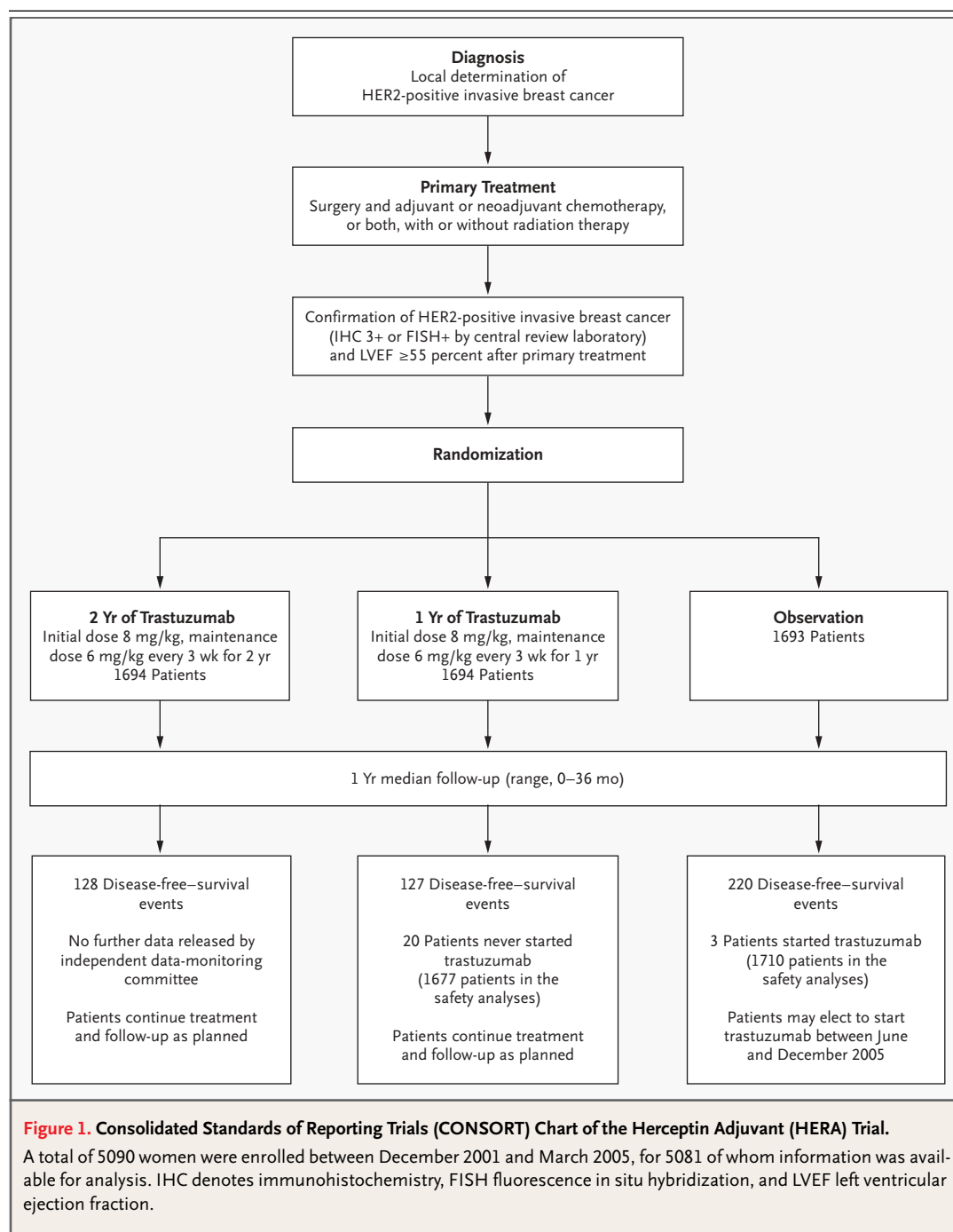sentinel node) if on pathological examination the tumor size was larger than 1 cm.

Adjuvant chemotherapy, neoadjuvant chemotherapy, or both, selected from a list of approved regimens consisting of at least four cycles (described in detail in Supplementary Appendix 1, available with the full text of this article at www.nejm.org), was completed before randomization. Adjuvant endocrine therapy, primarily tamoxifen, was given after chemotherapy to women with hormone-receptor–positive disease unless contraindicated. During the course of the trial, an amendment to the protocol allowed aromatase inhibitors to be used instead of, or in sequence with, tamoxifen.

Patients were required to have adequate baseline hepatic, renal, and bone marrow function. Patients were required to use adequate non–hormone-based contraceptive measures, if indicated. Patients were excluded if they had distant metastases, a previous invasive breast carcinoma, or a neoplasm not involving the breast, except for curatively treated basal-cell or squamous-cell carcinoma of the skin or in situ carcinoma of the cervix. Patients with clinical stage T4 tumors, including inflammatory breast cancers or involvement of supraclavicular nodes, were not eligible. Suspicious internal mammary nodes were an exclusion criterion, unless they were subjected to radiotherapy. Prior mediastinal irradiation (except internal mammary-node irradiation for the present breast cancer) and cumulative doses of anthracycline exceeding 360 mg per square meter of body-surface area for doxorubicin, or 720 mg per square meter for epirubicin or stem-cell support for chemotherapy were also exclusion criteria.

Only patients who, after completion of all chemotherapy and radiotherapy, had a normal left ventricular ejection fraction (LVEF) (≥55 percent as measured on echocardiography or multiple gated acquisition [MUGA] scanning) were eligible. Cardiac exclusion criteria included a history of documented congestive heart failure, coronary artery disease with previous Q-wave myocardial infarction, angina pectoris requiring medication, uncontrolled hypertension, clinically significant valvular disease, and unstable arrhythmias.

ADMINISTRATION OF TRASTUZUMAB

Trastuzumab was administered intravenously over a 90-minute period at all doses. Patients were closely observed for at least six hours after the start of the first dose of 8 mg per kilogram of body weight of trastuzumab. The second and all subsequent main-

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Chart of the Herceptin Adjuvant (HERA) Trial.

A total of 5090 women were enrolled between December 2001 and March 2005, for 5081 of whom information was available for analysis. IHC denotes immunohistochemistry, FISH fluorescence in situ hybridization, and LVEF left ventricular ejection fraction.

tenance doses were 6 mg per kilogram given every three weeks. Actual body weight was used to calculate the dose. If the administration of trastuzumab was delayed by more than seven days, treatment was restarted at the level of the initial dose of 8 mg per kilogram, which was followed by the usual maintenance dose (6 mg per kilogram every three weeks).

If nonhematologic grade 3 or 4 toxic effects occurred, trastuzumab was temporarily withheld until recovery to grade 2 or lower; it was discontinued if the recovery took more than five weeks, if the severe side effect recurred on readministration of trastuzumab, or if symptomatic congestive heart failure and an LVEF of 45 percent or less developed

Table 1. Baseline Characteristics of the Patients, Tumors, and Primary Treatments (Intention-to-Treat Groups).*

Variable	1 Yr of Trastuzumab (N=1694)	Observation (N=1693)
Region — no. (%)		
Western and Northern Europe, Canada, South Africa, Australia, New Zealand	1208 (71.3)	1222 (72.2)
Asia Pacific, Japan	203 (12.0)	202 (11.9)
Eastern Europe	189 (11.2)	175 (10.3)
Central and South America	94 (5.5)	94 (5.6)
Race — no. (%)†		
White	1411 (83.3)	1406 (83.0)
Asian	210 (12.4)	207 (12.2)
Black	12 (0.7)	8 (0.5)
Other	57 (3.4)	67 (4.0)
Missing	4 (0.2)	5 (0.3)
Age — no. (%)		
<35 yr	128 (7.6)	123 (7.3)
35–49 yr	751 (44.3)	739 (43.7)
50–59 yr	538 (31.8)	553 (32.7)
≥60 yr	274 (16.2)	275 (16.2)
Missing	3 (0.2)	3 (0.2)
Median age — yr	49	49
Menopausal status at randomization (after completion of chemotherapy) — no. (%)		
Premenopausal	272 (16.1)	261 (15.4)
Uncertain	642 (37.9)	629 (37.2)
Postmenopausal	779 (46.0)	797 (47.1)
Missing	1 (0.1)	6 (0.4)
Nodal status — no. (%)		
Not assessed (neoadjuvant chemotherapy)	186 (11.0)	172 (10.2)
Negative	543 (32.1)	557 (32.9)
1–3 Positive nodes	482 (28.5)	490 (28.9)
≥4 Positive nodes	480 (28.3)	473 (27.9)
Missing	3 (0.2)	1 (0.1)
Pathological tumor size — no. (%)		
Not assessed (neoadjuvant chemotherapy)	186 (11.0)	172 (10.2)
0–2 cm	664 (39.2)	683 (40.4)
>2–5 cm	756 (44.6)	723 (42.7)
>5 cm	75 (4.4)	97 (5.7)
Missing	13 (0.8)	18 (1.1)
Hormone-receptor status — no. (%)‡§		
Estrogen-receptor–negative and progesterone-receptor–negative	798 (47.1)	817 (48.3)
Estrogen-receptor–negative and progesterone-receptor–positive	88 (5.2)	85 (5.0)
Estrogen-receptor–negative and progesterone-receptor unknown	32 (1.9)	27 (1.6)
Estrogen-receptor–positive and progesterone-receptor– positive	526 (31.1)	459 (27.1)
Estrogen-receptor–positive and progesterone-receptor–negative	210 (12.4)	246 (14.5)
Estrogen-receptor–positive and progesterone-receptor unknown	36 (2.1)	59 (3.5)
Estrogen-receptor unknown and progesterone-receptor–positive	1 (0.1)	0
Missing	3 (0.2)	0

Table 1. (Continued.)		
Variable	1 Yr of Trastuzumab (N=1694)	Observation (N=1693)
Histologic grade of tumor — no. (%)		
3 (Poorly differentiated)	1015 (59.9)	1012 (59.8)
2 (Moderately differentiated)	546 (32.2)	554 (32.7)
1 (Well differentiated)	45 (2.7)	42 (2.5)
Not assessed	75 (4.4)	76 (4.5)
Missing	13 (0.8)	9 (0.5)
Surgery for the primary tumor — no. (%)		
Breast-conserving procedure	720 (42.5)	704 (41.6)
Mastectomy	972 (57.4)	987 (58.3)
Missing	2 (0.1)	2 (0.1)
Previous radiotherapy — no. (%)		
Yes	1308 (77.2)	1275 (75.3)
No	383 (22.6)	416 (24.6)
Missing	3 (0.1)	2 (0.1)
Type of adjuvant or neoadjuvant chemotherapy, or both — no. (%)		
No anthracyclines	102 (6.0)	104 (6.1)
Anthracyclines, no taxanes	1151 (67.9)	1156 (68.3)
Doxorubicin-based regimen at any time	397 (23.4)	416 (24.6)
Epirubicin-based regimen only	754 (44.5)	740 (43.7)
Anthracyclines and taxanes	440 (26.0)	433 (25.6)
Concurrent	103 (6.1)	105 (6.2)
Sequential	337 (19.9)	328 (19.4)
Paclitaxel	256 (15.1)	249 (14.7)
Docetaxel	184 (10.9)	184 (10.9)
Missing	1 (0.2)	0
Median cumulative dose of anthracyclines — mg/m²		
Doxorubicin-based regimen at any time	239	238
Epirubicin-based regimen only	397	405
Adjuvant endocrine therapy (861 patients in trastuzumab group and 849 in observation group with estrogen-receptor–positive or progesterone-receptor–positive status) — no. (%)‡		
No	87 (10.1)	60 (7.1)
Yes¶	774 (89.9)	789 (92.9)
Tamoxifen	683 (79.3)	693 (81.6)
Aromatase inhibitor	143 (16.6)	165 (19.4)
Ovarian-function suppressive therapy or ablation	148 (17.2)	143 (16.8)

* Because of rounding, not all percentages total 100.
† Race was determined on the basis of case report forms.
‡ P<0.05, but the difference between the two groups does not influence the results.
§ Hormone-receptor status was assessed at the local participating institution.
¶ Some patients received more than one type of adjuvant endocrine therapy.

Table 2. Adverse Events, with a Special Focus on Cardiotoxicity, among Patients Included in the Safety Analysis.*

Adverse Event	1 Yr of Trastuzumab (N=1677)	Observation (N=1710)	P Value
	no. (%)		
Patients with at least one grade 3 or 4 event†	132 (7.9)	75 (4.4)	<0.001
Patients with at least one serious adverse event‡	117 (7.0)	81 (4.7)	0.007
Fatal adverse events	6 (0.4)§	3 (0.2)¶	0.34
Treatment withdrawals‖	143 (8.5)	—	
Cardiac events			
Death from cardiac causes**	0	1 (0.06)	1.00
Severe CHF††	9 (0.54)	0	0.002
Symptomatic CHF, including severe CHF‡‡	29 (1.73)	1 (0.06)	<0.001
Decrease in LVEF§§	113 (7.08)	34 (2.21)	<0.001

*   CHF denotes congestive heart failure, and LVEF left ventricular ejection fraction.

†   Infection (22 patients [1.3 percent] in the trastuzumab group vs. 7 patients [0.4 percent] in the observation group) and vascular disorder (20 patients [1.2 percent] vs. 9 patients [0.5 percent], respectively) were the only grade 3 or 4 adverse events with an incidence greater than 1 percent in either group.

‡   Infection (29 patients [1.7 percent] in the trastuzumab group vs. 10 patients [0.6 percent] in the observation group) and cardiac disorder (17 patients [1.0 percent] vs. 4 patients [0.2 percent], respectively) were the only serious adverse events with an incidence greater than 1 percent in either group.

§   The fatal events in the trastuzumab group were of cerebral hemorrhage (1 patient), cerebrovascular accident (1 patient), sudden death (1 patient), appendicitis (1 patient), and death from unknown causes (2 patients).

¶   The fatal events in the observation group were cardiac failure (1 patient), suicide (1 patient), and death from unknown causes (1 patient).

‖   Reasons for withdrawal were reported as adverse event (5.5 percent of patients), refusal to continue (2.5 percent of patients), or other (0.5 percent of patients).

** Death from cardiac causes was defined as death due to CHF, myocardial infarction, documented primary arrhythmia, or sudden unexpected death within 24 hours after a definite or probable cardiac event without a documented alternative cause.

††Severe CHF was defined as New York Heart Association functional class III or IV, as confirmed by a cardiologist, and a decrease in the ejection fraction of 10 percentage points or more from baseline to an LVEF of less than 50 percent at any time. This category does not include death from cardiac causes.

‡‡Symptomatic CHF, which includes severe CHF, was defined as CHF that was considered symptomatic by a cardiologist, and a decrease in the ejection fraction of 10 percentage points or more from baseline to an LVEF of less than 50 percent at any time. This category does not include death from cardiac causes but does include severe CHF. The age distribution among patients in the trastuzumab group who had symptomatic CHF, including severe CHF (median age, 51 years; range, 30 to 69), was not significantly different from that in the study population (P=0.21).

§§ Decrease in LVEF was defined as a decrease in the ejection fraction of 10 percentage points or more from baseline to an LVEF of less than 50 percent at any time. Percentages are based on 1595 patients in the trastuzumab group and 1540 patients in the observation group who had a post-screening LVEF assessment.

or an LVEF of less than 50 percent with an absolute reduction of at least 10 percent from baseline developed. In patients without symptoms of congestive heart failure, the same criteria for left ventricular function were used to withhold treatment. Trastuzumab was discontinued if, in asymptomatic patients, left ventricular function did not return to a level above the criteria for withholding treatment after the therapy was stopped for three weeks.

FOLLOW-UP PROCEDURES

All patients adhered to the same schedule of follow-up visits, which required the recording of symptoms, side effects (graded according to the National Cancer Institute Common Toxicity Criteria [NCI-CTC] version 2.0), and findings on clinical examination every three months for the first two years, with hematologic and chemistry studies performed every six months. These assessments are scheduled to occur annually for year 3 to year 10. Annual chest radiography is required to year 5 and annual mammography to year 10.

CARDIAC MONITORING

Cardiac monitoring in the trastuzumab group and the observation group included responses to a cardiac questionnaire, physical examination, 12-lead

Table 3. Efficacy End-Point Events (Intention-to-Treat Groups).

Event	1 Yr of Trastuzumab (N=1694)	Observation (N=1693)
	no. (%)	
Disease-free–survival events		
Any recurrence, second primary event, or death without prior recurrence*	127 (7.5)	220 (13.0)
Local recurrence	17 (1.0)	37 (2.2)
Regional recurrence	10 (0.6)	13 (0.8)
Distant recurrence (site)	85 (5.0)	154 (9.1)
Soft tissue	6 (0.3)	19 (1.1)
Skeletal	24 (1.4)	38 (2.2)
Central nervous system	21 (1.2)	15 (0.9)
Other visceral site	34 (2.0)	82 (4.8)
Contralateral breast cancer	6 (0.4)	7 (0.4)
Second nonbreast malignant disease	3 (0.2)	6 (0.4)
Death without prior recurrence	6 (0.4)	3 (0.2)
Death		
From any cause	29 (1.7)	37 (2.2)
Breast-cancer related	23 (1.4)	34 (2.0)
Without cancer event	6 (0.4)	3 (0.2)
Cardiac failure	0	1 (0.1)
Cerebral hemorrhage	1 (0.1)	0
Cerebrovascular accident	1 (0.1)	0
Other cause	2 (0.1)	1 (0.1)
Unknown cause	2 (0.1)	1 (0.1)

* Almost 60 percent of the recurrences occurred in patients with estrogen-receptor–negative and progesterone-receptor–negative tumors (48 percent of the study cohort).

STATISTICAL ANALYSIS

Enrollment of 4482 patients was planned to detect a 23 percent relative reduction in the risk of a disease-free–survival event with 80 percent power, with the use of a two-sided significance level of 2.5 percent for each comparison: two years of trastuzumab versus observation and one year of trastuzumab versus observation. A total of 951 disease-free–survival events were required for the final analysis. One interim efficacy analysis was planned after 475 events, with a specified significance level of P≤0.001 required, with the use of a sequential plan according to the O'Brien–Fleming boundary as implemented by Lan and DeMets.[16] The independent data-monitoring committee reviewed data on patient enrollment, deaths, compliance, and safety every six months and conducted the interim cardiac safety and efficacy reviews as preplanned.

The efficacy analyses were conducted according to the intention-to-treat principle. Chi-square tests for categorical data and log-rank tests for time-to-event end points provided two-sided P values. Kaplan–Meier curves are presented. Cox proportional-hazards regression analysis was used to estimate hazard ratios and 95 percent confidence intervals.

RESULTS

INTERIM EFFICACY ANALYSIS

The 475 disease-free-survival events needed for the interim efficacy analysis were recorded in the database on March 29, 2005, and the database was locked on April 8, 2005; results were reviewed by the independent data-monitoring committee on April 25, 2005. The independent data-monitoring committee recommended release of the results because improvements in disease-free survival were highly significant, crossing the sequential boundary for both one year and two years of trastuzumab, as compared with observation. After a median follow-up period of 1 year (range, 0 to 36 months), the independent data-monitoring committee released detailed information only for the groups assigned to 1 year of treatment with trastuzumab or observation. These groups are the focus of this report; evaluation of the group assigned to two years of treatment with trastuzumab is ongoing.

STUDY POPULATION

Between December 2001 and March 2005, 5081 women for whom information was available for analysis were enrolled in the study. Of these, 1694

electrocardiogram, and an assessment of LVEF by echocardiography[15] or MUGA scanning at baseline and 3, 6, 12, 18, 24, 30, 36, and 60 months after randomization. Cardiac events are described in Table 2. A core laboratory reviewed the echocardiograms, and data management and clinical science staff reviewed the MUGA scan results of the first 900 patients who were followed for six months.

Three prespecified interim cardiac safety analyses were performed after 300, 600, and 900 patients had been enrolled and treated for at least six months. An absolute difference of more than 4 percentage points in the incidence of severe congestive heart failure or cardiac death between the trastuzumab group and the observation group would have triggered a recommendation by the independent data-monitoring committee to stop or modify the trial.

Figure 2. Kaplan–Meier Curves Showing Disease-free Survival (Panel A), Time to Distant Recurrence (Panel B), and Overall Survival (Panel C).

The hazard ratios (with 95 percent confidence intervals and P values) are for the patients assigned to receive trastuzumab for one year, as compared with those assigned to observation, and were obtained from the unadjusted Cox model. DFS denotes disease-free survival, CI confidence interval, TTDR time to distant recurrence, and OS overall survival.
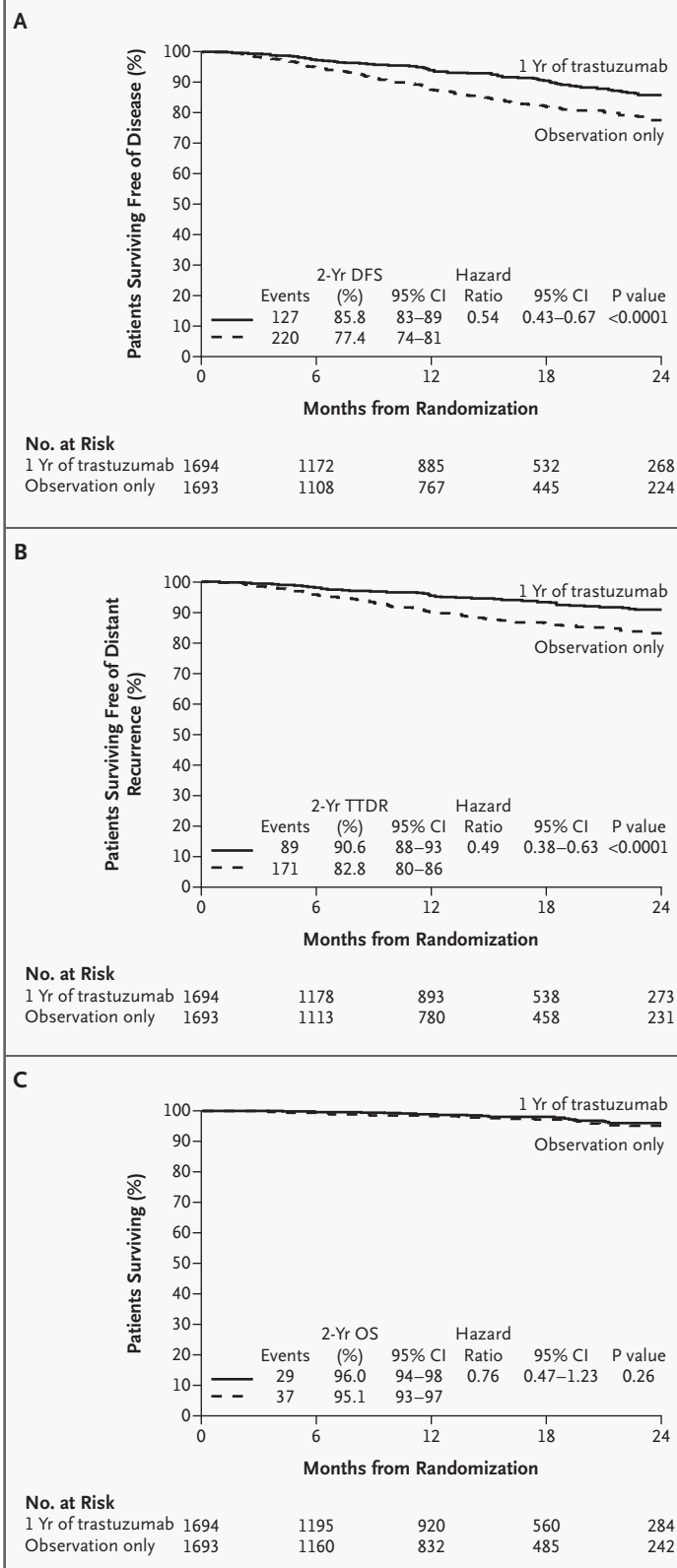
women were assigned to the trastuzumab group receiving the drug for one year and 1693 women were assigned to the observation group (Fig. 1). HER2-positive status as assessed by the central laboratory was IHC 3+ without FISH testing among 67 percent of the patients. Table 1 lists baseline characteristics of the patients, tumors, and primary treatment. The baseline characteristics of the two groups were well balanced (Table 1). The median age was 49 years, one third of the patients had node-negative disease, and 48 percent of the patients had hormone-receptor–negative tumors.

Chemotherapy was anthracycline-based in 94 percent of patients; 26 percent received a taxane, 76 percent received radiotherapy, and tamoxifen was the predominant endocrine therapy. The median time between diagnosis of breast cancer and the initiation of trastuzumab was 8.4 months (interquartile range, 7.1 to 9.6 months).

There were major eligibility violations in 11 patients (8 patients in the trastuzumab group and 3 patients in the observation group): LVEF less than 55 (4 patients), status of HER2-positive not centrally confirmed (3 patients), microinvasive breast cancer (3 patients), and metastatic disease (1 patient). In addition, 39 patients in the trastuzumab group and 52 patients in the observation group had node-negative disease with tumors 1 cm in diameter or less.

ADVERSE EFFECTS AND CARDIAC SAFETY

Twenty patients assigned to one year of trastuzumab did not receive treatment, and three patients assigned to observation received trastuzumab. These 23 patients are included in the alternative group for the safety analyses (Fig. 1 and Table 2). Table 2 shows a higher incidence of NCI-CTC grade 3 or 4 adverse events and serious adverse events in the trastuzumab group than in the observation group. There were six fatal adverse events in the trastuz-

umab group and three in the observation group (Table 2).

There was one cardiac death in the observation group, and nine patients (0.54 percent) in the trastuzumab group had severe congestive heart failure (as defined in Table 2). Symptomatic congestive heart failure, including the nine severe cases (as defined in Table 2), occurred in 1.7 percent of patients in the trastuzumab group and 0.06 percent of patients in the observation group; a decrease in LVEF (as defined in Table 2) was noted on at least one assessment among 7.1 percent of patients in the trastuzumab group and among 2.2 percent of those in the observation group.

TREATMENT COMPLIANCE

Trastuzumab was stopped before completion of the planned one-year treatment among 143 patients (8.5 percent) for reasons other than relapse. Reasons included an adverse event among 5.5 percent of patients, the patient's refusal among 2.5 percent, and other reasons among 0.5 percent.

EFFICACY

A total of 127 disease-free–survival events were reported in the trastuzumab group and 220 in the observation group (Table 3). The unadjusted hazard ratio for the risk of an event in the trastuzumab group, as compared with the observation group, was 0.54 (95 percent confidence interval, 0.43 to 0.67; P<0.0001 by the log-rank test, crossing the interim-analysis boundary) (Fig. 2A), which corresponded to an absolute benefit in disease-free survival of 8.4 percentage points at two years (95 percent confidence interval, 2.1 to 14.8).

Approximately two thirds of the reported first events were distant metastases (Table 3). The hazard ratio for time to a distant recurrence in the trastuzumab group, as compared with the observation group, was 0.49 (95 percent confidence interval, 0.38 to 0.63; P<0.0001) (Fig. 2B). With 29 deaths in the trastuzumab group and 37 in the observation group, the estimated reduction in the hazard ratio for death (24 percent) was not statistically significant (Fig. 2C). There was no evidence of substantial heterogeneity in the relative treatment effect among the subgroups (Fig. 3).

DISCUSSION

This study shows that trastuzumab can benefit women with HER2-positive breast cancer when giv-

Figure 3 (facing page). Analyses of Disease-free Survival According to Subgroup.
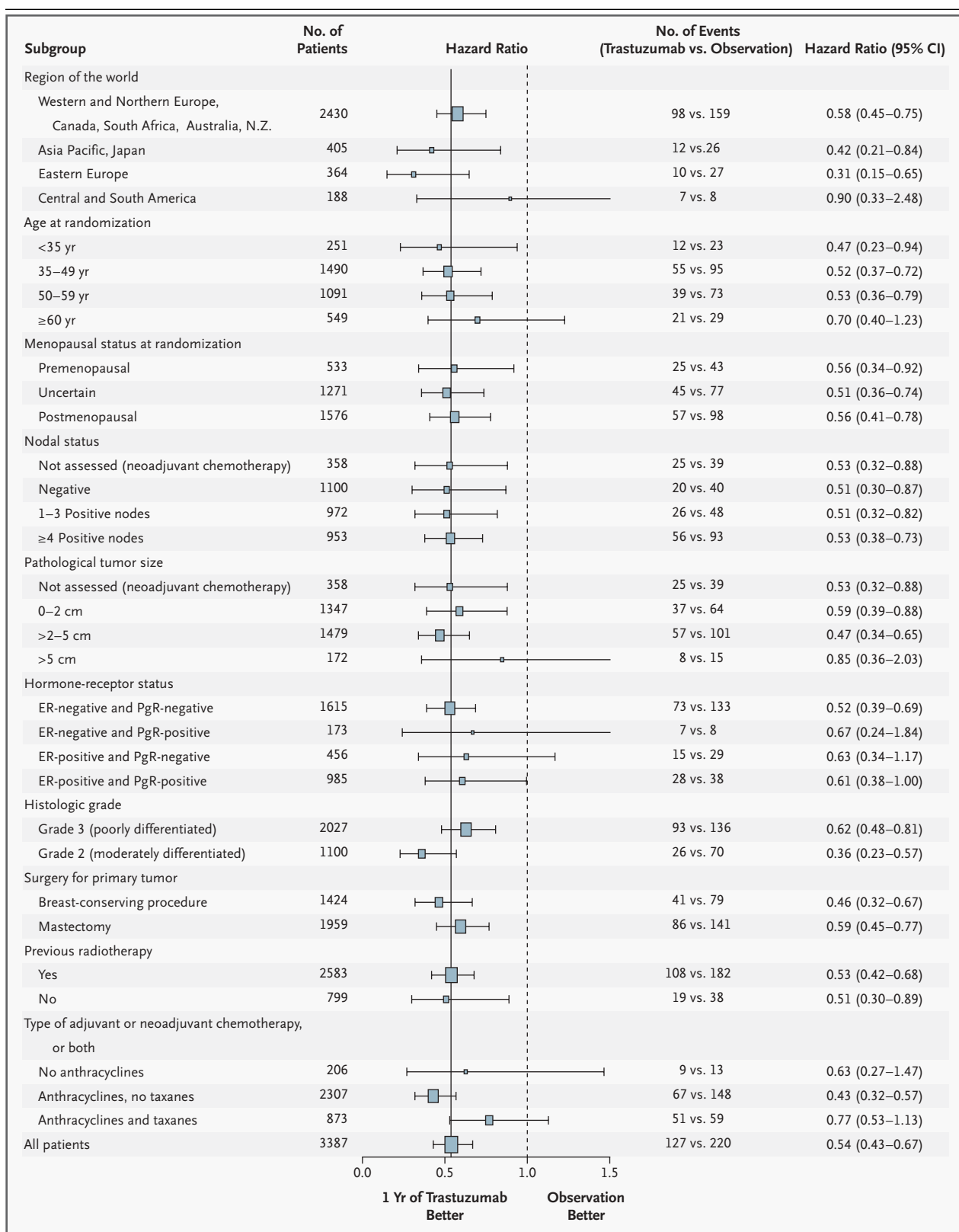
The hazard ratios (with 95 percent confidence intervals) are for the patients assigned to trastuzumab for one year, as compared with those assigned to observation, and were obtained from the unadjusted Cox model. The solid vertical line indicates a hazard ratio of 0.54, which is the value for all patients, and the dashed vertical line indicates a hazard ratio of 1.00, which is the null-hypothesis value. The size of the squares is proportional to the number of events in the subgroup. CI denotes confidence interval, N.Z. New Zealand, ER estrogen receptor, and PgR progesterone receptor.

en after completion of adjuvant chemotherapy. As compared with observation after primary therapy (including surgery with or without radiotherapy and neoadjuvant or adjuvant chemotherapy), trastuzumab given after primary therapy reduced the rate of recurrence, particularly distant recurrence, by approximately 50 percent. This degree of benefit in early breast cancer is the largest to be reported since the introduction of tamoxifen in hormone-receptor–positive disease. This trial is the culmination of a collaboration between basic research scientists and clinical investigators over the past two decades.[1-4,17-33]

The interpretation of our results must take into account the very short follow-up period — a median of 12 months and a maximum of 36 months. However, the pattern of early, and largely distant, relapse found among patients with HER2-positive breast cancer, and the clinically and statistically significant reduction in the risk of relapse achieved with trastuzumab, justified release of the results of the interim efficacy analysis.

We acknowledge that we have only an incomplete picture of the risks associated with trastuzumab. The risk of cardiotoxicity is currently low in our trial, but this could change with longer follow-up. Another concern is that longer follow-up may show that trastuzumab is not effective in reducing the incidence of disease recurrence in the central nervous system. Brain metastases developed in approximately one third of the women receiving trastuzumab as treatment for advanced breast cancer, despite control of systemic disease.[34] It is not clear whether such central nervous system metastases reflect aggressive disease or poor penetration of trastuzumab into the brain.

Will the benefit of adjuvant trastuzumab accrue to all women who have HER2-positive breast cancer

Subgroup	No. of Patients	Hazard Ratio	No. of Events (Trastuzumab vs. Observation)	Hazard Ratio (95% CI)
Region of the world				
Western and Northern Europe, Canada, South Africa, Australia, N.Z.	2430		98 vs. 159	0.58 (0.45–0.75)
Asia Pacific, Japan	405		12 vs.26	0.42 (0.21–0.84)
Eastern Europe	364		10 vs. 27	0.31 (0.15–0.65)
Central and South America	188		7 vs. 8	0.90 (0.33–2.48)
Age at randomization				
<35 yr	251		12 vs. 23	0.47 (0.23–0.94)
35–49 yr	1490		55 vs. 95	0.52 (0.37–0.72)
50–59 yr	1091		39 vs. 73	0.53 (0.36–0.79)
≥60 yr	549		21 vs. 29	0.70 (0.40–1.23)
Menopausal status at randomization				
Premenopausal	533		25 vs. 43	0.56 (0.34–0.92)
Uncertain	1271		45 vs. 77	0.51 (0.36–0.74)
Postmenopausal	1576		57 vs. 98	0.56 (0.41–0.78)
Nodal status				
Not assessed (neoadjuvant chemotherapy)	358		25 vs. 39	0.53 (0.32–0.88)
Negative	1100		20 vs. 40	0.51 (0.30–0.87)
1–3 Positive nodes	972		26 vs. 48	0.51 (0.32–0.82)
≥4 Positive nodes	953		56 vs. 93	0.53 (0.38–0.73)
Pathological tumor size				
Not assessed (neoadjuvant chemotherapy)	358		25 vs. 39	0.53 (0.32–0.88)
0–2 cm	1347		37 vs. 64	0.59 (0.39–0.88)
>2–5 cm	1479		57 vs. 101	0.47 (0.34–0.65)
>5 cm	172		8 vs. 15	0.85 (0.36–2.03)
Hormone-receptor status				
ER-negative and PgR-negative	1615		73 vs. 133	0.52 (0.39–0.69)
ER-negative and PgR-positive	173		7 vs. 8	0.67 (0.24–1.84)
ER-positive and PgR-negative	456		15 vs. 29	0.63 (0.34–1.17)
ER-positive and PgR-positive	985		28 vs. 38	0.61 (0.38–1.00)
Histologic grade				
Grade 3 (poorly differentiated)	2027		93 vs. 136	0.62 (0.48–0.81)
Grade 2 (moderately differentiated)	1100		26 vs. 70	0.36 (0.23–0.57)
Surgery for primary tumor				
Breast-conserving procedure	1424		41 vs. 79	0.46 (0.32–0.67)
Mastectomy	1959		86 vs. 141	0.59 (0.45–0.77)
Previous radiotherapy				
Yes	2583		108 vs. 182	0.53 (0.42–0.68)
No	799		19 vs. 38	0.51 (0.30–0.89)
Type of adjuvant or neoadjuvant chemotherapy, or both				
No anthracyclines	206		9 vs. 13	0.63 (0.27–1.47)
Anthracyclines, no taxanes	2307		67 vs. 148	0.43 (0.32–0.57)
Anthracyclines and taxanes	873		51 vs. 59	0.77 (0.53–1.13)
All patients	3387		127 vs. 220	0.54 (0.43–0.67)

0.0   0.5   1.0   1.5

1 Yr of Trastuzumab Better   Observation Better

who are treated outside clinical trials? Women with small (≤1 cm in diameter), node-negative invasive tumors were not eligible for this trial. Although at a median of one year of follow-up, trastuzumab improved the disease-free survival in all subgroups (Fig. 3), further follow-up may show that the magnitudes of absolute benefit differ across subgroups. For example, almost 60 percent of the disease-free–survival events observed so far occurred in the hormone-receptor–negative cohort (48 percent of the patients), but we cannot rule out the possibility that in the future disease-free–survival events may occur disproportionately more often among patients in the subgroup with hormone-receptor–positive tumors. By design, women with cardiac risk factors and an LVEF of less than 55 percent after completion of chemotherapy with or without radiotherapy were excluded from the study, and our data are not applicable to the treatment of such women.

In our study, HER2 overexpression or *HER2* amplification had to be confirmed by a central laboratory before randomization, thereby reducing the risk of false positive results. It is our view that adjuvant trastuzumab should be considered only if the HER2-positive status of the tumor has been determined by a high-volume laboratory with quality-control procedures.[35]

The results of the HERA trial should be widely applicable to women with HER2-positive breast cancer for the following reasons: different types of neoadjuvant or adjuvant chemotherapy were allowed before the initiation of trastuzumab; the schedule of administration of one dose every three weeks, which was shown in the metastatic setting to have efficacy, side effects, and pharmacokinetics similar to those of the weekly schedule,[6] was used; and patients with node-negative disease were included. It appears that trastuzumab is effective regardless of the type of chemotherapeutic regimens received before treatment with trastuzumab and the extent of nodal involvement.

We do not know if introducing trastuzumab early in the course of adjuvant systemic therapy, concomitantly with chemotherapy, could further improve the outcome. The question of timing is likely to remain unanswered, because early administration of trastuzumab, as studied in ongoing trials,[36,37] requires the drug to be used concurrently with specific chemotherapy regimens that are hypothesized to enhance the effectiveness of trastuzumab.[30,32]

The results of this trial indicate that one year of adjuvant trastuzumab should be considered a standard option on completion of locoregional therapy and neoadjuvant or adjuvant chemotherapy for women who fulfill the study eligibility criteria used in the HERA trial.

APPENDIX

The authors' affiliations are as follows: the Department of Medicine (M.J.P.-G.), the Breast International Group Secretariat (C.S.), and the Breast European Adjuvant Study Team Data Centre (M.S.D.), Jules Bordet Institute, Université Libre de Bruxelles, Brussels; Frontier Science (Scotland), Kingussie, Scotland (M.P., E.M., R.D.G.); the Department of Oncology, Gerald Bronfman Centre for Clinical Research in Oncology, McGill University, Montreal (B.L.-J.); the Department of Medicine, the European Institute of Oncology, Milan, and the Oncology Institute of Southern Switzerland, Bellinzona, Switzerland (A.G.); Klinik für Frauenheilkunde und Geburtshilfe, Ludwig-Maximilians-Universität München, Grosshadern, Munich, Germany (M.U.); the Breast Unit, Royal Marsden Hospital and the Institute of Cancer Research, London (I.S.); Struttura Complessa Oncologia Medica 1, Istituto Nazionale per lo Studie e la Cura dei Tumori, Milan (L.G.); the Medical Oncology Service, Vall d'Hebron University Hospital, Barcelona (J.B.); the Andrew Love Cancer Centre, Geelong Hospital, Geelong, Australia (R.B.); the Department of Gynecology, Philipps University of Marburg, Marburg, Germany (C.J.); the Department of Oncology, Western General Hospital, Edinburgh (D.C.); the Department of Academic Biochemistry, the Royal Marsden National Health Service Trust, London (M.D.); Hospital São Lucas, Pontificia Universidad Catòlica do Rio Grande do Sul School of Medicine, Porto Alegre, Brazil (C.H.B.); the Department of Internal Medicine, Medical University of Vienna, Vienna (G.S.); the Department of Surgery, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei (C.-S.H.); the Department of Oncology, Finsen Center, Rigshospitalet University Hospital, Copenhagen (M.A.); the Tel Aviv Sourasky Medical Center, Tel Aviv, Israel (M.I.); N.N. Blokhin Cancer Research Center, Moscow (M.L.); the Department of Oncology, National Institute of Oncology, Budapest, Hungary (I.L.); Frauenklinik der Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany (U.N.); Department of Breast Oncology, Aichi Cancer Center, Aichi, Japan (H.I.); Klinik und Poliklinik für Gynäkologie, Universitätsklinikum Hamburg Eppendorf, Hamburg, Germany (C.T.); Department of Medical Oncology, British Columbia Cancer Agency, Vancouver Centre, Vancouver, B.C., Canada (C.L.); Swiss Cardiovascular Center, Bern, Switzerland (T.M.S.); Institut für Pathologie, Klinikum Kassel, Kassel, Germany (J.R.); F. Hoffmann–La Roche, Basel, Switzerland (T.S., V.G., C.W.); and the Department of Biostatistics and Computational Biology, Dana–Farber Cancer Institute, Boston (R.D.G.).

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