ORIGINAL ARTICLE

Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

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ABSTRACT

BACKGROUND

We present the combined results of two trials that compared adjuvant chemotherapy with or without concurrent trastuzumab in women with surgically removed HER2-positive breast cancer.

METHODS

The National Surgical Adjuvant Breast and Bowel Project trial B-31 compared doxorubicin and cyclophosphamide followed by paclitaxel every 3 weeks (group 1) with the same regimen plus 52 weeks of trastuzumab beginning with the first dose of paclitaxel (group 2). The North Central Cancer Treatment Group trial N9831 compared three regimens: doxorubicin and cyclophosphamide followed by weekly paclitaxel (group A), the same regimen followed by 52 weeks of trastuzumab after paclitaxel (group B), and the same regimen plus 52 weeks of trastuzumab initiated concomitantly with paclitaxel (group C). The studies were amended to include a joint analysis comparing groups 1 and A (the control group) with groups 2 and C (the trastuzumab group). Group B was excluded because trastuzumab was not given concurrently with paclitaxel.

RESULTS

By March 15, 2005, 394 events (recurrent, second primary cancer, or death before recurrence) had been reported, triggering the first scheduled interim analysis. Of these, 133 were in the trastuzumab group and 261 in the control group (hazard ratio, 0.48; $P<0.0001$). This result crossed the early stopping boundary. The absolute difference in disease-free survival between the trastuzumab group and the control group was 12 percent at three years. Trastuzumab therapy was associated with a 33 percent reduction in the risk of death ($P=0.015$). The three-year cumulative incidence of class III or IV congestive heart failure or death from cardiac causes in the trastuzumab group was 4.1 percent in trial B-31 and 2.9 percent in trial N9831.

CONCLUSIONS

Trastuzumab combined with paclitaxel after doxorubicin and cyclophosphamide improves outcomes among women with surgically removed HER2-positive breast cancer. (clinicaltrials.gov numbers, NCT00004067 and NCT00005970.)

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Trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 protein, was approved in 1998 as a first-line treatment in combination with paclitaxel for HER2-positive metastatic breast cancer.[1] The benefit of this approach in patients with metastatic disease and the poor prognosis of HER2-positive breast cancer[2,3] motivated the National Cancer Institute (NCI) to sponsor two trials of adjuvant treatment with trastuzumab, led by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the North Central Cancer Treatment Group (NCCTG).

NSABP trial B-31, which began accrual in February 2000, compares four cycles of doxorubicin and cyclophosphamide followed by paclitaxel (group 1) with the same chemotherapy plus 52 weeks of trastuzumab beginning on day 1 of paclitaxel therapy (group 2). NCCTG trial N9831 began enrollment in May 2000 and compares three regimens: four cycles of doxorubicin and cyclophosphamide followed by weekly paclitaxel for 12 weeks (group A), four cycles of doxorubicin and cyclophosphamide followed by 52 weeks of trastuzumab after the completion of paclitaxel therapy (group B), and four cycles of doxorubicin and cyclophosphamide followed by 52 weeks of trastuzumab beginning on day 1 of paclitaxel therapy (group C).

The control groups of the trials, as well as group 2 in trial B-31 and group C in trial N9831, differed in terms of the scheduling of paclitaxel treatment and some aspects of hormonal therapy and radiotherapy but were otherwise identical. For this reason, the NCI and the Food and Drug Administration approved a joint-analysis plan developed by the NSABP and NCCTG to combine data from group 1 and group A (referred to as the control group) for comparison with group 2 and group C (referred to as the trastuzumab group). Group B of trial N9831 was excluded because the protocol required trastuzumab to be administered after the completion of chemotherapy.

The plan required a first interim analysis after the occurrence of 355 events. Before the data were locked, 2043 patients (of a planned total of 2700) were enrolled in trial B-31 and 1633 patients (of a total of 2000 for the comparison of group A with group C) were enrolled in trial N9831. In April 2005, the independent data-monitoring committees of each trial recommended closing enrollment and releasing the results.

METHODS

ELIGIBILITY AND ENROLLMENT

Enrollment required a pathological diagnosis of adenocarcinoma of the breast with immunohistochemical staining for HER2 protein of 3+ intensity or amplification of the *HER2* gene on fluorescence in situ hybridization. Initially, both trials required patients to have histologically proven, node-positive disease; as of May 2, 2003, patients with high-risk node-negative disease (defined as a tumor that was more than 2 cm in diameter and positive for estrogen receptors or progesterone receptors or as a tumor that was more than 1 cm in diameter and negative for both estrogen receptors and progesterone receptors) were eligible for trial N9831. Other requirements were adequate hematopoietic, hepatic, and renal function and a left ventricular ejection fraction (LVEF) that met or exceeded the lower limit of normal. Patients with clinical or radiologic evidence of metastatic disease were excluded. Findings suggestive of metastasis were confirmed or refuted by additional radiologic evaluation or biopsy. Complete resection of the primary tumor and axillary-node dissection were required (negative sentinel-node biopsy was allowed in trial N9831). Patients were ineligible if they had angina pectoris requiring antianginal medication, arrhythmia requiring medication, a severe conduction abnormality, clinically significant valvular disease, cardiomegaly on chest radiography, left ventricular hypertrophy on echocardiography (trial B-31 only), poorly controlled hypertension, clinically significant pericardial effusion (trial N9831 only), or a history of myocardial infarction, congestive heart failure, or cardiomyopathy.

Participating institutions obtained the approval of their human investigations committee or institutional review board and filed assurances with the Department of Health and Human Services. Written informed consent was required for enrollment.

In trial B-31, treatment assignments were balanced according to nodal status, the planned hormonal therapy, the type of surgery (lumpectomy vs. mastectomy), the intended radiotherapy, and institution with the use of a biased-coin minimization algorithm.[4] Trial N9831 used a dynamic allocation procedure that balanced the marginal distributions of nodal status and hormone-receptor status between groups.[5] The procedures used for HER2 testing in the two trials are provided in the Supple-

mentary Appendix (available with the full text of this article at www.nejm.org).

TREATMENT REGIMENS

In trial B-31, treatment consisted of 60 mg of doxorubicin per square meter of body-surface area and 600 mg of cyclophosphamide per square meter every 21 days for four cycles, followed by 175 mg of paclitaxel per square meter every 3 weeks for four cycles (group 1), or the same chemotherapy regimen plus trastuzumab, beginning with a loading dose of 4 mg per kilogram of body weight, given with the first dose of paclitaxel, and followed by weekly doses of 2 mg per kilogram for 51 weeks (group 2) (Fig. 1). Beginning on May 16, 2003, paclitaxel could also be given weekly for 12 weeks at a dose of 80 mg per square meter at the investigator's discretion. Group A in trial N9831 used the same regimen of doxorubicin and cyclophosphamide as in trial B-31, followed by 12 weekly doses of paclitaxel at a dose of 80 mg per square meter. Group B received the same chemotherapy regimen, followed by trastuzumab, beginning with a loading dose of 4 mg per kilogram and followed by weekly doses of 2 mg per kilogram for 51 weeks. Group C received the same chemotherapy regimen plus trastuzumab, beginning with a loading dose of 4 mg per kilogram, given with the first dose of paclitaxel, and followed by weekly doses of 2 mg per kilogram for 51 weeks (Fig. 1).

In both trials, patients treated with lumpectomy were to receive whole-breast radiotherapy with an optional boost to the tumor bed. Regional radiotherapy after lumpectomy or mastectomy was optional in trial B-31 but required in trial N9831 for patients with at least four positive nodes. In both studies, radiotherapy was initiated after the completion of chemotherapy, and there was no irradiation of the internal-mammary nodes. Trastuzumab treatment was continued during radiotherapy. Women with estrogen-receptor–positive or progesterone-receptor–positive tumors were to receive 20 mg of tamoxifen per day for five years. In trial N9831, hormonal therapy was given after chemotherapy. In trial B-31, tamoxifen was initiated on day 1 of the first cycle of doxorubicin and cyclophosphamide until an amendment on January 14, 2003, required hormonal therapy to be started after chemotherapy, in response to the findings of Southwest Oncology Group trial 8814.[6] Following the report of the Arimidex, Tamoxifen Alone or in Combination trial,[7] trial N9831 was amended on July 19, 2002, to permit treatment with any aromatase inhibitor in postmenopausal patients with estrogen-receptor–positive or progesterone-receptor–positive tumors. Beginning January 14, 2003, trial B-31 permitted treatment with anastrozole in these patients.

ASSESSMENT OF CARDIAC FUNCTION

In both trials, LVEF was assessed before entry, after the completion of doxorubicin and cyclophosphamide therapy, and 6, 9, and 18 months after randomization. Trial B-31 required multiple gated acquisition scanning, whereas trial N9831 allowed multiple gated acquisition scanning or echocardiography. The initiation of trastuzumab required an LVEF after doxorubicin and cyclophosphamide therapy that met or exceeded the lower limit of normal and a decrease of less than 16 percentage points from baseline. Patients in whom clinically significant cardiac symptoms developed while they were receiving doxorubicin and cyclophosphamide were excluded from subsequent trastuzumab therapy. The six- and nine-month cardiac assessments were used to determine whether trastuzumab should be continued in patients without cardiac symptoms. If the LVEF had declined 16 or more percentage points from baseline or 10 to 15 percentage points from baseline to below the lower limit of normal, trastuzumab was withheld for four weeks, at which time the LVEF was reassessed. If the LVEF remained below these levels or if the patient had symptomatic cardiac dysfunction while receiving trastuzumab, administration of the antibody was permanently discontinued.

ROLE OF THE SPONSOR

Both studies were conducted under a corporate research and development agreement between Genentech and the NCI. Genentech provided trastuzumab and partial funding support but did not participate in the design of the studies or the collection of data. The joint analysis was developed and analyzed by the NSABP and the NCCTG. The lead authors wrote the manuscript, which was reviewed by all authors. A draft was provided to Genentech for comment, but no changes in content or conclusions were requested by Genentech. The authors vouch for the completeness and accuracy of the data.

STATISTICAL ANALYSIS

The primary end point was disease-free survival. Events determining disease-free survival were lo-

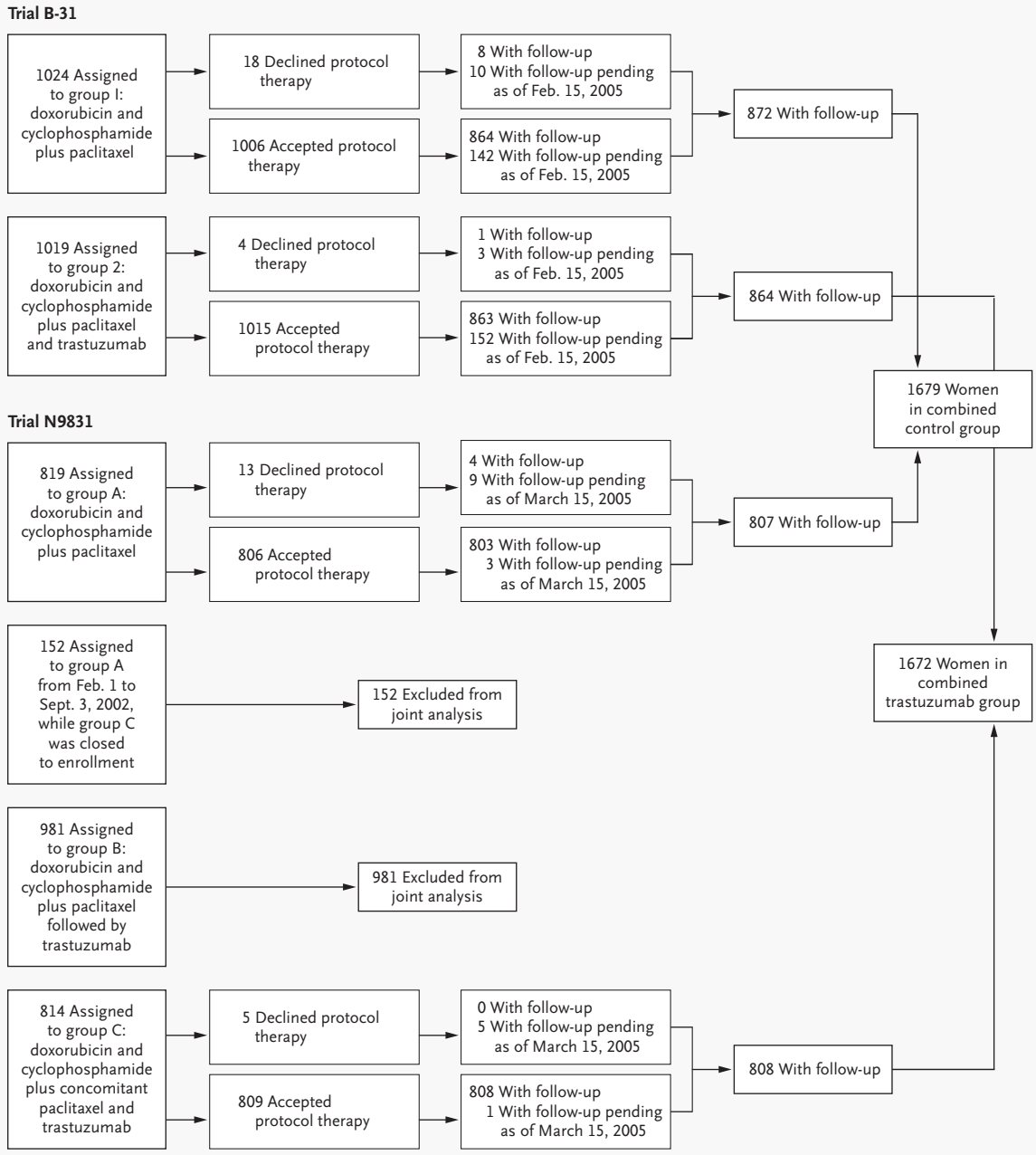

Figure 1. Enrollment, Patients, and the Timing of Chemotherapy and Trastuzumab in Trial B-31 and Trial N9831.

cal, regional, and distant recurrence; contralateral breast cancer, including ductal carcinoma in situ; other second primary cancers; and death before recurrence or a second primary cancer. Comparison of the two groups was based on a log-rank test, stratified according to the study (trial B-31 vs. trial N9831), intended paclitaxel schedule (every three weeks vs. weekly), nodal status (0, 1 to 3, 4 to 9, or 10 or more positive nodes), and hormone-receptor status (estrogen-receptor–positive or progesterone-receptor–positive vs. estrogen-receptor–negative and progesterone-receptor–negative). Disease-free survival was estimated according to the Kaplan–Meier method. The primary cohort includ-

ed all enrolled patients with follow-up data, analyzed according to the intention-to-treat principle (Fig. 1). All reported P values are two-sided.

Other end points were overall survival, time to distant recurrence, death from breast cancer, contralateral breast cancer, and other second primary cancers. The Supplementary Appendix defines these end points. We counted deaths as having been caused by breast cancer if they took place after recurrence or if they were attributed to breast cancer.

Timing of Analyses

Definitive analysis was scheduled after 710 primary end-point events had occurred to provide the study with a statistical power of 90 percent to detect a 25 percent reduction in the event rate, allowing for a number of attenuating factors. The first interim analysis was to take place after 355 events had been reported. Subsequent interim analyses were scheduled to take place semiannually. Consideration was to be given to early reporting if disease-free survival differed at the nominal 0.0001 level. If this boundary was not crossed, alpha spending function was to be applied to the final test so that the overall type I error rate would be 0.05.

Secondary Analyses

Cox models were fitted to adjust for nodal status (0 to 3, 4 to 9, or 10 or more positive nodes), tumor size (2.0 cm or less, 2.1 to 4.0 cm, or 4.1 cm or more), receptor status (estrogen-receptor–positive or progesterone-receptor–positive vs. estrogen-receptor–negative and progesterone-receptor–negative), age (39 years or younger, 40 to 49 years, 50 to 59 years, or 60 years of age or older), grade (poor vs. other), histologic findings (ductal carcinoma vs. other), and trial (B-31 vs. N9831). Forest plots were constructed to show the effects according to the study and subgroups of patients.[8] Hazard ratios were computed and compared according to the length of follow-up (one year or less, one to two years, two to three years, or more than three years after randomization).

Sensitivity Analysis

The protocols required a secondary analysis that excluded patients who were ineligible, did not continue therapy after receiving doxorubicin and cyclophosphamide, or were HER2-negative on central review. Also excluded were patients with symptoms of adverse cardiac effects or declines in LVEF during doxorubicin and cyclophosphamide therapy that would preclude the initiation of trastuzumab had they been randomly assigned to the investigational group.

Data Lock

Patients in trial B-31 include those enrolled as of February 15, 2005, with follow-up as of that date. Patients in trial N9831 include those enrolled by November 1, 2004, with follow-up as of March 15, 2005.

RESULTS

PATIENTS

As of February 15, 2005, 2043 patients had been enrolled in trial B-31; 1736 of these women had at least one follow-up evaluation (end-point follow-up was not required for six months after randomization). By November 1, 2004, 1633 patients had been enrolled in groups A and C of trial N9831, 1615 of whom had follow-up data submitted by March 15, 2005 (Fig. 1). Table 1 shows the characteristics of patients with follow-up. Except for 191 patients with node-negative breast cancer who were enrolled in trial N9831, the groups from each study were similar.

COMPLIANCE

Chemotherapy

In the combined trials, 31 of 1843 patients assigned to the control group declined therapy, as did 9 of 1833 women randomly assigned to the trastuzumab group. Of the patients who began chemotherapy with doxorubicin and cyclophosphamide, 97.9 percent received four cycles; 2.7 percent of patients who completed doxorubicin and cyclophosphamide treatment did not begin treatment with paclitaxel; of those who did, 94.7 percent completed all cycles.

Eligibility for Trastuzumab

Of 3497 patients who had an evaluation of LVEF after doxorubicin and cyclophosphamide therapy, 233 (6.7 percent) had an LVEF that declined at least 16 percentage points from baseline or that declined below the lower limit of normal or had cardiac symptoms during such treatment that would preclude the initiation of trastuzumab therapy.

Discontinuation of Trastuzumab

Of 1159 patients with an adequate LVEF after doxorubicin and cyclophosphamide treatment who be-

Table 1. Characteristics of the Patients.

Characteristic	Control Group		Trastuzumab Group		All Patients (N=3351)
	Trial B-31 (N=872)	Trial N9831 (N=807)	Trial B-31 (N=864)	Trial N9831 (N=808)	
Ineligible — no. (%)	20 (2.3)	14 (1.7)	19 (2.2)	11 (1.4)	64 (1.9)
Age at randomization — no. (%)					
≤39 yr	146 (16.7)	138 (17.1)	140 (16.2)	129 (16.0)	553 (16.5)
40–49 yr	304 (34.9)	274 (34.0)	306 (35.4)	272 (33.7)	1156 (34.5)
50–59 yr	294 (33.7)	272 (33.7)	280 (32.4)	261 (32.3)	1107 (33.0)
≥60 yr	128 (14.7)	123 (15.2)	138(16.0)	146 (18.1)	535 (16.0)
Histologically positive nodes — no. (%)					
Unknown	0	4 (0.5)	0	0	4 (0.1)
0	0	102 (12.6)	0	89 (11.0)	191 (5.7)
1–3	494 (56.7)	386 (47.8)	496 (57.4)	403 (49.9)	1779 (53.1)
4–9	253 (29.0)	203 (25.2)	251 (29.1)	205 (25.4)	912 (27.2)
≥10	125 (14.3)	112 (13.9)	117 (13.5)	111 (13.7)	465 (13.9)
Estrogen-receptor status — no. (%)					
Unknown	5 (0.6)	2 (0.2)	0	1 (0.1)	8 (0.2)
Negative	407 (46.7)	379 (47.0)	416 (48.1)	393 (48.6)	1595 (47.6)
Positive	460 (52.8)	426 (52.8)	448 (51.9)	414 (51.2)	1748 (52.2)
Progesterone-receptor status — no. (%)					
Unknown	7 (0.8)	2 (0.2)	1 (0.1)	4 (0.5)	14 (0.4)
Negative	504 (57.8)	472 (58.5)	526 (60.9)	486 (60.1)	1988 (59.3)
Positive	361 (41.4)	333 (41.3)	337 (39.0)	318 (39.4)	1349 (40.3)
Tumor size — no. (%)					
Unknown	19 (2.2)	10 (1.2)	12 (1.4)	4 (0.5)	45 (1.3)
≤2.0 cm	355 (40.7)	323 (40.0)	322 (37.3)	307 (38.0)	1307 (39.0)
2.1–4.0 cm	372 (42.7)	372 (46.1)	386 (44.7)	382 (47.3)	1512 (45.1)
≥4.1 cm	126 (14.4)	102 (12.6)	144 (16.7)	115 (14.2)	487 (14.5)
Tumor grade — no. (%)					
Unknown	21 (2.4)	14 (1.7)	15 (1.7)	15 (1.9)	65 (1.9)
Good	23 (2.6)	8 (1.0)	20 (2.3)	13 (1.6)	64 (1.9)
Intermediate	256 (29.4)	212 (26.3)	239 (27.7)	217 (26.9)	924 (27.6)
Poor	572 (65.6)	573 (71.0)	590 (68.3)	563 (69.7)	2298 (68.6)
Planned hormonal therapy — no. (%)					
Unknown	0	83 (10.3)	0	73 (9.0)	156 (4.7)
None	378 (43.3)	331 (41.0)	382 (44.2)	349 (43.2)	1440 (43.0)
Tamoxifen or aromatase inhibitor	494 (56.7)	393 (48.7)	482 (55.8)	386 (47.8)	1755 (52.4)
Intended paclitaxel schedule — no. (%)					
Every 3 wk	806 (92.4)	0	805 (93.2)	0	1611 (48.1)
Weekly	66 (7.6)	807 (100)	59 (6.8)	808 (100)	1740 (51.9)

gan treatment with trastuzumab and have completed therapy, 364 (31.4 percent) discontinued the treatment before 52 weeks. Reasons for discontinuation were recurrence in the case of 22 patients (1.9 percent), a confirmed asymptomatic decline in LVEF in 164 (14.2 percent), symptoms of congestive heart failure or other adverse cardiac effect in 54 (4.7 percent), noncardiac adverse effect or death

in 27 (2.3 percent), patient-initiated discontinuation in 70 (6.0 percent), and other reasons in 27 (2.3 percent).

DISEASE-FREE SURVIVAL, OVERALL SURVIVAL, AND TIME TO DISTANT RECURRENCE

The median follow-up was 2.0 years (2.4 years in trial B-31 and 1.5 years in trial N9831). There were 261 events in the control group and 133 events in the trastuzumab group. The hazard ratio for a first event in the trastuzumab group, as compared with the control group, was 0.48 (95 percent confidence interval, 0.39 to 0.59; P<0.0001) (Fig. 2A). The percentages of patients alive and disease-free at three years were 75.4 percent in the control group and 87.1 percent in the trastuzumab group (absolute difference, 11.8 percentage points; 95 percent confidence interval, 8.1 to 15.4 percentage points). At four years, the respective percentages were 67.1 percent and 85.3 percent (absolute difference, 18.2 percentage points; 95 percent confidence interval, 12.7 to 23.7 percentage points). This difference crossed the early stopping boundary.

There were 62 deaths in the trastuzumab group, as compared with 92 deaths in the control group (hazard ratio, 0.67; 95 percent confidence interval, 0.48 to 0.93; P=0.015) (Fig. 2B). The absolute survival rate at three years was 94.3 percent in the trastuzumab group and 91.7 percent in the control group (absolute difference, 2.5 percentage points; 95 percent confidence interval, 0.1 to 5.0 percentage points); at four years, the respective rates were 86.6 percent and 91.4 percent (absolute difference, 4.8 percentage points; 95 percent confidence interval, 0.6 to 9.0 percentage points).

Distant metastases were reported in 193 patients in the control group and 96 in the trastuzumab group. The hazard ratio for a first distant recurrence was 0.47 in the trastuzumab group as compared with the control group (95 percent confidence interval, 0.37 to 0.61; P<0.0001) (Fig. 3). At three years, 90.4 percent of women in the trastuzumab group were free of distant recurrence, as compared with 81.5 percent of women in the control group (absolute difference, 8.8 percentage points; 95 percent confidence interval, 5.5 to 12.1 percentage points); the respective rates at four years were 89.7 percent and 73.7 percent (absolute difference, 15.9 percentage points; 95 percent confidence interval, 11.1 to 20.8 percentage points).

SITES OF FIRST REPORTED EVENTS

The benefit of trastuzumab was evident at both local–regional and distant sites (Table 2). The num-

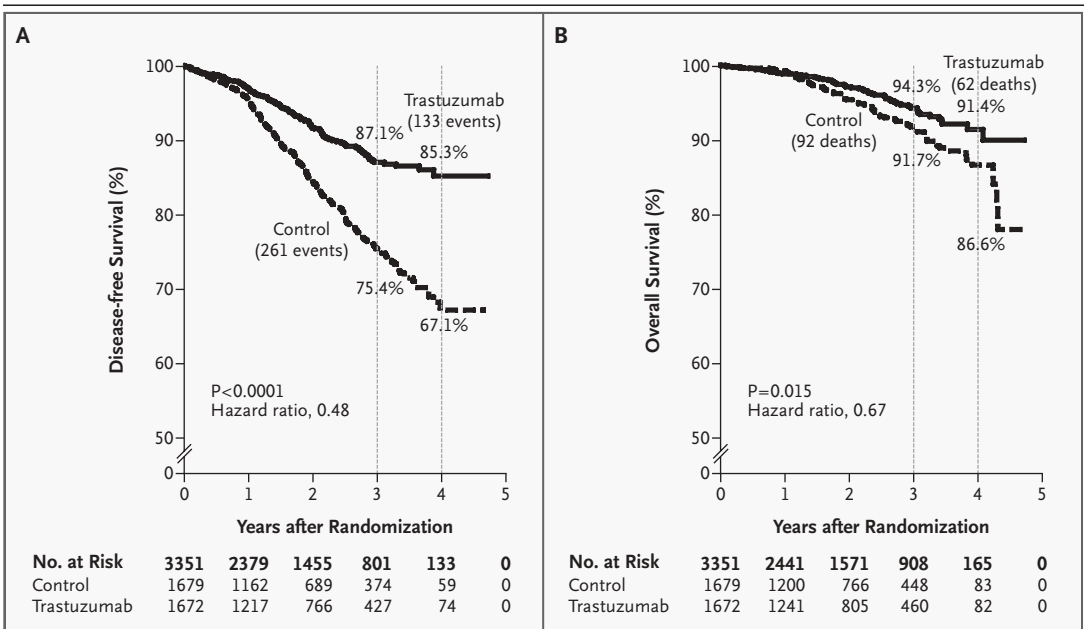

Figure 2. Kaplan–Meier Estimates of Disease-free Survival (Panel A) and Overall Survival (Panel B).
The hazard ratios are for the comparison of the trastuzumab group with the control group.

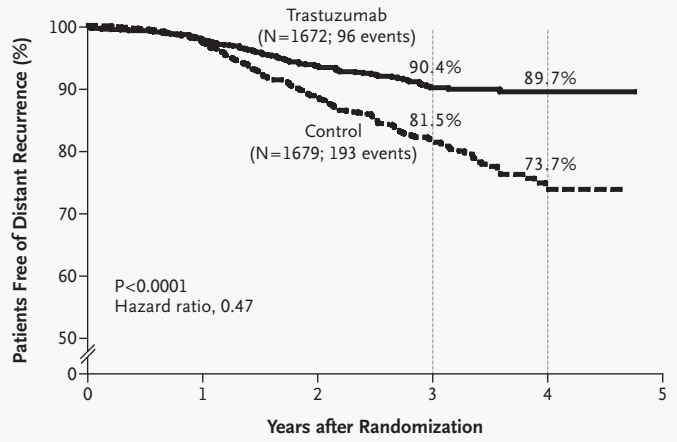

Figure 3. Kaplan–Meier Estimates of Freedom from Distant Recurrence.
The hazard ratios are for the comparison of the trastuzumab group with the control group.

ber of contralateral breast cancers was insufficient to evaluate the effect of trastuzumab. There was a reduction in nonbreast second primary cancers in trial B-31 in the trastuzumab group as compared with the control group, but the results of trial N9831 did not confirm (or refute) this trend.

Six patients in the control group died without recurrence or second cancers, as did eight patients in the trastuzumab group. These included three treatment-related deaths that occurred in patients who received paclitaxel and trastuzumab, one as a result of cardiomyopathy and two as a result of interstitial pneumonitis.

An increased frequency of brain metastases has been reported among patients with metastatic breast cancer treated with trastuzumab.[9-11] In both trials, the incidence of isolated brain metastases as first events was higher in the trastuzumab group than in the control group (21 vs. 11 in trial B-31 and 12 vs. 4 in trial N9831). Since patients in trial B-31 were followed for additional recurrences beyond the first distant event, we could determine whether the imbalance was due to masking of the incidence of brain metastases in the control group as a result of earlier failures in other organs. In trial B-31, brain metastases as a first or subsequent event were diagnosed in 28 patients in the trastuzumab group, as compared with 35 patients in the control group (hazard ratio, 0.79; P=0.35). The imbalance in brain metastases as first events can therefore be attributed to earlier failures at other distant sites among patients in the control group.

ADDITIONAL SECONDARY END POINTS

Table 3 summarizes additional secondary end points, including the time to recurrence, death from breast cancer, the occurrence of contralateral breast cancer, and the occurrence of other second primary cancers. Sites of second cancers are summarized in Table 4.

ESTIMATED TREATMENT BENEFIT AFTER ADJUSTMENT FOR ADDITIONAL CHARACTERISTICS

A Cox model was fitted to disease-free survival to control for treatment assignment, nodal status, pathological tumor size, hormone-receptor status, age, tumor grade, histologic appearance of the tumor, and trial. Adjustment for these factors minimally altered the effect of trastuzumab, as compared with that of control therapy (hazard ratio for a first

Table 2. Sites of First Events.

Patients	Trial B-31		Trial N9831	
	Control Group	Trastuzumab Group	Control Group	Trastuzumab Group
	number of patients			
All patients with follow-up	872	864	807	808
Patients alive and event-free	701	781	717	758
Patients with any first event	171	83	90	50
Local or regional recurrence	35	15	22	12
Distant recurrence	111	60	63	30
Contralateral breast cancer	6	2	0	1
Other second primary cancer	15	2	3	3
Death with no evidence of disease	4	4	2	4

Table 3. Summary of Efficacy End-Point Analyses.*

End Point	Trastuzumab Group	Control Group	Total	Hazard Ratio (95% CI)	P Value
	no. of patients				
Disease-free survival (primary end point)	133	261	394	0.48 (0.39–0.59)†	<0.0001
Time to recurrence	117	235	352	0.47 (0.38–0.59)	<0.0001
Time to distant recurrence	96	193	289	0.47 (0.37–0.61)	<0.0001
Overall survival	62	92	154	0.67 (0.48–0.93)‡	0.015
Death from breast cancer	53	79	132	0.66 (0.47–0.94)	0.02
Contralateral breast cancer	4	6	10	0.64 (0.18–2.27)	0.48
Other second primary cancer	5	20	25	0.24 (0.09–0.64)	0.002

* All P values were two-sided. CI denotes confidence interval.
† The hazard ratio is for a first event.
‡ The hazard ratio is for death.

event, 0.46; 95 percent confidence interval, 0.37 to 0.56; P<0.001). The number of positive nodes, pathological tumor size, hormone-receptor status, and tumor grade were significant predictors of disease-free survival. There was no evidence that the benefit of trastuzumab differed significantly between the two studies (P=0.38) (see Figure 1 in the Supplementary Appendix).

SUBGROUPS

A Forest plot of the hazard ratios for first events is shown in Figure 2 in the Supplementary Appendix. Only in subgroups in which there were a negligible number of events (negative nodes and a low tumor grade) did the 95 percent confidence interval fail to exclude 1. Plots of disease-free survival according to nodal and estrogen-receptor status are also shown in Figure 3 in the Supplementary Appendix.

SENSITIVITY ANALYSIS

A secondary analysis excluded ineligible patients, those who had received only doxorubicin and cyclophosphamide, those found on central testing to be HER2-negative, and those who had symptomatic cardiac dysfunction during therapy with doxorubicin and cyclophosphamide or reductions in LVEF that would preclude treatment with trastuzumab. As compared with the control group, the trastuzumab group had improved disease-free survival (hazard ratio for a first event, 0.45; P<0.0001), a longer time to recurrence (hazard ratio, 0.45; P<0.0001), a longer time to distant recurrence (hazard ratio, 0.46; P<0.0001), and improved overall survival (hazard ratio for death, 0.61; P=0.01).

VARIATION IN HAZARD RATES OVER TIME

Figure 4 in the Supplementary Appendix includes plots of the hazard rates for first events, first recurrence, distant recurrence, and death as a function of time since randomization. After the first year, the hazard rate for distant recurrence rose sharply in the control group; in the trastuzumab group, it first rose and then decreased markedly after year 2.

ADVERSE CARDIAC EVENTS

The principal adverse event associated with trastuzumab therapy among patients with prior exposure to anthracycline is cardiac dysfunction.[12,13] In trial B-31, of the patients who remained free of cardiac symptoms during doxorubicin and cyclophosphamide therapy and who had LVEF values that met requirements for the initiation of trastuzumab therapy, the cumulative incidence of New York Heart Association class III or IV congestive heart failure or death from cardiac causes at three years was 0.8 percent in the control group (4 patients had congestive heart failure, and 1 died from cardiac causes) and 4.1 percent in the trastuzumab group (31 patients had congestive heart failure). Of the 31 women in the trastuzumab group who had congestive heart failure, 27 have been followed for at least six months after the onset of heart failure, and only 1 reported persistent symptoms of heart failure at the most recent follow-up visit. Details of the cardiac effects of trastuzumab in trial B-31 are reported elsewhere.[14] In trial N9831, the three-year cumulative incidence of New York Heart Association class III or IV congestive heart failure or death from cardiac causes was 0 percent in the

Table 4. Incidence of Second Primary Cancers.

Site or Type of Second Primary Cancer	Control Group	Trastuzumab Group	Total
		no. of patients	
Esophagus	1	1	2
Stomach	0	1	1
Colon	1	0	1
Pancreas	1	0	1
Lung	2	1	3
Bone	1	0	1
Melanoma	3	0	3
Contralateral breast	6	4	10
Endometrium	1	1	2
Ovary	3	0	3
Thyroid	4	0	4
Multiple myeloma	1	0	1
Acute myelogenous leukemia	2	1	3
Total	26	9	35

control group and 2.9 percent in the trastuzumab group (20 patients had congestive heart failure, 1 of whom died of cardiomyopathy).

OTHER ADVERSE EVENTS

During treatment with paclitaxel alone or with trastuzumab, there was little imbalance between treatment groups in the incidence of any Common Toxicity Criteria version 2.0 category except for a higher incidence of left ventricular dysfunction in the trastuzumab group. However, rare cases of interstitial pneumonitis were reported that in some cases appeared to be related to trastuzumab therapy. In trial B-31, four patients in the trastuzumab group had interstitial pneumonitis, one of whom died. In the N9831 trial, five patients in the trastuzumab group had grade 3+ pneumonitis or pulmonary infiltrates, one of whom died.

DISCUSSION

The addition of trastuzumab to paclitaxel after a regimen of doxorubicin and cyclophosphamide reduced the rates of recurrence by half among women with HER2-positive breast cancer. The absolute decreases in distant recurrence were 8.8 percentage points after three years and 15.9 percentage points after four years, although the latter value had a wide confidence interval (11.1 to 20.8 percentage points). The reduction was similar among women with hormone-receptor–negative tumors and women with hormone-receptor–positive tumors. No subgroups that did not appear to benefit from trastuzumab therapy were identified. Since only 191 women with node-negative breast cancer were included in these studies and only 3 had had an event at the time of the analysis, we cannot comment on the effect of trastuzumab in this subgroup.

The addition of trastuzumab reduced the mortality rate by one third (P=0.015). Among eligible patients who continued treatment after doxorubicin and cyclophosphamide and who were HER2-positive on central testing, the relative reduction in the mortality rate associated with trastuzumab was 39 percent (P=0.01). Although relatively little follow-up information is available beyond three years, current data rule out a risk of distant recurrence among trastuzumab-treated women of greater than 27 per 1000 women per year, in contrast to a risk of 90 per 1000 women per year in the control group (see Figure 4 in the Supplementary Appendix). Since the risk of distant recurrence should remain appreciable in the control group for some time, a substantial additional survival benefit related to trastuzumab can be anticipated.

The effect of trastuzumab was substantial in both trials (see Figure 1 in the Supplementary Appendix), a finding that is noteworthy given differences in the paclitaxel schedule and the timing of hormonal therapy. The benefit of trastuzumab was evident at local or regional and distant sites. Although isolated brain metastases were more common first events in the trastuzumab group than in the control group, the imbalance can be attributed to the occurrence of earlier failures at other distant sites in the control group.

Data from trial B-31 suggested that trastuzumab reduced the incidence of nonbreast second primary cancers, an unanticipated effect requiring independent verification. There was no obvious pattern of site or histologic type (Table 4).

The primary concern regarding the safety of trastuzumab is the increased risk of cardiac dysfunction associated with past or concurrent anthracycline treatment.[12,13] In both studies, the cumulative three-year incidence of congestive heart failure increased by about 3 percentage points with the addition of trastuzumab. Most episodes occurred during trastuzumab treatment, but additional follow-up will be needed to define the long-term

cardiotoxicity of trastuzumab. Clearly, appropriate selection and careful cardiac monitoring of patients are essential. Trastuzumab did not increase the overall frequency or severity of noncardiac adverse effects associated with the chemotherapy regimens, but we did see rare cases of interstitial pneumonitis in patients receiving trastuzumab during or shortly after the paclitaxel phase of treatment. Two cases were fatal.

Trial N9831 was also designed to address the efficacy of trastuzumab initiated concurrently with paclitaxel as opposed to sequentially (group C vs. group B), but this comparison requires substantially longer follow-up than was needed for the assessment of concurrent trastuzumab therapy in the joint analysis. However, after reviewing the results of the first joint interim efficacy analysis, the data-monitoring committee overseeing trial N9831 requested an unplanned comparison of groups B and C and subsequently recommended disclosure of the results. Though early, the comparison suggested delayed administration of trastuzumab may be less effective than concurrent administration.[15] Recent data from the Herceptin Adjuvant (HERA) Trial showed that treatment with trastuzumab begun after the completion of chemotherapy substantially reduced the rate of recurrence relative to the rate associated with chemotherapy alone.[16] Since only 26 percent of patients received taxanes in the HERA trial, comparison of those results with ours may be problematic. Therefore, further follow-up of groups B and C in trial N9831 is necessary for an adequate evaluation of the efficacy of concurrent as compared with sequential administration of trastuzumab.

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APPENDIX

The following institutions and principal investigators enrolled at least 25 patients in the B-31 trial or N9831 trial: **Trial B-31** — Kaiser Permanente, Northern California Region, Vallejo, Calif., L. Fehrenbacher; University of Pittsburgh, Pittsburgh, V.G. Vogel; Atlanta Regional Community Clinical Oncology Program (CCOP), Atlanta, T.E. Seay; Colorado Cancer Research Program, CCOP, Denver, E.R. Pajon; Metro Minnesota CCOP, St. Louis Park, Minn., P.J. Flynn; Franklin Square Hospital Center, Baltimore, J.L. Zapas; Kaiser Permanente, San Diego, Calif., J. Polikoff; Dayton CCOP, Dayton, Ohio, H.M. Gross; Christiana Care Health Services CCOP, Newark, Del., D.D. Biggs; Southeast Cancer Control Consortium CCOP, Winston-Salem, N.C., J.N. Atkins; Huntsman Cancer Institute, Salt Lake City, Utah, R.D. Noyes; Puget Sound Oncology Consortium, Seattle, R.B. Clarfeld; Columbus CCOP, Columbus, Ohio, J.P. Kuebler; Northwest CCOP, Tacoma, Wash., L.K. Colman; Scripps Clinic, La Jolla, Calif., J.F. Kroener; Illinois Oncology Research Association CCOP, Peoria, J.W. Kugler; Evanston Northwestern Healthcare CCOP/Kellogg Cancer Center, Evanston, Ill., D. Merkel; Kansas City CCOP, Kansas City, Mo., W.T. Stephenson; Montana Cancer Consortium CCOP, Billings, P.W. Cobb; **Trial N9831** — Indiana University Cancer Center, Indianapolis, P.J. Loehrer; Johns Hopkins University, Baltimore, A.A. Forastiere; Vanderbilt University, Nashville, D.H. Johnson; Northern New Jersey CCOP, Hackensack, R.J. Rosenbluth; University of Chicago Medical Center, Chicago, G. Fleming; Dana–Farber Cancer Institute, Boston, G.P. Canellos; Duke University Medical Center, Durham, N.C., J. Crawford; Mount Sinai School of Medicine, New York, L.R. Silverman; Memorial Sloan-Kettering Cancer Center, New York, C. Hudis; Loyola University Medical Center, Maywood, Ill., P.J. Stiff; Ohio State University Medical Center, Columbus, C.D. Bloomfield; Georgetown University Medical Center, Washington, D.C., E. Gelmann; Moffitt Cancer Center, Tampa, Fla., J.A. Kish; Mayo Clinic, Rochester, Minn., S.R. Alberts; Toledo CCOP, Toledo, Ohio, P.L. Schaefer; Metro Minnesota CCOP, St. Louis Park, Minn., P.J. Flynn; Wichita CCOP, Wichita, Kans., S. Dakhil; Ann Arbor CCOP, Ann Arbor, Mich., P.J. Stella; Missouri Valley Cancer Consortium CCOP, Omaha, Nebr., J.A. Mailliard.

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