VOLUME 29 · NUMBER 25 · SEPTEMBER 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Four-Year Follow-Up of Trastuzumab Plus Adjuvant Chemotherapy for Operable Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Joint Analysis of Data From NCCTG N9831 and NSABP B-31

Edith A. Perez, Edward H. Romond, Vera J. Suman, Jong-Hyeon Jeong, Nancy E. Davidson, Charles E. Geyer Jr, Silvana Martino, Eleftherios P. Mamounas, Peter A. Kaufman, and Norman Wolmark

Edith A. Perez, Mayo Clinic, Jacksonville, FL; Edward H. Romond. University of Kentucky, Lexington, KY; Vera J. Suman, Mayo Clinic, Rochester, MN; Jong-Hyeon Jeong, University of Pittsburgh; Nancy E. Davidson, University of Pittsburgh Cancer Institute; Charles E. Geyer Jr and Norman Wolmark, Allegheny General Hospital, Pittsburgh, PA; Silvana Martino, The Angeles Clinic and Research Institute, Santa Monica, CA; Eleftherios P. Mamounas, Aultman Cancer Center, Canton, OH; and Peter A. Kaufman, Dartmouth Hitchcock Medical Center, Lebanon, NH.

Submitted February 10, 2011; accepted May 16, 2011; published online ahead of print at www.jco.org on July 18, 2011.

Written on behalf of the North Central Cancer Treatment Group N9831 and the National Surgical Adjuvant Breast and Bowel Project B-31 trial teams.

Supported by National Institutes of Health Grants No. U10-CA25224 and RO1-CA129949; National Surgical Adjuvant Breast and Bowel Project Grants No. U10-CA12027, U10-CA69651, U10-CA37377, and U10-CA69974; the Breast Cancer Research Foundation; and Genentech (35-03). P.A.K. received research funding from Cancer and Leukemia Group B.

Presented in part at the 43rd Annual Meeting of the American Society of Clinical Oncology, June 1-5, 2007, Chicago, IL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Edith A. Perez, MD, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224; e-mail: perez.edith@mayo.edu.

0732-183X/11/2925-3366/$20.00

DOI: 10.1200/JCO.2011.35.0868

ABSTRACT

Purpose
Trastuzumab is a humanized monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). The clinical benefits of adjuvant trastuzumab have been demonstrated in interim analyses of four large trials. Initial data of the combined analysis of the North Central Cancer Treatment Group (NCCTG) N9831 Intergroup trial and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial were reported in 2005. Long-term follow-up results on disease-free survival (DFS) and overall survival (OS) have been awaited.

Patients and Methods
Patients with HER2-positive operable breast cancer were randomly assigned to doxorubicin plus cyclophosphamide followed by paclitaxel with or without trastuzumab in the NCCTG N9831 and NSABP B-31 trials. The similar design of both trials allowed data from the control and trastuzumab-containing arms to be combined in a joint analysis.

Results
At 3.9 years of median follow-up, there continues to be a highly statistically significant reduction in DFS event rate in favor of the trastuzumab-containing arm ($P < .001$). Similarly, there continues to be a statistically significant 39% reduction in death rate in favor of the trastuzumab-containing arm ($P < .001$).

Conclusion
These data demonstrate consistent DFS and OS advantages of adjuvant trastuzumab over time, with the longest follow-up reported to date. The clinical benefits continue to outweigh the risks of adverse effects.

J Clin Oncol 29:3366-3373. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Trastuzumab[1] is a humanized monoclonal antibody against the human epidermal growth factor receptor 2 (HER2), which is amplified and/or overexpressed in about 15% to 20% of invasive breast cancers.[2-4] HER2-positive breast tumors are more aggressive and more susceptible to recurrence than HER2-normal tumors.[4,5]

In the metastatic setting, trastuzumab provides significant clinical benefit as monotherapy and in combination with chemotherapy as either first- or second-line therapy.[6-11] Significant clinical benefits of trastuzumab in the treatment of early-stage breast cancer have also been observed. Four large trials (and several smaller trials) evaluating adjuvant trastuzumab demonstrated significant improvements in disease-free survival (DFS; 36% to 52% reduction in DFS events) and overall survival (OS; 33% to 37% reduction in deaths), irrespective of tumor size, nodal status, hormone receptor status, or age.[12-16] On the basis of data from these trials, adjuvant trastuzumab has become the foundation of care for HER2-positive early breast cancer.

The North Central Cancer Treatment Group (NCCTG) N9831 and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trials assessed the efficacy and safety of adding 52 weeks of trastuzumab to standard anthracycline/taxane-based chemotherapy (doxorubicin plus cyclophosphamide [AC] followed by paclitaxel). These trials were designed similarly, enabling a joint analysis of the two studies. The interim analysis reported in 2005, with a median follow-up of 2 years, demonstrated a 52% reduction in DFS event rate with the addition of trastuzumab ($P < .001$) and a 33% early improvement in OS ($P = .015$).[13] Data from a second interim analysis with a median follow-up of 2.9

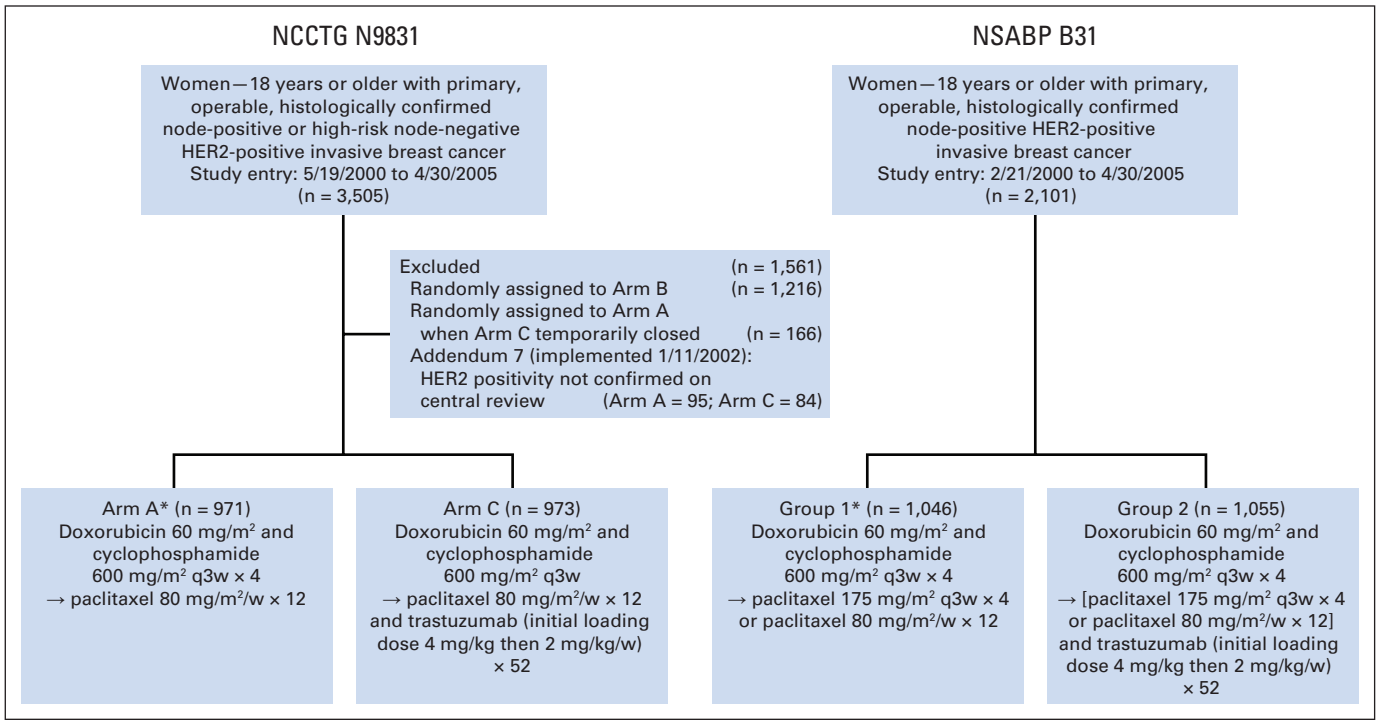

Fig 1. CONSORT diagram. HER2, human epidermal growth factor receptor 2; q3w, every 3 weeks; w, weeks.

years presented at the American Society of Clinical Oncology annual meeting in 2007 demonstrated a continued reduction in DFS event rate and a statistically significant 35% reduction in mortality ($P < .001$).[12]

Determining the long-term implications of adjuvant trastuzumab is of great value for patient care. The first joint analysis of N9831 arms A and C with B-31 arms 1 and 2 was based on the 3,351 patients who enrolled before a prespecified calendar date and had at least one follow-up evaluation. Here, we present the findings of the joint analysis based on all 4,045 patients enrolled onto these treatment arms before the enrollment was terminated.

PATIENTS AND METHODS

Study Design

The NCCTG N9831 trial is a three-arm phase III randomized trial. Eligible patients were randomly assigned to AC followed by weekly paclitaxel (control arm, arm A); AC followed by weekly paclitaxel followed by trastuzumab (sequential arm, arm B); or AC followed by weekly paclitaxel plus trastuzumab followed by trastuzumab alone (concurrent arm, arm C). Radiation and/or hormonal therapy were administered after completion of chemotherapy, when indicated (Fig 1, Fig 2).

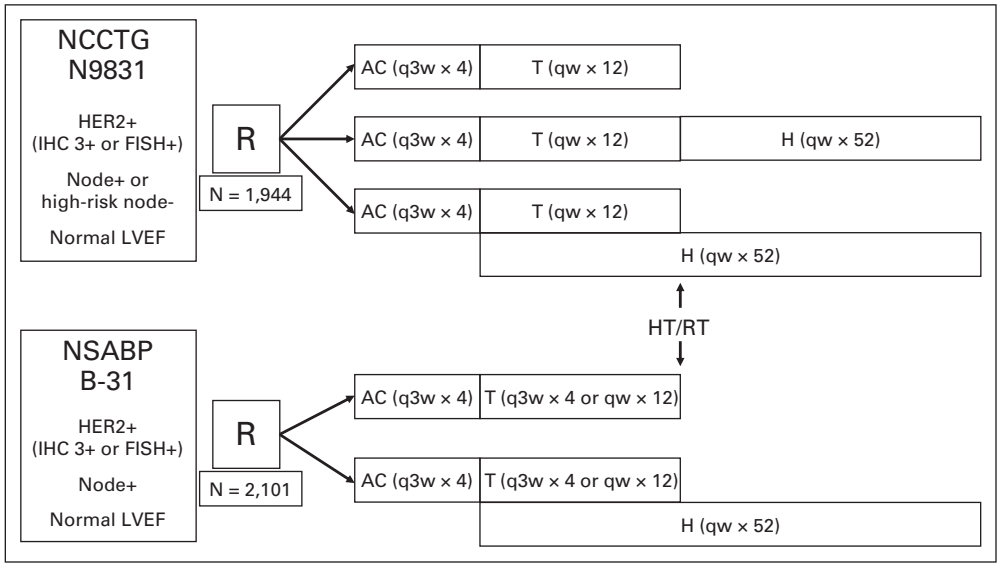

Fig 2. Trial schema of North Central Cancer Treatment Group (NCCTG) N9831 and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31. Timing of chemotherapy, trastuzumab (H), radiation therapy (RT), and hormonal therapy (HT) in B-31 and N9831. AC, doxorubicin and cyclophosphamide; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; LVEF, left ventricular ejection fraction; q3w, every 3 weeks; qw, every week; T, paclitaxel.

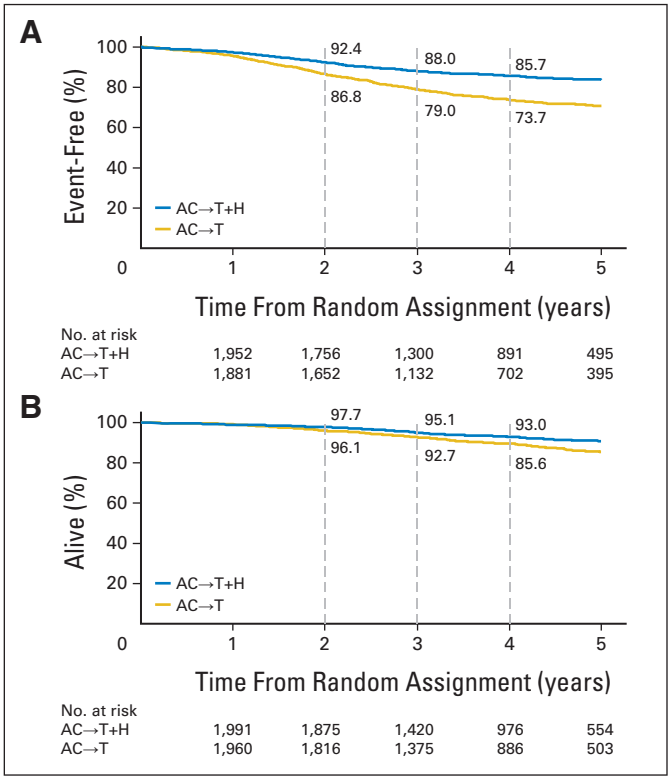

Fig 3. Kaplan-Meier estimates of (A) event-free survival and (B) overall survival. Disease events include local, regional, or distant recurrence; contralateral breast cancer; second primary cancers; or death as a result of any cause. Overall survival is measured from the time of study enrollment to last contact or death. AC, doxorubicin and cyclophosphamide; H, trastuzumab; T, paclitaxel.

The NSABP B-31 trial is a two-arm phase III randomized trial. Eligible patients were randomly assigned to AC followed by paclitaxel every 3 weeks (arm 1) or to AC followed by paclitaxel every 3 weeks plus trastuzumab followed by trastuzumab alone (arm 2). An amendment allowing the option of administering weekly paclitaxel was activated after 39 months of accrual to B-31. When indicated, radiation therapy was given after completion of chemotherapy. Hormonal therapy was given at the start of AC before January 14, 2003, and after that, after completion of chemotherapy (Fig 1, Fig 2).

For purposes of the joint analysis, arm A from NCCTG N9831 and arm 1 from NSABP B-31 were combined for the control arm as were arm C from N9831 and arm 2 from B-31 for the trastuzumab arm; both were approved by the study teams, the National Cancer Institute (NCI), and the US Food and Durg Administration.

Eligibility

Women age ≥ 18 years with primary, operable, and histologically confirmed node-positive (both trials) or high-risk node-negative invasive breast cancer (N9831 only), with no evidence of metastases, were eligible. Tumors had to be strongly HER2 positive (immunohistochemistry [IHC] score of 3+ by reference laboratory testing or gene amplified by fluorescence in situ hybridization [FISH]) by local or reference laboratory testing (B-31) or confirmed at the study central laboratory (N9831) using the manufacturer's definition. This was done using ≥ 10% positive membrane stain as the cutoff for IHC and HER2:CEP17 ratio of ≥ 2.0 or ≥ four copies of the *HER2* gene for FISH eligibility. Additional requirements included adequate hematopoietic, hepatic, and renal function and a left ventricular ejection fraction (LVEF) greater than or equal to the institution's lower limit of normal (LLN).

Contraindications to study entry included angina pectoris or arrhythmia requiring medications, severe conduction abnormality, significant valvular heart disease, cardiomegaly on chest radiography, left ventricular hypertrophy on echocardiography (B-31), poorly controlled hypertension, clinically significant pericardial effusion (N9831), or a history of myocardial infarction, congestive heart failure (CHF), or cardiomyopathy. Participating institutions obtained approval from their institutional review board and filed assurances with the Department of Health and Human Services. Written informed consent was required for enrollment.

LVEF Requirements

Initiation of trastuzumab was not permitted in patients whose LVEF had decreased by more than 15 percentage points from registration value, irrespective of the LLN, or ≤ 15 percentage points from registration level to less than the LLN, at the post-AC (3-month) LVEF evaluation. For these patients, the study did not allow initiation of trastuzumab even if a repeat LVEF assessment was ≥ the LLN. Trastuzumab was not permitted in patients who showed symptoms related to left ventricular dysfunction, cardiac ischemia, or arrhythmia while receiving AC.

After release of the first joint analysis results at the American Society of Clinical Oncology annual meeting in 2005, patients previously randomly assigned to arm A of N9831 were allowed to receive trastuzumab if they had an acceptable LVEF level compared with value at registration and 6 months, at most, had passed since completion of chemotherapy. Patients randomly assigned to arm 1 of B-31 were allowed to receive trastuzumab if they were receiving AC or paclitaxel at the time when study results were disclosed, or if they had been randomly assigned on or after April 26, 2004, had completed chemotherapy, and had met the protocol requirements regarding post-AC LVEF scan results to initiate the investigational trastuzumab.

Role of the Funding Source

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 trials, collection, or data analyses. The joint analysis was developed and analyzed by the NCCTG and NSABP, with approval obtained from the NCI and US Food and Drug Administration.

Statistical Analysis

The joint analysis included all patients enrolled onto B-31 and onto N9831 from arms A and C, excluding 152 patients in arm A who were randomly assigned between January 24, 2002, and September 2, 2002 (while accrual to arm C was temporarily suspended), and 193 patients whose disease was found not to be *HER2* gene amplified by FISH and/or IHC 3+ by central testing after the implementation of Addendum 7 (required HER2-positive status by central testing) in the protocol. Patients randomly assigned to arm 1 of B-31 and arm A of N9831 who received trastuzumab after release of the first joint analysis results were included in the analysis according to their original treatment assignment (Fig 1).

The primary study end point was DFS, defined as the time from random assignment to documentation of the first of the following events: local, regional, or distant recurrence of breast cancer; a contralateral breast cancer; a second primary cancer; or death as a result of any cause. Patients alive without a disease event were censored at the time of their last disease evaluation (ie, patients randomly assigned to the non–trastuzumab-containing regimens who chose to receive trastuzumab after the release of the first joint analysis of N9831 and B-31 were not censored when they began trastuzumab). Secondary end points included OS, time to recurrence, death from breast cancer, contralateral breast cancer, and other second primary cancers. OS was defined as the time from random assignment to death as a result of any cause.

The overall distributions of DFS and OS were estimated using the Kaplan-Meier method. Stratified proportional hazards modeling was used to assess whether DFS or OS differed with respect to treatment. The strata were study (B-31 *v* N9831), intended paclitaxel schedule (every 3 weeks *v* weekly), number of positive nodes (zero to three *v* four to nine *v* ≥ 10 nodes), and hormone receptor status (estrogen receptor and/or progesterone receptor positive *v* estrogen receptor and progesterone receptor negative). Age, tumor size, and tumor grade were assessed for their impact on DFS and OS. Proportional hazards modeling was then used to assess the impact of trastuzumab on DFS and OS after adjusting for the stratification factors and other significant patient or disease characteristics.

RESULTS

The study cohort consisted of the 2,101 women enrolled onto B-31 and the 1,944 women enrolled onto arm A or arm C of N9831 during the period both arms were open to enrollment and who, after January 11, 2002, were found to have *HER2* gene amplification or IHC 3+ disease by central or reference laboratory testing. Pretreatment characteristics of these 4,045 women are listed in Table 1. The study populations differ because women with high-risk, node-negative disease were eligible for N9831 but not for B-31; 14.5% of patients enrolled onto N9831 had node-negative disease.

AC Chemotherapy

Thirty-nine women (29 on the control arm and 10 on the trastuzumab arm) did not begin study treatment because they were found to be ineligible or refused their assigned treatment. Of the

Table 1. Patient Demographics and Clinical Characteristics

	B-31				N9831			
	Control Arm (n = 1,046)		Trastuzumab Arm (n = 1,055)		Control Arm (n = 971)		Trastuzumab Arm (n = 973)	
Demographic or Characteristic	No. of Patients	%*	No. of Patients	%*	No. of Patients	%*	No. of Patients	%*
Age at random assignment, years								
18-39	170	16.3	172	16.3	163	16.8	150	15.4
40-49	351	33.6	367	34.8	324	33.4	329	33.8
50-59	355	33.9	343	32.5	328	33.8	310	31.9
≥ 60	170	16.3	173	16.4	156	16.1	184	18.9
Extent of surgery								
Mastectomy	628	60.0	640	60.7	587	60.5	603	62.0
Breast sparing	407	38.9	408	38.7	383	39.4	370	38.0
Unknown	11	1.1	7	0.7	1	0.1	0	0
Tumor size, cm								
≤ 2.0	422	40.3	401	38.0	392	40.4	370	38.0
2.1-5.0	527	50.4	528	50.1	509	52.4	521	53.6
> 5.0	79	7.6	112	10.6	69	7.1	82	8.4
Unknown	18	1.7	14	1.3	1	0.1	0	0
Histologically positive nodes								
0	0	0	0	0	149	15.4	133	13.7
1-3	601	57.5	611	57.9	456	47.0	476	48.9
4-9	304	29.1	302	28.6	236	24.3	240	24.7
≥ 10	141	13.5	142	13.5	129	13.3	124	12.7
Unknown	0	0	0	0	1	0.1	0	0
Tumor grade								
1	29	2.8	23	2.2	10	1.0	14	1.4
2	311	29.7	289	27.4	256	26.4	259	26.6
3	683	65.3	724	68.6	693	71.4	684	70.3
Unknown	23	2.2	19	1.8	12	1.2	16	1.6
Estrogen receptor status								
Positive	547	52.3	549	52.0	499	51.4	484	49.7
Negative	488	46.7	499	47.3	471	48.5	489	50.3
Unknown	11	1.0	7	0.7	1	0.1	0	0
Progesterone receptor status								
Positive	422	40.3	410	38.9	383	39.4	369	37.9
Negative	611	58.4	637	60.4	587	60.5	601	61.8
Unknown	13	1.2	8	0.8	1	0.1	3	0.3
Intended paclitaxel schedule								
Every 3 weeks	878	83.9	885	83.9	0	0	0	0
Weekly	168	16.1	170	16.1	971	100	973	100
Adjuvant radiation therapy								
Yes	800	76.5	811	76.9	631	65.0	655	67.3
No	246	24.5	244	24.1	246	25.3	256	26.3
Unknown	0	0	0	0	94	9.7	62	6.4
Hormonal therapy								
Yes	585	55.9	591	56.0	498	51.3	496	51.0
No	461	44.1	464	44.0	461	47.5	470	48.3
Unknown	0	0	0	0	12	1.2	7	0.7

*Percentages have been rounded.

Table 2. First DFS Events by Trial Arms

Event	B-31				N9831			
	Control Arm (n = 1,046)		Trastuzumab Arm (n = 1,055)		Control Arm (n = 971)		Trastuzumab Arm (n = 973)	
	No. of Patients	%*	No. of Patients	%*	No. of Patients	%*	No. of Patients	%*
Patients with a DFS event	290	27.7	162	15.3	199	20.5	128	13.2
DFS events								
Local, regional, or distant recurrence	243	23.2	137	13.0	174	17.9	100	10.3
Contralateral breast cancer	10	1.0	7	0.7	5	0.5	9	0.9
Other second primary cancer	28	2.7	11	1.0	15	1.5	12	1.2
Death without evidence of disease	9	0.9	8	0.8	5	0.5	7	0.7
No. of DFS events with brain involvement	17		32		19		29	

Abbreviation: DFS, disease-free survival.
*Percentages have been rounded.

4,006 women who began AC chemotherapy, 101 women (2.5%) did not complete all four treatment cycles; 174 women (4.3%) completed AC chemotherapy but met the criteria for preclusion of trastuzumab because of cardiac symptoms or a post-AC LVEF that declined by ≥ 16 percentage points from pretreatment levels or declined to less than the institutional LLN; 3,646 women (91.0%) completed AC chemotherapy with a satisfactory post-AC cardiac evaluation; and 85 women (2.1%) completed AC without undergoing a post-AC cardiac evaluation.

Paclitaxel ± Trastuzumab

After initial results of the joint analysis released in April 2005, 339 patients randomly assigned to the control arm received trastuzumab (concurrently with paclitaxel or up to 6 months after the completion of AC). The durations of trastuzumab among the 1,845 patients randomly assigned to a trastuzumab-containing regimen who began post-AC treatment were as follows: none (4.7%); 0.1 to 3 months (7.9%); 3.1 to 6 months (7.9%); 6.1 to 9 months (5.1%); and 9.1 to 12 months (74.5%). Cardiac adverse events including asymptomatic decreases in LVEF (n = 259), confirmed CHF (n = 41), and other severe (NCI Common Toxicity Criteria version 2.0 grade ≥ 3) cardiac toxicities (n = 20) led to the early discontinuation of trastuzumab in the patients who experienced these events. The overall CHF rates (based on assessment by the patient's primary oncology team) were 1.3% and 0.9% in the control arms of B-31 and N9831, respectively, and 3.8% and 2.3% in the concurrent trastuzumab arms of B-31 and N9831, respectively.

Clinical Course

The median follow-up time of patients alive at last contact was 3.9 years (for the combined trials). Among the 2,028 women on the trastuzumab arm at last contact, 1,739 women (85.8%) are alive without evidence of disease; 143 women (7.1%) are alive with disease recurrence, a second primary cancer, and/or contralateral breast disease; 131 women (6.5%) are dead with disease recurrence, second primary cancer, and/or contralateral breast disease; three women (< 0.1%) are dead as a result of treatment-related causes; and 12 women (0.6%) are dead without disease recurrence as a result of other or unknown causes.

Among the 2,017 women on the control arm at last contact, 1,528 women (75.8%) are alive without evidence of disease; 261 women (12.9%) are alive with disease recurrence, a second primary cancer, and/or contralateral breast disease; 214 women (10.6%) are dead with disease recurrence, second primary cancer, and/or contralateral breast disease; two women (< 0.1%) are dead as a result of treatment-related causes; and 12 women (0.6%) are dead without disease recurrence as a result of other or unknown causes.

Impact of Trastuzumab on DFS

The types of first disease event for each treatment group are listed in Table 2. Women randomly assigned to the trastuzumab arm had a significantly increased DFS ($P < .001$; stratified hazard ratio [HR], 0.52; 95% CI, 0.45 to 0.60; Fig 2A) and OS ($P < .001$; stratified HR, 0.61; 95% CI, 0.50 to 0.75; Fig 2B) compared with women randomly assigned to the control arm.

The incidence of a DFS event per 1,000 women per year for each year of follow-up is shown in Appendix Figure A1 (online only). There is a marked increase in this incidence in both treatment arms 12 to 24 months after registration (ie, for the trastuzumab-containing regimens, the last 6 months of trastuzumab and the first 6 months of no adjuvant systematic therapy). Notably, there is a continued dampening of the incidence of a DFS event after the discontinuation of trastuzumab compared with the control group.

Table 3 lists the results of multivariate proportional hazards modeling. OS was significantly decreased for women with larger tumors who were older than age 60 years at study entry after accounting for the stratification factors. Moreover, women randomly assigned to the trastuzumab arm had a significantly increased OS (adjusted HR, 0.59; 95% CI, 0.48 to 0.73) after adjusting for all these factors (Table 3).

DFS was also found to be significantly decreased for women with larger tumors after accounting for the stratification factors. Moreover, women randomly assigned to the trastuzumab arm had a significantly increased DFS (adjusted HR, 0.51; 95% CI, 0.44 to 0.59) after adjusting for these factors (Table 3). Appendix Figure A2 (online only) depicts the hazard of a DFS event among women randomly assigned to trastuzumab-containing regimen relative to women randomly assigned to nontrastuzumab regimen in a variety of patient subpopulations. In addition, Table 4 lists the 4-year DFS rates in these subpopulations by regimen.

Table 3. Estimated HRs From Multivariate Proportional Hazards Modeling

Factor	DFS		Overall Survival	
	HR	95% CI	HR	95% CI
No. of positive nodes				
0-3	1.00		1.00	
4-9	1.50	1.27 to 1.77	1.77	1.39 to 2.28
10+	2.79	2.34 to 3.34	3.43	2.66 to 4.42
Intended paclitaxel schedule				
Weekly	1.00		1.00	
Every 3 weeks	1.43	1.01 to 2.03	1.23	0.71 to 2.13
Receptor status				
ER and PR negative	1.00		—	
ER or PR positive	0.66	0.57 to 0.76	0.57	0.46 to 0.69
Trial				
B-31	1.00		1.00	
N9831	1.12	0.79 to 1.60	0.96	0.55 to 1.66
Tumor size, cm				
≤ 2	1.00		1.00	
2.01-5.0	1.62	1.38 to 1.91	1.51	1.19 to 1.90
> 5.0	2.20	1.73 to 2.79	1.64	1.16 to 2.32
Age, years				
< 60	—		1.00	
≥ 60	—		1.38	1.08 to 1.76
Treatment arm				
Control arm	1.00		1.00	
Trastuzumab arm	0.51	0.44 to 0.59	0.59	0.48 to 0.73

Abbreviations: DFS, disease-free survival; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.

Table 4. N9831/B-31 Joint Analysis

Factor	4-Year DFS Rate by Regimen (%)	
	Control Arm (n = 2,017)	Trastuzumab Arm (n = 2,028)
Age, years		
< 40	69.2	84.2
40-49	75.7	87.4
50-59	75.8	84.6
≥ 60	70.0	86.1
No. of positive nodes		
0	89.6	86.9
1-3	80.6	89.7
4-9	71.1	83.5
≥ 10	46.5	73.7
Hormone receptors		
ER and PR negative	69.4	81.6
ER and/or PR positive	77.2	89.4
Tumor size, cm		
0-2	81.6	90.9
2.1-5.0	70.3	83.2
> 5.0	52.0	78.2
Tumor grade		
Low/intermediate	77.0	88.5
High	72.0	84.4

Abbreviations: DFS, disease-free survival; ER, estrogen receptor; PR, progesterone receptor.

DISCUSSION

These updated joint analysis data indicate that after 4-years of follow-up, the addition of adjuvant trastuzumab to chemotherapy maintains both a significant DFS and OS benefit compared with chemotherapy alone. At the time of the initial report (with median follow-up of 2 years),[13] the relative reduction in DFS event rate was 52% (HR, 0.48; $P < .001$), and at 2.9 years, the relative reduction in death rate was 35% (HR, 0.65; $P < .001$).[12] With the additional follow-up, the relative reduction in DFS event rate was 48% ($P < .001$), and the relative reduction in death rate was 39% ($P < .001$). Thus, our data demonstrate long-term continued benefit with trastuzumab administered concurrently with chemotherapy (anthracycline/cyclophosphamide followed by paclitaxel + trastuzumab, with 1 year of trastuzumab treatment). Absolute differences in DFS increased by number of nodes; it was most pronounced for patients with ≥ 10 involved nodes, who had an unprecedented 27% absolute improvement.

Cardiac safety in these trials has been studied extensively.[17-20] In N9831, at a median follow-up of 3.75 years, the 3-year cumulative incidence of cardiac events (ie, symptomatic CHF or probable or definite cardiac death) was 0.3% without trastuzumab, 2.8% with sequential paclitaxel and trastuzumab, and 3.3% with concurrent paclitaxel and trastuzumab.[18] There was no evidence of a significant increase in cardiac events over time.[18] In B-31, the 5-year cumulative incidence of cardiac events was 0.9% without trastuzumab and 3.8% with concurrent paclitaxel and trastuzumab.[19] There was no evidence of an increase in cardiac events over time.[19] The findings of an independent board of cardiologists reviewing the data from patients reported to have had cardiac events (n = 173) in N9831 and B-31 have recently been reported.[20] The panel concluded that the rate of symptomatic heart failure was 0.5% with chemotherapy alone and 2.0% with AC followed by paclitaxel and trastuzumab. Moreover, the panel reported that 86% of patients (31 of 36 patients) in the trastuzumab arms had either complete or partial resolution of the cardiac event in follow-up. Analyses of risk factors for cardiac events in N9831 have shown that patients ≥ 60 years old ($P = .003$), patients with prior or current use of antihypertensive medication ($P = .005$), and patients with LVEF near the LLN at registration ($P = .033$) were at increased risk for such events.[18] On the basis of our own data, we are reassured of the favorable therapeutic ratio (benefit over toxicity) of the AC followed by paclitaxel/trastuzumab adjuvant regimen as administered in NCCTG N9831 and NSABP B-31.[12,13,17-20]

A marked increase in the incidence of a DFS event was noted 1 year after random assignment in both treatment arms. This is an expected pattern in the clinical course of these patients, but the trastuzumab-containing arm continued to report a lower disease incidence after the discontinuation of trastuzumab compared with controls.

A number of phase III clinical trials have examined the impact of combining trastuzumab with chemotherapy on DFS, varying the type of chemotherapy, duration of trastuzumab, and timing of introduction of trastuzumab in relationship to chemotherapy.[12,15,16,21] The Breast Cancer International Research Group 006 trial, with a median follow-up of more than 5 years, demonstrated significant improvements in DFS and OS with a nonanthracycline regimen (docetaxel, carboplatin, and trastuzumab [TCH]) and with AC followed by trastuzumab and concurrent docetaxel (AC-TH) compared with AC followed by docetaxel.[12] The study was not powered to compare the two trastuzumab-containing arms. Notably, the number of deaths from

any cause, number of deaths from breast cancer, and number of progression events were greater in the TCH arm relative to the AC-TH arm. The incidence of symptomatic CHF was greater in the AC-TH arm than in the TCH arm (2.0% *v* 0.4%, respectively; $P < .001$). There were no reported cardiac deaths. The Herceptin Adjuvant (HERA) trial assessed the impact of 1 year of trastuzumab after standard chemotherapy in the neoadjuvant or adjuvant setting.[15,16] At 2 years of follow-up, there was a significant DFS and OS benefit in patients receiving 1 year of trastuzumab compared with observation only.[16] At 3.6 years of median follow-up, rates of cardiotoxicity were relatively low, but patients in the trastuzumab group, compared with the observation group, had a greater incidence of severe CHF (0.8% *v* 0%, respectively) and symptomatic CHF (1.9% *v* 0.1%, respectively).[21] The smaller Neoadjuvant Herceptin (NOAH) study evaluated the clinical benefit of chemotherapy alone (ie, doxorubicin plus paclitaxel followed by paclitaxel followed by cyclophosphamide, methotrexate, and fluorouracil) or with trastuzumab starting concurrently with doxorubicin in patients with HER2-positive locally advanced or inflammatory breast cancer.[22] Patients in the trastuzumab arm received trastuzumab for a total of 1 year, starting in the neoadjuvant portion. At 3 years of follow-up, the addition of trastuzumab to chemotherapy significantly improved rates of pathologic complete response and event-free survival and reduced risks of recurrence, progression, or death compared with patients who did not receive trastuzumab. Trastuzumab therapy was well tolerated, with treatment-responsive symptomatic CHF in 2% of patients (two of 115 patients) being the most notable adverse event.

In conclusion, longer term analysis of N9831 and B-31 demonstrates continued benefit of adding 1 year of trastuzumab to standard anthracycline-based chemotherapy. A number of adjuvant treatment combinations of chemotherapy with trastuzumab are now available, allowing physicians to select a regimen they consider most appropriate for patients with early-stage invasive HER2-positive breast cancer. Longer-term follow-up and identification of predictive biomarkers will provide further insight into optimal trastuzumab adjuvant therapies. For patients with eligibility consistent with our adjuvant trastuzumab trials, the AC-TH regimen remains an excellent choice of treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Charles E. Geyer Jr, Genentech (C); Eleftherios P. Mamounas, Genentech (C); Peter A. Kaufman, Genentech (C); Norman Wolmark, Genentech/Roche (U) **Stock Ownership:** None **Honoraria:** Charles E. Geyer Jr, Genentech; Eleftherios P. Mamounas, Genentech **Research Funding:** Edith A. Perez, Genentech, GlaxoSmithKline, sanofi-aventis; Peter A. Kaufman, Genentech **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Edith A. Perez, Edward H. Romond, Vera J. Suman, Nancy E. Davidson, Silvana Martino, Eleftherios P. Mamounas, Norman Wolmark

Financial support: Edith A. Perez

Administrative support: Edith A. Perez, Charles E. Geyer Jr, Silvana Martino, Norman Wolmark

Provision of study materials or patients: Edith A. Perez, Edward H. Romond, Nancy E. Davidson, Charles E. Geyer Jr, Silvana Martino, Eleftherios P. Mamounas, Peter A. Kaufman

Collection and assembly of data: Edith A. Perez, Vera J. Suman, Jong-Hyeon Jeong, Charles E. Geyer Jr, Eleftherios P. Mamounas, Peter A. Kaufman

Data analysis and interpretation: Edith A. Perez, Edward H. Romond, Vera J. Suman, Jong-Hyeon Jeong, Nancy E. Davidson, Charles E. Geyer Jr, Silvana Martino, Eleftherios P. Mamounas, Peter A. Kaufman

Manuscript writing: All authors

Final approval of manuscript: All authors

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