

## ORIGINAL ARTICLE

# HER2 and Response to Paclitaxel in Node-Positive Breast Cancer

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## ABSTRACT

**BACKGROUND**

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The status of human epidermal growth factor receptor type 2 (HER2) in breast-cancer cells predicts clinical outcomes in women who receive adjuvant anthracycline-based chemotherapy. We hypothesized that HER2 positivity predicts a benefit from adjuvant doxorubicin doses above standard levels, from the addition of paclitaxel after adjuvant chemotherapy with doxorubicin plus cyclophosphamide, or from both.

**METHODS**

We randomly selected 1500 women from 3121 women with node-positive breast cancer who had been randomly assigned to receive doxorubicin (60, 75, or 90 mg per square meter of body-surface area) plus cyclophosphamide (600 mg per square meter) for four cycles, followed by four cycles of paclitaxel (175 mg per square meter) or observation. Tissue blocks from 1322 of these 1500 women were available. Immunohistochemical analyses of these tissue specimens for HER2 with the CB11 monoclonal antibody against HER2 or with a polyclonal-antibody assay kit and fluorescence in situ hybridization for HER2 amplification were performed.

**RESULTS**

No interaction was observed between HER2 positivity and doxorubicin doses above 60 mg per square meter. HER2 positivity was, however, associated with a significant benefit from paclitaxel. The interaction between HER2 positivity and the addition of paclitaxel to the treatment was associated with a hazard ratio for recurrence of 0.59 ( $P=0.01$ ). Patients with a HER2-positive breast cancer benefited from paclitaxel, regardless of estrogen-receptor status, but paclitaxel did not benefit patients with HER2-negative, estrogen-receptor-positive cancers.

**CONCLUSIONS**

The expression or amplification, or both, of *HER2* by a breast cancer is associated with a benefit from the addition of paclitaxel after adjuvant treatment with doxorubicin (<60 mg per square meter) plus cyclophosphamide in node-positive breast cancer, regardless of estrogen-receptor status. Patients with HER2-negative, estrogen-receptor-positive, node-positive breast cancer may gain little benefit from the administration of paclitaxel after adjuvant chemotherapy with doxorubicin plus cyclophosphamide.

**A**DJUVANT CHEMOTHERAPY IMPROVES disease-free and overall survival in early-stage breast cancer,<sup>1</sup> and anthracyclines and taxanes are two of the most active agents in such treatment.<sup>2</sup> The Cancer and Leukemia Group B (CALGB) 8541 trial showed that increasing the dose of a doxorubicin (Adriamycin)-based regimen from a relatively low dose (30 mg per square meter of body-surface area) to what is now considered to be a standard dose (60 mg per square meter) is highly beneficial.<sup>3,4</sup> Subsequently, a randomized trial (CALGB 9344/INT0148) examined the effects of increased doses of doxorubicin, above 60 mg per square meter, when combined with cyclophosphamide (Cytoxan) at a dose of 600 mg per square meter, plus four subsequent cycles of paclitaxel (Taxol). Overall, there was no benefit from doses of doxorubicin above 60 mg per square meter, but the addition of paclitaxel improved both disease-free survival and overall survival.<sup>5</sup>

Adjuvant chemotherapy causes substantial morbidity and occasional life-threatening toxic effects, and it is costly. No biomarkers have been identified that can reliably predict a clinical benefit from paclitaxel or escalating doses of doxorubicin in women with breast cancer. *HER2*, a member of the epidermal growth factor receptor family, is amplified, overexpressed, or both in 15 to 20% of breast cancers.<sup>6</sup> *HER2* overexpression and amplification in breast-cancer cells are strong predictors of a benefit from treatment with trastuzumab,<sup>7</sup> and the status of *HER2* in the tumor might predict the results of other treatments of breast cancer.<sup>8</sup> In a correlative study of breast-cancer tissues from trial 8541, *HER2* amplification and overexpression were associated with benefits from standard doses of doxorubicin but not from low doses of doxorubicin.<sup>9-11</sup> However, no studies have examined whether the overexpression or amplification of *HER2* can predict a benefit of increasing the dose of doxorubicin above 60 mg per square meter. Results of pre-clinical studies and preliminary clinical studies regarding an interaction between *HER2* status and paclitaxel are inconsistent.<sup>12-23</sup> For these reasons, we investigated whether *HER2* expression in the tumor identifies patients with breast cancer who are likely to benefit from doses of doxorubicin above 60 mg per square meter, the addition of paclitaxel after adjuvant treatment with doxorubicin plus cyclophosphamide, or both.

## METHODS

### PATIENTS

Patients eligible for CALGB 9344/INT0148 (enrollment period, May 1994 to April 1999) were women with node-positive breast cancer who had completed surgery with negative margins and were appropriate candidates for adjuvant chemotherapy.<sup>5</sup> A total of 3121 patients were treated according to this protocol. All patients provided written informed consent.

### TISSUE COLLECTION, PROCESSING, STORAGE, AND DISTRIBUTION

Approximately 90% of women enrolled in this trial gave written informed consent for the collection, storage, and analysis of formalin-fixed paraffin-embedded primary breast-cancer tissue. A tissue block or unstained tissue sections were requested from each patient's primary institution by the pathology coordinating office of each of the participating cooperative groups (CALGB, Southwest Oncology Group, Eastern Cooperative Oncology Group, and North Central Cancer Treatment Group) and were collected at the CALGB pathology coordinating office. Coded tissue sections were placed on glass slides without any patient identifiers and were distributed to the various investigators' laboratories for analysis in a blinded fashion. *HER2* data were submitted by each investigator to the CALGB Statistical Center for correlations with clinical outcomes.

Estrogen-receptor status was determined by the local institutions by means of standard procedures, and positive or negative status was designated according to each institution's policy as recorded on the case-report form submitted to CALGB. Estrogen-receptor data were available for 99.4% of patients enrolled in the clinical trial.

### IMMUNOHISTOCHEMICAL ANALYSIS FOR *HER2* EXPRESSION

Immunohistochemical analysis with the CB11 monoclonal antibody was performed as previously described.<sup>9-11</sup> Tissue specimens were considered to be positive for *HER2* if 50% or more of breast-cancer cells stained with CB11.<sup>9-11</sup>

Immunohistochemical analysis with a polyclonal-antibody kit (Herceptest, Dako) was performed by the clinical histology laboratory of the Fletcher Allen Health Care Center according to the instructions of the manufacturer (Dako). The

standard scoring method was used, and only 3+ staining was considered to be positive for HER2 overexpression.<sup>24</sup>

#### FLUORESCENCE IN SITU HYBRIDIZATION FOR HER2 AMPLIFICATION

Fluorescence in situ hybridization (FISH) was performed with the use of the PathVysion HER-2 DNA FISH Kit according to the instructions of the manufacturer (Vysis). For each case, 60 nonoverlapping invasive cancer nuclei were scored for the centromere enumeration probe (CEP) 17 and *HER2* signals. Tissue specimens were considered to be amplified in *HER2* if the *HER2*:CEP17 ratio was 2.00 or more.<sup>11</sup>

#### STATISTICAL ANALYSIS

The statistical analyses were specified in advance in a written correlative protocol that was approved by the Breast Cancer Intergroup of North America Correlative Science Committee and subsequently by the institutional review board of each of the laboratory investigators' institutions. The immunohistochemical assay with the CB11 monoclonal antibody and FISH for *HER2* amplification constituted the principal objectives of this study; results of the polyclonal-antibody test were also evaluated. To preserve tissue and resources, a sampling scheme was developed prospectively. Two distinct and randomly selected groups of tissue samples from 750 patients were identified from the full sample of nearly 2800 available specimens. The two groups of patients were similar with respect to the number of positive lymph nodes, estrogen-receptor status, age, and treatment assignment. Results of the two principal assays in the combined groups were analyzed, whereas results of the polyclonal-antibody test were analyzed in only one group. We requested tissue specimens from 1500 women who participated in the clinical trial, and we obtained 643 and 679 tissue specimens from groups 1 and 2, respectively (a total of 1322 specimens).

The primary end point was disease-free survival, defined in the parent study as the interval from study entry until the first local or distant recurrence or death due to any cause. The interaction effect was defined as the ratio of the hazard ratios for recurrence or death with paclitaxel treatment in women with *HER2*-positive tumors and in those with *HER2*-negative tumors.

The principal analysis was based on a multivariate Cox proportional-hazards model for dis-

ease-free survival with the following covariates: paclitaxel therapy, dose of doxorubicin, square root of the number of positive nodes, tumor size, menopausal status (premenopausal vs. perimenopausal or postmenopausal), estrogen-receptor status, *HER2* status, and the presence or absence of an interaction between *HER2* positivity and paclitaxel. Adjustments for multiple comparisons were not performed.

Disease-free survival for the paclitaxel and no-paclitaxel groups was estimated with Kaplan-Meier curves. Third-order interactions of *HER2* positivity or negativity with estrogen-receptor status and receipt or nonreceipt of paclitaxel were analyzed for hypothesis generation, and no significance levels are given for such interactions. The two methods of assessing each of the biomarkers were compared by calculating their level of agreement with the use of the kappa statistic. Results of this study are presented in accordance with reporting recommendations for tumor-marker prognostic studies (REMARK) criteria.<sup>25</sup>

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## RESULTS

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#### OUTCOMES AND CHARACTERISTICS OF SELECTED SUBGROUPS

The overall results of the CALGB 9344 trial with approximately 5 years of follow-up have been reported.<sup>5</sup> With approximately 10 years of follow-up, the results have remained qualitatively similar. No significant differences in either disease-free survival or overall survival were observed for doxorubicin doses above 60 mg per square meter. The hazard ratios for recurrence and death with the use of doxorubicin doses of 60 mg per square meter as compared with 90 mg per square meter were 0.97 (95% confidence interval [CI], 0.86 to 1.13;  $P=0.73$ ) and 1.03 (95% CI, 0.89 to 1.23;  $P=0.56$ ), respectively. The addition of paclitaxel resulted in significant improvements in disease-free and overall survival. The hazard ratios for recurrence and death with the addition of paclitaxel after doxorubicin plus cyclophosphamide were 0.81 (95% CI, 0.73 to 0.91;  $P<0.001$ ) and 0.81 (95% CI, 0.72 to 0.92;  $P=0.001$ ), respectively.

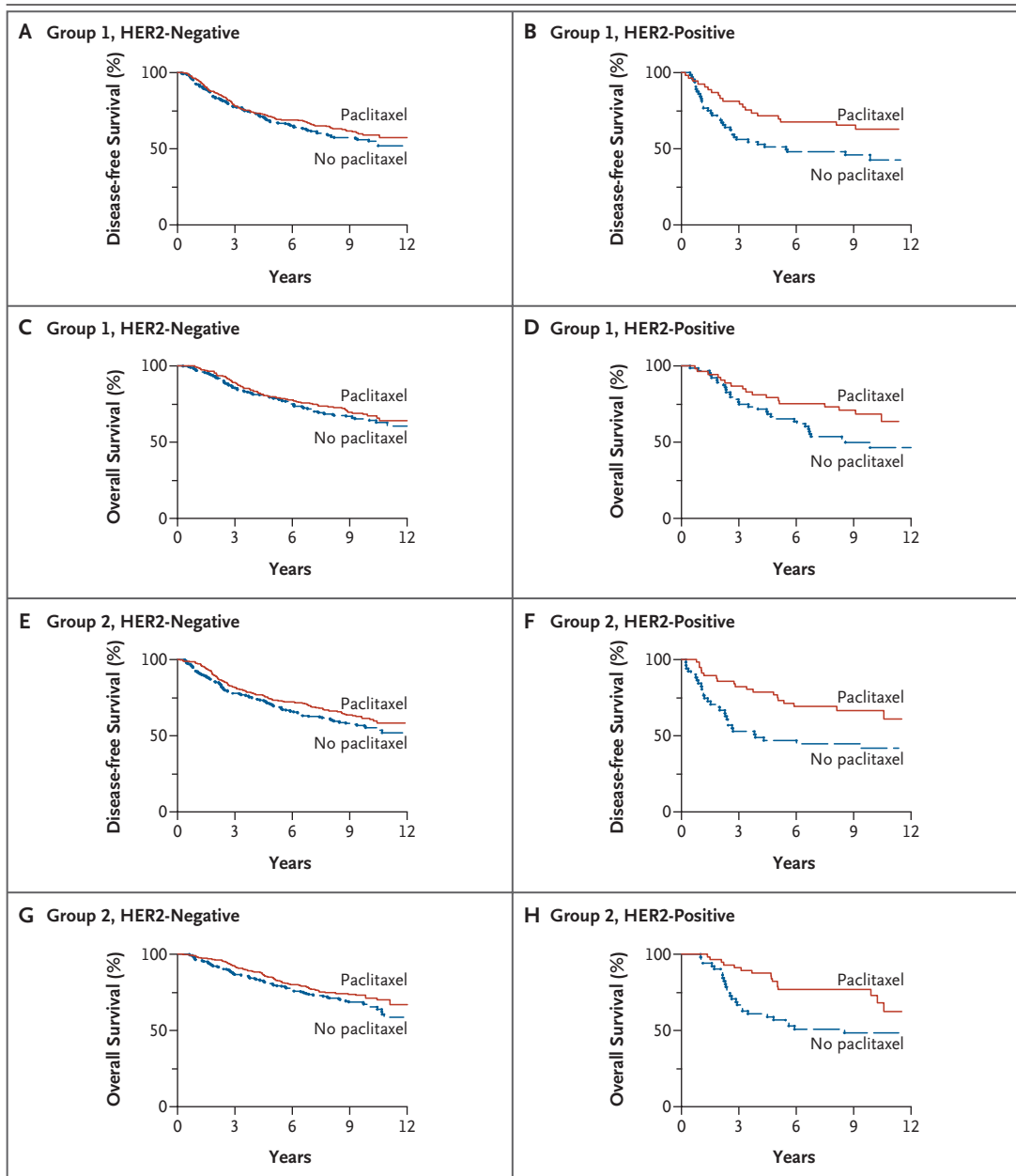
To verify that each group of selected patients was representative of the entire population of women in the 9344 trial, we compared the number of involved lymph nodes, tumor size, estrogen-receptor status, and assigned treatment in the test groups and all treated patients in the trial (Table 1). There were no detectable differences in

**Table 1. Characteristics of All Treated Patients in the 9344 Trial and in This Study.\***

Variable	All Treated Patients (N=3121)	Subgroup of Patients with HER2 Data Included in This Study		Other Patients (N=1799)
		Group 1 (N=643)	Group 2 (N=679)	
<i>number of patients (percent)</i>				
Treatment				
Doxorubicin (60 mg/m <sup>2</sup> ) plus cyclophosphamide (600 mg/m <sup>2</sup> ) plus paclitaxel	533 (17)	104 (16)	121 (18)	308 (17)
Doxorubicin (60 mg/m <sup>2</sup> ) plus cyclophosphamide (600 mg/m <sup>2</sup> )	515 (16)	106 (16)	104 (15)	305 (17)
Doxorubicin (75 mg/m <sup>2</sup> ) plus cyclophosphamide (600 mg/m <sup>2</sup> ) plus paclitaxel	517 (17)	115 (18)	111 (16)	291 (16)
Doxorubicin (75 mg/m <sup>2</sup> ) plus cyclophosphamide (600 mg/m <sup>2</sup> )	523 (17)	108 (17)	105 (15)	310 (17)
Doxorubicin (90 mg/m <sup>2</sup> ) plus cyclophosphamide (600 mg/m <sup>2</sup> ) plus paclitaxel	520 (17)	94 (15)	128 (19)	298 (17)
Doxorubicin (90 mg/m <sup>2</sup> ) plus cyclophosphamide (600 mg/m <sup>2</sup> )	513 (16)	116 (18)	110 (16)	287 (16)
Age				
<40 yr	636 (20)	131 (20)	133 (20)	372 (21)
40–49 yr	1248 (40)	259 (40)	257 (38)	732 (41)
50–59 yr	843 (27)	176 (27)	206 (30)	461 (26)
≥60 yr	394 (13)	77 (12)	83 (12)	234 (13)
Race or ethnic group†				
White	2611 (84)	537 (84)	572 (84)	1502 (83)
Hispanic	127 (4)	35 (5)	26 (4)	66 (4)
Black	296 (9)	49 (8)	58 (9)	189 (11)
Asian	52 (2)	13 (2)	14 (2)	25 (1)
Other	35 (1)	9 (1)	9 (1)	17 (1)
Menopausal status				
Premenopausal	1925 (62)	392 (61)	417 (61)	1116 (62)
Perimenopausal or postmenopausal	1196 (38)	251 (39)	262 (39)	683 (38)
Tumor size				
≤2 cm	1096 (35)	215 (33)	240 (35)	641 (36)
>2 cm	2008 (64)	427 (66)	434 (64)	1147 (64)
Missing data	17 (<1)	1 (<1)	5 (<1)	11 (<1)
Estrogen-receptor status				
Positive	1840 (59)	364 (57)	418 (62)	1058 (59)
Negative or unknown	1281 (41)	279 (43)	261 (38)	741 (41)
Positive lymph nodes				
1–3	1452 (46)	306 (48)	314 (46)	832 (46)
4–9	1310 (42)	259 (40)	293 (43)	758 (42)
≥10	360 (12)	78 (12)	72 (11)	210 (12)
Mastectomy as primary treatment	2177 (70)	457 (71)	477 (70)	1243 (69)
5-yr survival <i>percent (95 percent confidence interval)</i>				
Disease-free	67 (66–69)	67 (64–71)	70 (67–74)	67 (65–69)
Overall	78 (77–80)	78 (75–81)	80 (77–83)	78 (76–80)

\* None of the variables differed significantly between groups. Percentages may not sum to 100 because of rounding.

† Race or ethnic group was reported by the patients.



**Figure 1. Clinical Outcomes in Patients Treated with or without Paclitaxel, According to HER2 Status.**

Patients were randomly assigned to receive four cycles of paclitaxel (175 mg per square meter) or no further chemotherapy with paclitaxel after completion of four cycles of doxorubicin plus cyclophosphamide. Disease-free survival for group 1 (Panels A and B), overall survival for group 1 (Panels C and D), disease-free survival for group 2 (Panels E and F), and overall survival for group 2 (Panels G and H) were assessed according to negative or positive HER2 expression, as determined by means of immunohistochemical analysis with the CB11 monoclonal antibody.

demographic or prognostic features between groups 1 and 2 or between these groups and the remaining, unselected patients. In the combined groups, 97.4% of the patients with estrogen-receptor-positive tumors received tamoxifen,

a proportion that was similar to that for the entire study (96.8%). Five-year disease-free and overall survival rates were similar for group 1 and group 2 and for the remaining, unselected patients (Table 1).

**Table 2. Results of Multivariate Models of the Interaction of HER2 Positivity and Paclitaxel Treatment.\***

End Point	Group 1 (N=643)		Group 2 (N=679)		Combined Groups 1 and 2 (N=1322)	
	Hazard Ratio†	P Value	Hazard Ratio†	P Value	Hazard Ratio†	P Value
Recurrence	0.63	0.15	0.52	0.03	0.59	0.01
Death	0.61	0.17	0.52	0.03	0.57	0.01

\* HER2 positivity was analyzed by means of immunohistochemical analysis with the CB11 monoclonal antibody and categorized according to whether there were <50% or ≥50% positive cells.

† The values shown are the hazard ratio for recurrence in the interaction between HER2 positivity and the addition of paclitaxel.

#### DOXORUBICIN DOSE AND HER2 STATUS

No significant association between HER2 overexpression, according to immunohistochemical analysis with the CB11 monoclonal antibody, and escalation of the doxorubicin dose to 75 mg per square meter or 90 mg per square meter was observed in group 1 or 2 or in the combined groups. The rate of disease-free survival at 5 years in the combined groups for patients with a HER2-positive tumor who received 60 mg per square meter or for those who received 90 mg per square meter was 63% (95% CI, 52 to 76) and 63% (95% CI, 53 to 73), respectively, whereas the rate of disease-free survival at 5 years for patients with a HER2-negative tumor who received 60 mg per square meter and for those who received 90 mg per square meter was 72% (95% CI, 67 to 77) and 69% (95% CI, 64 to 74), respectively.

#### PACLITAXEL AND HER2 STATUS

Disease-free survival and overall survival among patients who did or did not receive paclitaxel were analyzed according to HER2 status as established by immunohistochemical analysis with the CB11 monoclonal antibody (Fig. 1). The apparent interaction between HER2 positivity and the addition of paclitaxel in group 1 was not significant (hazard ratio for recurrence in the interaction between HER2 positivity and the addition of paclitaxel, 0.63;  $P=0.15$ ) (Table 2) (Fig. 1A through 1D). We further examined this interaction in group 2. In group 2, the hazard ratio for recurrence in the interaction between HER2 positivity and the addition of paclitaxel was 0.52 ( $P=0.03$ ) (Table 2) (Fig. 1E through 1H). When the two groups were combined, in multivariate analyses the hazard ratio for recurrence in the interaction between HER2 positivity and the addition of paclitaxel to the treatment was 0.59 ( $P=0.01$ ) (Table 3). The hazard ratio for death in the combined groups for the HER2–paclitaxel interaction was 0.57 ( $P=0.01$ ) (Table 2).

**Table 3. Multivariate Analysis of Disease-free Survival for Groups 1 and 2 Combined.\***

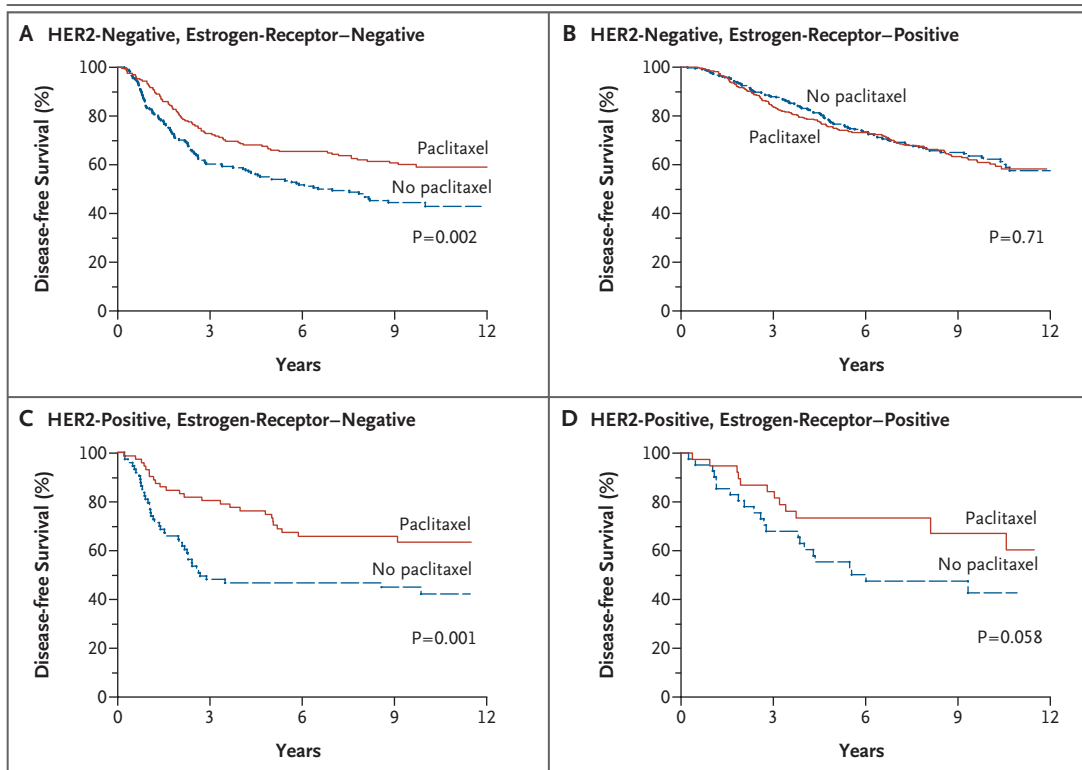
Variable	Hazard Ratio for Recurrence	P Value
No. of positive nodes (square root)	1.49	<0.001
Tumor size	1.34	0.002
Positive estrogen-receptor status	0.65	<0.001
Age	1.00	0.61
Paclitaxel treatment	0.85	0.09
Positive HER2 status	1.00	0.04
HER2–paclitaxel interaction	0.59†	0.01

\* HER2 positivity was analyzed by means of immunohistochemical analysis with the CB11 monoclonal antibody and categorized according to whether there were <50% or ≥50% positive cells.

† The value shown is the hazard ratio for recurrence in the interaction between HER2 positivity and the addition of paclitaxel.

#### PACLITAXEL AND HER2 AND ESTROGEN-RECEPTOR STATUS

Since an estrogen-receptor–positive tumor can be a negative predictive factor for the response to chemotherapy in breast cancer,<sup>26–28</sup> we performed an exploratory analysis of the benefit of paclitaxel based on HER2 positivity and estrogen-receptor status (Fig. 2). For this analysis, we examined disease-free survival in the combined groups, and HER2 was evaluated with the CB11 antibody. Figure 2 shows Kaplan–Meier curves for disease-free survival in the paclitaxel and no-paclitaxel groups for each estrogen-receptor–HER2 combination. Log-rank  $P$  values are provided as a measure of discordance and should be viewed as descriptive, not inferential. In this analysis, paclitaxel was associated with improved disease-free survival among patients with HER2-positive tumors, an effect that was independent of estrogen-receptor status (Fig. 2C and 2D). In the small subgroup of patients with cancers that were estrogen-receptor–positive and HER2-positive, paclitaxel appeared



**Figure 2.** Disease-free Survival among Patients Treated with or without Paclitaxel According to Estrogen-Receptor Status and HER2 Expression.

Patients were randomly assigned to receive four cycles of paclitaxel (175 mg per square meter) or no further chemotherapy with paclitaxel after completion of four cycles of doxorubicin and cyclophosphamide. Disease-free survival for patients in groups 1 and 2 combined was determined according to negative HER2 expression (Panels A and B) or positive HER2 expression (Panels C and D), as determined by immunohistochemical analysis with the CB11 monoclonal antibody, or according to negative estrogen-receptor (Panels A and C) or positive estrogen-receptor (Panels B and D) expression, as determined at the local institutions. The log-rank P value in each panel is for the comparison of Kaplan-Meier disease-free survival curves in the paclitaxel and no-paclitaxel groups and does not represent the three-way interaction among HER2 positivity, estrogen-receptor negativity, and a benefit from paclitaxel.

to be beneficial (Fig. 2D). However, paclitaxel did not benefit patients with estrogen-receptor-positive, HER2-negative cancers (Fig. 2B). This subgroup included more than 50% of patients in this study.

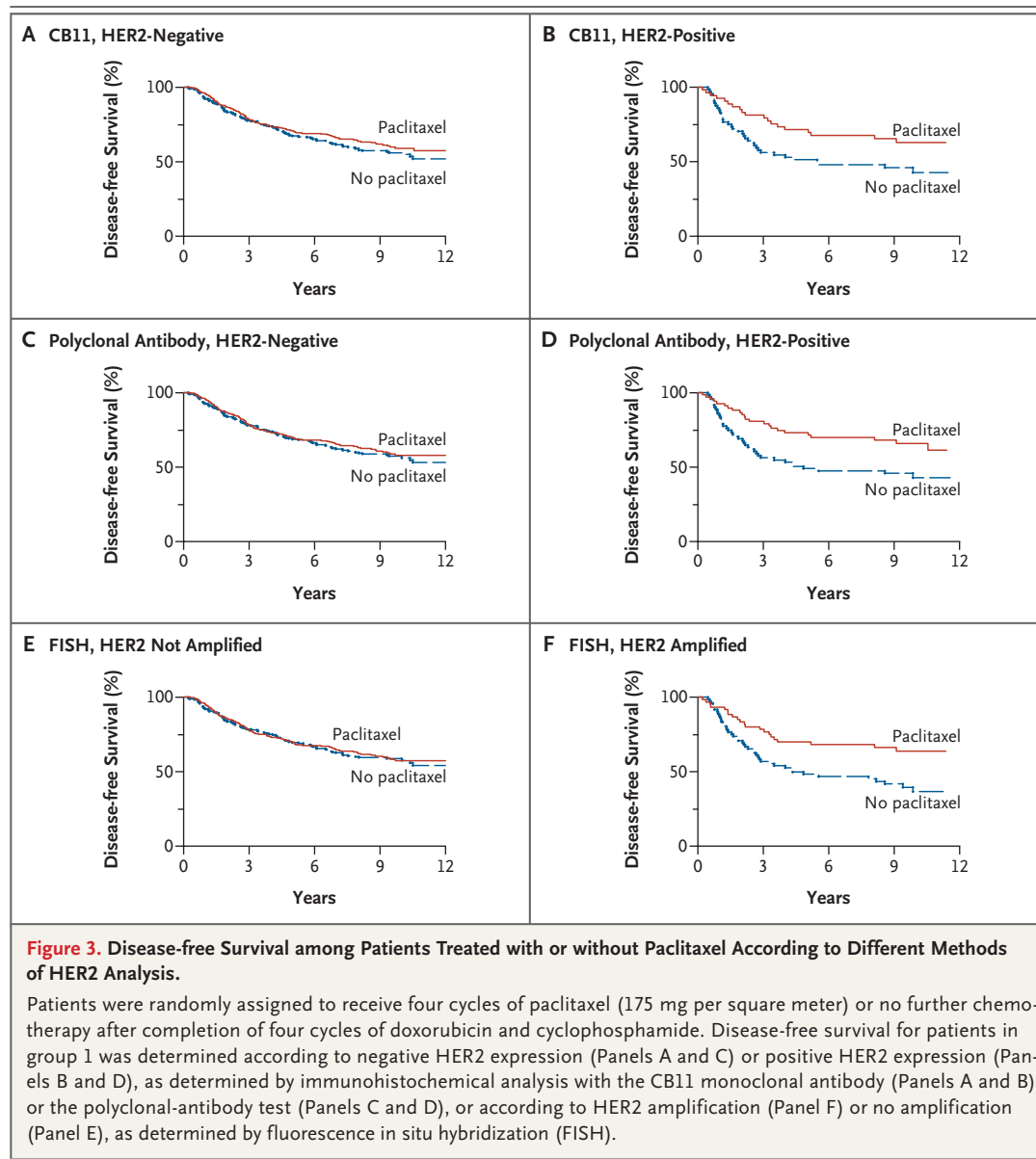
#### PACLITAXEL AND METHOD OF HER2 ANALYSIS

We compared the results of immunohistochemical analysis with the CB11-antibody test, with the polyclonal-antibody test, and with FISH. The qualitative results of all three assays were similar (Fig. 3). The interaction term between HER2 expression and a benefit from paclitaxel (within group 1 only) reached significance in only one of the three comparisons (with the polyclonal-antibody test,  $P=0.04$ ;  $P=0.06$  with FISH). The mean ( $\pm$ SD)

kappa statistic was  $85\pm 2.6\%$  for the level of agreement between immunohistochemical analysis with the CB11-antibody test and the polyclonal-antibody test,  $79\pm 3.2\%$  for the level of agreement between immunohistochemical analysis with the CB11-antibody test and FISH, and  $80\pm 3.0\%$  for the level of agreement between the polyclonal-antibody test and FISH.

#### DISCUSSION

We observed a significant interaction between the HER2 status of the tumor and the benefit of adjuvant paclitaxel in patients with node-positive breast cancer who received four cycles of doxorubicin plus cyclophosphamide. Our results indicate



that HER2 positivity can predict improvement in disease-free survival and overall survival by the addition of paclitaxel to doxorubicin plus cyclophosphamide. In contrast, no interaction was observed between HER2 status and doses of doxorubicin above 60 mg per square meter.

The HER2–paclitaxel interaction was observed regardless of whether HER2 positivity was determined by means of either of two immunohistochemical methods or whether *HER2* gene amplification was determined by means of FISH. Our data do not suggest that one assay is more robust

than any other of the three. In this study, we used dichotomous cutoffs to designate whether a tumor was positive or negative for expression or amplification of HER2. A panel convened by the American Society of Clinical Oncology and the College of American Pathologists recently issued guidelines for HER2 testing by means of immunohistochemical analysis or FISH in which they proposed categories of HER2 results that should be considered to be equivocal.<sup>29,30</sup> In our study, these categories applied to only 13 and 16 patients, respectively, precluding meaningful analyses.

In an exploratory analysis, we observed an apparent three-way interaction among HER2 positivity, estrogen-receptor negativity, and a benefit from paclitaxel. We found no benefit of paclitaxel in patients with HER2-negative, estrogen-receptor-positive breast cancer (Fig. 2B). This subgroup represents more than half the patients with node-positive breast cancer who participated in the CALGB 9344 trial and who would, under most current circumstances, receive a taxane with or after cyclophosphamide plus an anthracycline. Our studies suggest that such patients could avoid the toxic effects associated with adjuvant paclitaxel when given after doxorubicin plus cyclophosphamide.<sup>5</sup> Our results require validation before adoption into clinical practice, however.

CALGB trials that enrolled patients with node-positive breast cancer from 1985 to 1997, including the CALGB 9344 trial, showed incremental benefits in disease-free survival and overall survival.<sup>4,5,31</sup> These studies compared what would now be considered insufficient doses of cyclophosphamide, doxorubicin, and fluorouracil with higher doses of the same regimen (CALGB 8541), the addition of paclitaxel to standard doses of doxorubicin and cyclophosphamide (CALGB 9344), and more recently, the administration of doxorubicin, cyclophosphamide, and paclitaxel every 2 weeks instead of every 3 weeks (CALGB 9741). In each case, the additional benefit of the investigational strategy as compared with the standard treatment was substantially greater in patients with estrogen-receptor-negative breast cancer than in patients with estrogen-receptor-positive breast cancer.<sup>28</sup> However, this differential benefit was not limited to the estrogen-receptor-negative subgroup in any of these studies, suggesting that estrogen-receptor status is not an absolute predictor of a benefit from additional or dose-dense chemotherapy. The results of the present study suggest that HER2 assessment can refine predictions of a benefit from chemotherapy.

Previous studies have shown that the response to regimens containing doxorubicin at a dose of up to 60 mg per square meter is strongly correlated with HER2 amplification, overexpression, or both.<sup>9-11</sup> Other investigators showed that any benefit from an anthracycline is associated with HER2 status and that HER2 positivity may be a surrogate for abnormalities in the *topoisomerase II* gene, which is present on the same amplicon as

HER2.<sup>8,32</sup> Our data, however, indicate that there is no detectable HER2-doxorubicin effect when the dose of doxorubicin is higher than 60 mg per square meter.

Preclinical data regarding HER2 status and the response to taxanes are contradictory.<sup>18,33-38</sup> However, in one trial, patients with HER2-positive metastatic breast cancer were more likely to benefit from a paclitaxel-containing regimen than patients with HER2-negative disease<sup>19</sup>; this finding is consistent with our results.

Trastuzumab, a humanized monoclonal antibody against HER2, decreases the risks of recurrence and death among women with HER2-positive breast cancer by approximately one half and one third, respectively.<sup>39-42</sup> We cannot speculate on how the addition of trastuzumab might affect our results. However, the benefits of trastuzumab would not affect our observation that paclitaxel appeared to have little, if any, benefit in patients with HER2-negative, estrogen-receptor-positive tumors.

We found a significant association between HER2 positivity and a benefit from the addition of paclitaxel after adjuvant treatment with doxorubicin plus cyclophosphamide in women with node-positive, stage II breast cancer. Our data raise the possibility of a three-way interaction among HER2 negativity, estrogen-receptor positivity, and a lack of benefit from paclitaxel.

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Drs. Norton, Goldstein, and Berry report receiving consulting fees from Bristol-Myers Squibb; Dr. Berry, consulting fees from Abbott; and Drs. Winer and Goldstein, clinical research support from Bristol-Myers Squibb. No other potential conflict of interest relevant to this article was reported.

The views expressed in this article are solely those of the authors and do not necessarily represent the official views of the National Cancer Institute.

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## APPENDIX

The following investigators participated in the CALGB trial: Fox Chase Cancer Center, Philadelphia — L. Goldstein; Mayo Clinic, Rochester, MN — J.N. Ingle; CALGB Statistical Center, Duke University Medical Center, Durham, NC — S. George, J. Crawford; Dana-Farber Cancer Institute, Partners HealthCare, Boston — E.P. Winer; Dartmouth Medical School, Norris Cotton Cancer Center, Lebanon, NH — M.S. Ernstoff; Long Island Jewish Medical Center, Lake Success, NY — M. Citron; Massachusetts General Hospital, Boston — M.L. Grossbard; Medical University of South Carolina, Charleston — M. Green; Memorial Sloan-Kettering Cancer Center, New York — C. Hudis; Mount Sinai School of Medicine, New York — L.R. Silverman; North Shore University Hospital, Manhasset, NY — D.R. Budman; Rhode Island Hospital, Providence, RI — W. Sikov; Roswell Park Cancer Institute, Buffalo, NY — E. Levine; State University of New York Upstate Medical University, Syracuse — S.L. Graziano; University of Alabama at Birmingham, Birmingham — R. Diasio; University of California at San Diego, La Jolla — J. Mortimer; University of California at San Francisco, San Francisco — A.P. Venook; University of Chicago, Chicago — G. Fleming; University of Illinois, Chicago — L.E. Feldman; University of Iowa, Iowa City — G. Clamon; University of Maryland Greenebaum Cancer Center, Baltimore — M. Edelman; University of Massachusetts Medical School, Worcester — W.V. Walsh; University of Minnesota, Minneapolis — B.A. Peterson; University of Missouri, Ellis Fischel Cancer Center, Columbia — M.C. Perry; University of Nebraska Medical Center, Omaha — A. Kessinger; University of North Carolina at Chapel Hill, Chapel Hill — T.C. Shea; University of Tennessee, Memphis — H.B. Niell; Vermont Cancer Center, Burlington — H.B. Muss; Wake Forest University School of Medicine, Winston-Salem, NC — D.D. Hurd; Walter Reed Army Medical Center, Washington, DC — T. Reid; Washington University School of Medicine, St. Louis — N. Bartlett; Weill Medical College of Cornell University, New York — S. Wadler.

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