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ORIGINAL REPORT

Randomized Phase III Trial of Weekly Compared With Every-3-Weeks Paclitaxel for Metastatic Breast Cancer, With Trastuzumab for all HER-2 Overexpressors and Random Assignment to Trastuzumab or Not in HER-2 Nonoverexpressors: Final Results of Cancer and Leukemia Group B Protocol 9840

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ABSTRACT

Purpose

Phase II trials suggested that weekly paclitaxel might be more effective and less toxic than every-3-weeks administration for metastatic breast cancer (MBC). Cancer and Leukemia Group B (CALGB) protocol 9840 was initiated to address this question. Subsequently trastuzumab was demonstrated to improve outcomes of paclitaxel therapy for human epidermal growth factor receptor-2 (HER-2)–positive patients, and was therefore incorporated. Because inhibition of HER-family signaling had potential efficacy even without HER-2 overexpression, we randomly assigned for trastuzumab in this population.

Patients and Methods

Patients were randomly assigned to paclitaxel 175 mg/m^2 every 3 weeks or 80 mg/m^2 weekly. After the first 171 patients, all HER-2–positive patients received trastuzumab; HER-2 nonoverexpressors were randomly assigned for trastuzumab, in addition to paclitaxel schedule. A total of 577 patients were treated on 9840. An additional 158 patients were included in analyses, for combined sample of 735. The primary end point was response rate (RR); secondary end points were time to progression (TTP), overall survival, and toxicity. Primary comparisons were between weekly versus every-3-weeks paclitaxel, and trastuzumab versus no trastuzumab in HER-2 nonoverexpressors.

Results

In the combined sample, weekly paclitaxel was superior to every-3-weeks administration: RR (42% *v* 29%, unadjusted odds ratio [OR] = 1.75; $P = .0004$), TTP (median, 9 *v* 5 months; adjusted HR = 1.43; $P < .0001$), and survival (median, 24 *v* 12 months; adjusted HR = 1.28; $P = .0092$). For HER-2 nonoverexpressors, trastuzumab did not improve efficacy. Grade 3 neuropathy was more common with weekly dosing (24% *v* 12%; $P = .0003$).

Conclusion

Weekly paclitaxel is more effective than every-3-weeks administration for MBC. Trastuzumab did not improve efficacy for HER-2 nonoverexpressors. Neurotoxicity is a treatment-limiting toxicity for weekly paclitaxel.

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INTRODUCTION

Few single chemotherapeutic agents have been studied as rigorously as the taxanes regarding dose and schedule for breast cancer. Three-hour infusions were found to be similarly effective and more convenient than 24[1] and 96-hour[2] infusions. Dose escalation of paclitaxel from 175 to 210 and 250 mg/m^2 offered no improvement in efficacy, but increased neurotoxicity.[3] Phase II clinical trials of weekly 1-hour paclitaxel in metastatic breast cancer (MBC) have demonstrated promising efficacy and favorable tolerability, including with trastuzumab.[4-10]

In 1998, Cancer and Leukemia Group B (CALGB) protocol 9840 began as a prospective randomized comparison of weekly and every-3-weeks (3-weekly) paclitaxel. This trial began in the pretrastuzumab era,[13] and the first 171 patients enrolled

had tumors of unknown human epidermal growth factor receptor 2 (HER-2) status. The protocol was subsequently revised, and all patients with HER-2–overexpressing breast cancer received trastuzumab. Recognizing that no assessment of HER-2 status is perfect and that there were many unanswered questions about the role of trastuzumab in breast cancer,[14-16] we also tested the potential value of trastuzumab in patients with HER-2–nonoverexpressing tumors.

PATIENTS AND METHODS

Patients

The CALGB 9840 study population consisted of women with measurable, histologically confirmed MBC. Up to one line of prior chemotherapy for locally advanced or metastatic disease was allowed. Bone-only, CNS, lymphangitic pulmonary metastases, and previously irradiated tumors without subsequent progression were considered nonmeasurable. As per the protocol stipulated design, data from MBC patients who received paclitaxel at 175 mg/m^2 on CALGB 9342 were incorporated into the analysis.[3] Random assignment was weighted (60:40), favoring weekly paclitaxel.

A total of 585 patients were accrued to CALGB 9840; 577 patients began protocol therapy and 158 patients from the 175 mg/m^2 arm of CALGB 9342 are included in this analysis, for a total of 735 patients (Fig 1).

Prior taxane was allowed as adjuvant therapy, provided that 1 year had transpired from its completion to protocol entry. Adequate renal, hepatic, and hematologic parameters were required (Appendix, online only). After trastuzumab was added to protocol therapy, a normal baseline left ventricular ejection fraction (LVEF) was required. Patients with CNS metastases were eligible if asymptomatic, not receiving corticosteroids, and more than 6 months from cranial irradiation.

Methods

Baseline imaging was performed within 30 days of registration, and an ECG within 42 days. Women of child-bearing potential required a negative serum β-human chorionic gonadotropin test. Each participant signed an institutional review board–approved, protocol-specific informed consent in accordance with federal and institutional guidelines.

Patients were stratified by prior chemotherapy: (1) no chemotherapy in the metastatic setting or recurrence more than 6 months of completion of adjuvant therapy and (2) one prior regimen in the metastatic setting, or no prior chemotherapy for metastases but recurred less than 6 months from completing adjuvant therapy. Subsequent to the amendment requiring HER-2 testing, patients were also stratified by HER-2 status. The first 171 patients were not required to have HER-2 testing and were randomly assigned to paclitaxel 80 mg/m^2 weekly via 1-hour infusion, or to paclitaxel 175 mg/m^2 every 3 weeks via 3-hour infusion. For the first six infusions, weekly paclitaxel was dosed at 100 mg/m^2 but subsequently continued at 80 mg/m^2. A 30% incidence of grade 3 peripheral sensory neuropathy resulted in an amended starting dose of 80 mg/m^2 weekly. Paclitaxel was to be continued until disease progression or limiting toxicity. CBC was obtained every 3 weeks. Prophylactic hematopoietic growth factor support could be used as required for treatment-limiting neutropenia or anemia. A 21-day cycle of therapy could be initiated in weekly paclitaxel patients provided that the absolute granulocyte count (AGC) was at least 1,000/μL; for 3-weekly paclitaxel, the AGC was to be at least 1,500/μL. Platelets had to be at least 100,000/μL for both schedules on day 1 of each cycle. Standard premedication with dexamethasone 10 mg, diphenhydramine 50 mg, and either cimetidine 300 mg or ranitidine 50 mg intravenously 30 to 60 minutes before paclitaxel infusion was required.[17]

The protocol was amended on March 15, 2000, to require HER-2 status assessment by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). Those patients with HER-2–positive disease (IHC 3+ or FISH+) received weekly trastuzumab 2 mg/kg via 30-minute infusion following a 4-mg/kg loading dose administered over 90 minutes. HER-2–normal patients were randomly assigned 50:50 to receive or not receive trastuzumab. Patients were to receive a minimum of two cycles of therapy unless there was rapid disease progression. Prior trastuzumab became an exclusion criterion, and patients were stratified by HER-2-status for paclitaxel schedule.

Treatment Schedule and Dose Modification

Hematologic toxicity. Filgrastim was prescribed for febrile neutropenia or severe neutropenia (absolute neutrophil count [ANC] $<$ 500/mm^3 or WBC count $<$ 1,000/mm^3 for $\geq$7 days) as a 5-μg/kg injection daily beginning on day 2, continuing until the ANC was more than 10,000/mm^3 (3-weekly arm) or subcutaneously daily from day 2 to 5, or until the ANC was more than 10,000/mm^3, whichever came first (weekly arm). Filgrastim was continued in subsequent cycles. A paclitaxel dose reduction with the next course of therapy was to occur if grade 4 thrombocytopenia (platelets $<$ 25,000/mm^3) occurred, with further dose reductions possible (Table 1), with no re-escalation. Dose-level reductions are described in Table 1.

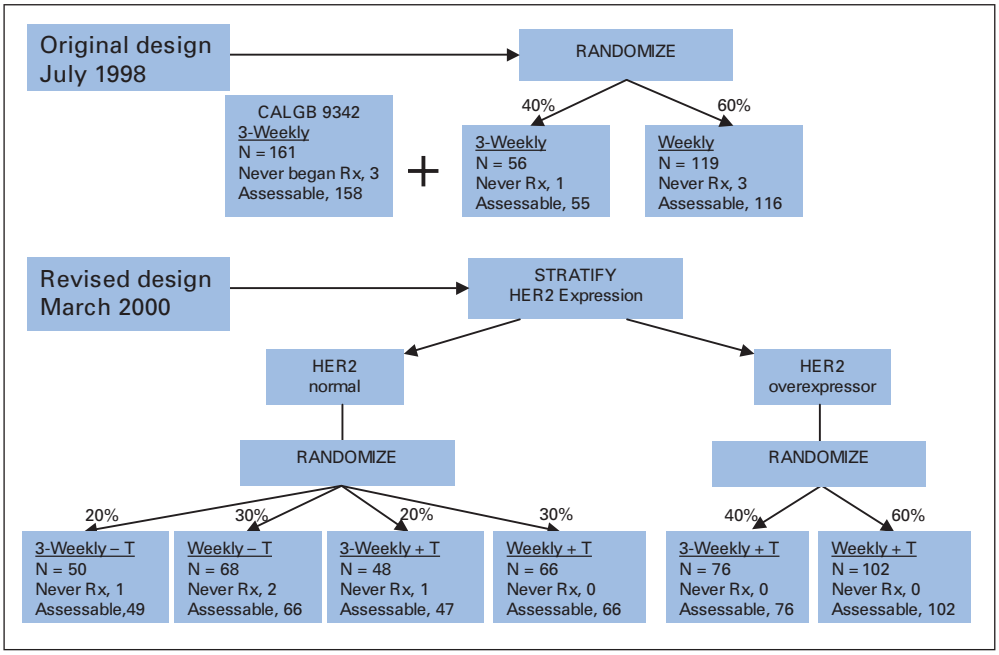

Fig 1. Consort diagram. CALGB, Cancer and Leukemia Group B; 3-weekly, every 3 weeks; Rx, treatment; T, trastuzumab.

Table 1. Paclitaxel Dose Reductions

Starting Dose (mg/m^2)	Dose Reduction (mg/m^2)			
	Level 1	Level 2	Level 3	Level 4
175 over 3 hours	150	125	105	90
80 over 1 hour	70	60	50	40

Nonhematologic toxicity. Dosing guidelines for nonhematologic toxicity are described in detail in the Appendix (online only).

Statistical Methods

The primary study end point was tumor response. Secondary end points were overall survival (OS), time to disease progression (TTP), and treatment-related toxicity. OS was measured from date of study entry until date of death resulting from any cause. Surviving patients were censored at the date they were last known to be alive. TTP was measured from date of study entry until date of first disease progression in any site or death resulting from any cause, whichever occurred first. Surviving patients without disease progression were censored at the date last known to be progression-free.

Power was based on the two primary study objectives: (1) to determine whether weekly paclitaxel results in a significantly higher response rate (RR) than 3-weekly paclitaxel, regardless of HER-2 status and assignment to trastuzumab, and (2) to determine whether trastuzumab significantly increases RR among HER-2 nonoverexpressors, regardless of paclitaxel schedule. Regarding Peretz et al,[1] 95% power to test a 50% increase in response incidence from 25% on standard paclitaxel to 37.5% on weekly paclitaxel required 700 patients randomly assigned equally to standard or weekly schedule. Regarding Holmes et al,[2] 85% power to detect a 50% increase in response incidence from 25% to 37.5% with trastuzumab required 490 patients randomly assigned to receive or not receive trastuzumab. Both calculations assumed a two-sided α of .05. Because protocol therapy for the standard arm of CALGB 9342, a precursor to the current study, was identical to the standard arm of the current study, the former group of patients was included in the current study analysis to conserve patient resources, reducing accrual from 700 to 580. Inclusion of the CALGB 9342 patients necessitated a 60:40 weighted random assignment of treatment assignment (weekly:3-weekly). The CALGB Statistical Center performed all random assignment using a permuted block scheme.

Data Analyses

Primary analyses were performed separately using both the CALGB 9840 + CALGB 9342 sample (combined) and the CALGB 9840 sample (limited). The primary analysis used multivariate logistic regression to relate treatment schedule with response. Secondary analyses used proportional hazards regression and Wald χ^2 tests to model and assess the relationship of treatment with OS and TTP. Multivariate models for each end point were built using variables of known prognostic importance in MBC: number of metastatic sites, ER status, performance status, prior adjuvant chemotherapy, and prior radiotherapy. Also included were line of therapy, HER-2 status, and trastuzumab use. Two or more proportions were compared using contingency table analysis; their 95% CIs used exact binomial methods. OS and TTP distributions were plotted using the Kaplan-Meier method. Estimates of treatment effect and their corresponding significance levels were derived using multivariate models that adjust for prognostic variables were labeled "adjusted"; those derived from univariate models were labeled "unadjusted." All *P* values are two-sided. Because the study was not powered to address therapeutic effect within subsets of patients, comparisons within HER-2 subsets are exploratory only; *P* values are provided as descriptive measures only.

CALGB 9840 was monitored biannually by an independent data safety monitoring board beginning within 6 months of activation and continuing until November 2003. Formal interim analyses on tumor response used two-sided bounds constructed from the O'Brien-Fleming approach[18] and the Lan-DeMets[19] spending function. As part of CALGB's quality-assurance program, study data were reviewed by the study chair and randomly selected patient charts were audited on site at least once every 3 years. CALGB study statisticians performed statistical analyses using SAS 9.0 (SAS Institute, Cary, NC) on data extracted from the CALGB database in February 2006.

RESULTS

Patient Characteristics

Table 2 presents patient characteristics in the combined sample

Table 2. Patient Characteristics

Characteristic	CALGB 9342 (3-Weekly)	CALGB 9840			
		3-Weekly	Weekly	3-Weekly + Trastuzumab	Weekly + Trastuzumab
Total patients treated					
No.	158	104	182	123	168
%	100	100	100	100	100
Study stratifiers, %					
2nd line of therapy	75	20	20	14	12
HER-2 nonoverexpressor	0	47	36	38	39
Demographics, %					
Age < 50 years	32	23	31	42	31
Premenopausal	13	15	16	26	24
African American race	25	13	19	15	15
Clinicopathologic characteristics, %					
ER negative	39	38	37	44	44
PgR negative	44	46	42	56	52
Performance score of 0	42	52	45	50	43
1 measurable involved site at study entry	54	63	60	50	51
Prior hormone therapy	62	51	57	48	49
Prior chemotherapy	82	57	65	54	54
Prior radiotherapy	56	54	56	43	49

Abbreviations: CALGB, Cancer and Leukemia Group B; 3-weekly, every 3 weeks; HER-2, human epidermal growth factor receptor 2; ER, estrogen receptor; PgR, progesterone receptor.

by stratification factors (HER-2 status and line of therapy), demographics (age, race), and pretreatment clinical characteristics.

Efficacy

Primary end point and tumor response. Table 3 summarizes the RR for the combined and limited samples. For the combined sample, the RR of weekly paclitaxel is 42% versus 29% for 3-weekly paclitaxel, with an unadjusted odds ratio (OR) of 1.75 ($P = .0004$). In the limited sample, trastuzumab in HER-2–nonoverexpressing tumors did not significantly improve RR (38% *v* 32%; $P = .28$).

TTP. Figure 2A shows TTP by paclitaxel schedule (combined sample) and by trastuzumab use in HER-2 nonoverexpressors (limited sample). An early and persistent advantage for weekly paclitaxel over standard paclitaxel was observed. Median TTP for patients receiving weekly paclitaxel was prolonged by 4 months (9 *v* 5 months; adjusted hazard ratio [HR] = 1.43; $P < .0001$). Because patients enrolled onto CALGB 9342 were more likely to have been in the second-line setting compared with CALGB 9840, we adjusted for line of therapy. Treatment outcomes were similar in the two studies. Figures 3A and 3B demonstrate the comparability of the CALGB 9342 and CALGB 9840 populations when adjusting for line of therapy. The addition of trastuzumab to paclitaxel in patients with HER-2–normal breast cancer was not associated with significantly longer TTP (7 *v* 6 months; $P = .28$; Figure 2B).

Overall survival. Appendix Figure A1A (online only) shows overall survival (OS) by paclitaxel schedule in the combined sample. After adjusting for line of therapy, HER-2 status, trastuzumab, tumoral estrogen-receptor status, and performance score, the HR of 3-weekly to weekly paclitaxel was 1.28 (95% CI, 1.06 to 1.54; $P = .0092$); in the limited sample, the HR was 1.17 (95% CI, 0.95 to 1.44; $P = .14$). The addition of trastuzumab in HER-2 nonoverexpressors did not have a significant impact on OS (Fig A1B, online only).

Toxicity. Adverse event data are presented for the limited sample only. Hematologic toxicity was generally mild, and is summarized in Tables 4 and 5. Although grade 3 or worse granulocytopenia was more frequent with standard versus weekly paclitaxel (15% *v* 9%; $P = .017$), febrile neutropenia requiring hospitalization was infrequent with either schedule (4% *v* 3%). Trastuzumab did not contribute to hematologic toxicity.

Nonhematologic toxicities occurring with at least 5% incidence are summarized in Tables 6 and 7. Grade 2 and 3 sensory neuropathy was encountered in 21% and 24% of patients receiving weekly paclitaxel versus 21% and 12% receiving standard paclitaxel, respectively (comparison of grades 2 and worse; $P = .0046$). Grade 2 and 3 motor neuropathy was noted in 8% and 9% of weekly versus 5% and 4% of

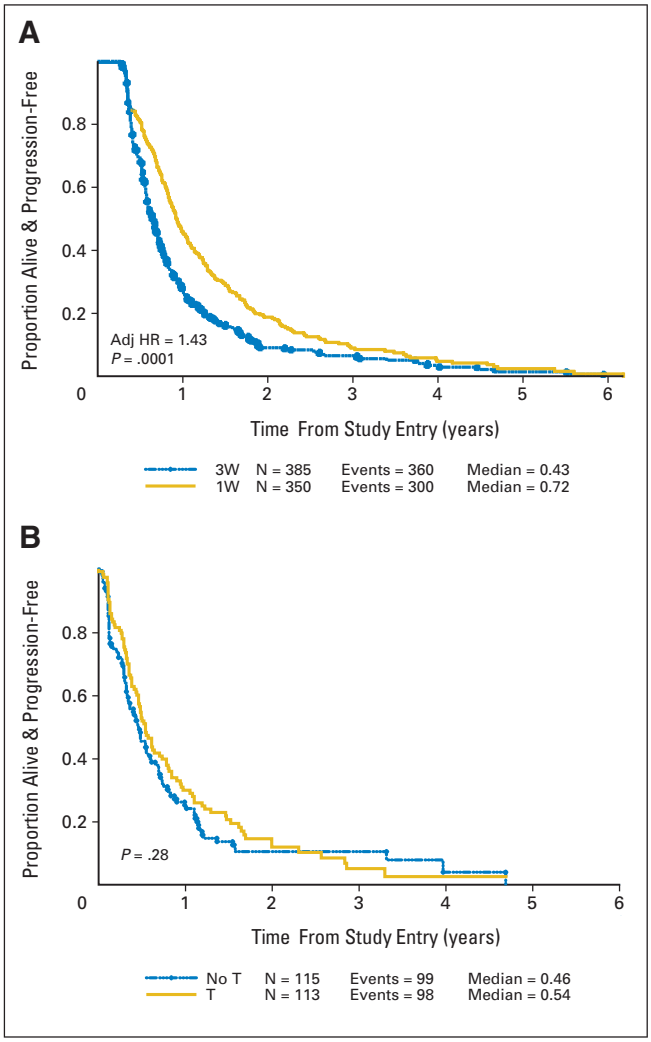

Fig 2. (A) Time to progression by paclitaxel schedule (combined sample). Adjusted hazard ratio = 1.43; $P < .0001$. (B) Time to progression by trastuzumab use in HER-2 nonoverexpressors (limited sample). 1W, weekly, 3W, every 3 weeks; HER-2, human epidermal growth factor receptor 2; T, trastuzumab.

Table 3. Tumor Response

Patient Population	Comparison	No. of Patients	Response (%)	95% CI for Response	OR*	95% CI for OR	Unadjusted χ^2 *P*
All patients (combined)	3-weekly	383	29	25 to 34	1.75	1.28 to 2.37	.0004
	Weekly	346	42	37 to 47			
All patients (limited)	3-weekly	225	35	28 to 41	1.36	0.96 to 1.93	.083
	Weekly	346	42	37 to 47			
HER-2 negative (limited)	3-weekly	94	24	16 to 34	2.28	1.27 to 4.08	.0053
	Weekly	132	42	34 to 51			
HER-2 negative (limited)	No trastuzumab	114	32	23 to 41	1.35	0.78 to 2.34	.28
	Trastuzumab	112	38	29 to 48			
HER-2 positive (limited)	3-weekly	76	58	46 to 69	0.89	0.49 to 1.63	.71
	Weekly	98	55	45 to 65			

Abbreviations: OR, odds ratio; 3-weekly, every 3 weeks; HER-2, human epidermal growth factor receptor 2.
*Unadjusted OR; the ratio of the odds of tumor response in the second group to the first group (eg, weekly *v* 3-weekly).

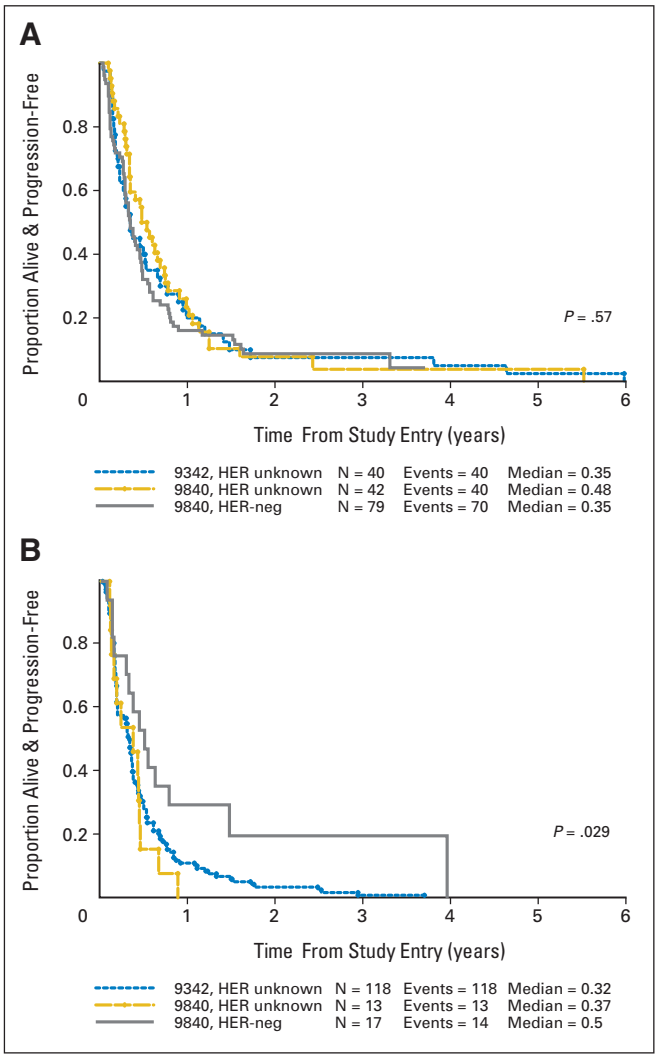

Fig 3. Time to progression by study. (A) First-line patients with unknown HER-2 status receiving 3-weekly paclitaxel. (B) Second-line patients with unknown HER-2 status receiving 3-weekly paclitaxel. HER-2, human epidermal growth factor receptor 2; 3-weekly, every 3 weeks.

conventionally dosed patients, resepctively (comparison of grades 2 and worse; $P = .013$). The incidence of neurosensory toxicity with weekly paclitaxel is inflated as a result of the excess neuropathy encountered in the first 116 patients who received 100 mg/m^2 dosing for the first six infusions; for these patients, the incidence of grade 3 neuropathy was 30%, compared with 21% for the subsequent 232 patients who received constant dosing of paclitaxel at 80 mg/m^2. Slightly more patients receiving 3-weekly paclitaxel experienced grade 3 or worse myalgia and arthralgia, whereas slightly more weekly paclitaxel patients experienced grade 3 or worse dyspnea. Other grade 3 and 4 nonhematologic toxicities were rare, including serious hypersensitivity reactions, as a result of the all-parenteral premedication regimen employed.[17]

The use of trastuzumab was associated with a 2.7% incidence of National Cancer Institute Common Toxicity Criteria grade 3 cardiac dysfunction, versus 0% among patients not receiving trastuzumab. Clinically significant cardiac events prompting serious adverse event reporting and hospitalization occurred in four patients receiving trastuzumab and in one patient not receiving trastuzumab; there were no deaths attributable to cardiac toxicity.

Two treatment-related deaths occurred, attributable to pneumonia, in patients randomly assigned to weekly paclitaxel alone. Two secondary malignancies occurred, both renal cell carcinomas, one in each paclitaxel schedule, both without trastuzumab.

Table 4. Grade 3-4 Hematologic Toxicity by Paclitaxel Dosing Schedule (n = 572)

Measure	Treatment Arm	Toxicity Grade 3 (severe) No.	3 (severe) %	4 (life threatening) No.	4 (life threatening) %
WBC	3-weekly	17	8	2	1
	Weekly	21	6	7	2
Platelets	3-weekly	4	2	0	0
	Weekly	3	1	2	1
Hemoglobin	3-weekly	6	3	0	0
	Weekly	17	5	1	< 1
Granulocytes/bands	3-weekly	22	10	12	5
	Weekly	19	5	11	3
Lymphocytes	3-weekly	19	8	9	4
	Weekly	53	15	14	4

Abbreviation: 3-weekly, every 3 weeks.

DISCUSSION

Weekly paclitaxel was superior to 3-weekly paclitaxel as treatment of MBC in RR and TTP. Importantly, this study also demonstrated a lack of therapeutic effect for trastuzumab in HER-2–nonoverexpressing breast cancer.

Weekly paclitaxel improved RR over standard paclitaxel (42% *v* 29%), and nearly doubled TTP, from 5 to 9 months. This improved efficacy was accompanied by increased neurotoxicity, but did not influence overall quality-of-life scores (assessed prospectively and reported previously).[18] Strategies to prevent cumulative neurotoxicity with weekly paclitaxel administration are needed

Table 5. Grade 3-4 Hematologic Toxicity by Trastuzumab Use (n = 572)

Measure	Trastuzumab	Toxicity Grade 3 (severe) No.	3 (severe) %	4 (life threatening) No.	4 (life threatening) %
WBC	No trastuzumab	23	8	8	3
	Trastuzumab	15	5	1	< 10
Platelets	No trastuzumab	6	2	1	< 1
	Trastuzumab	1	0	1	< 1
Hemoglobin	No trastuzumab	15	5	0	0
	Trastuzumab	8	3	1	< 1
Granulocytes/bands	No trastuzumab	19	7	18	6
	Trastuzumab	22	8	5	2
Lymphocytes	No trastuzumab	43	15	18	6
	Trastuzumab	29	10	5	2

Table 6. Grade 3-4 Nonhematologic Toxicity by Paclitaxel Dosing Schedule (n = 572)

		Toxicity Grade			
		3 (severe)		4 (life threatening)	
Toxicity	Treatment	No.	%	No.	%
Infection	3-weekly	10	4	0	0
	Weekly*	16	5	3	1
Diarrhea	3-weekly	6	3	0	0
	Weekly	16	5	0	0
Dyspnea	3-weekly	7	3	3	1
	Weekly	18	5	8	2
Edema	3-weekly	2	1	0	0
	Weekly	18	5	2	1
Neurosensory	3-weekly	27	12	0	0
	Weekly	84	24	1	< 1
Neuromotor	3-weekly	9	4	0	0
	Weekly	30	9	0	0
Malaise/fatigue	3-weekly	11	5	0	0
	Weekly	20	6	1	< 1
Hyperglycemia	3-weekly	15	7	2	1
	Weekly	14	4	3	1

Abbreviation: 3-weekly, every 3 weeks.
*There was one lethal infection.

and might include the "intermittent weekly" approach used in other studies (ie, Eastern Cooperative Oncology Group [ECOG] protocol 2100).[28]

Five previously reported randomized trials ([1-3, 21,22]) have used paclitaxel at 175 mg/m^2 via 3-hour infusion 3-weekly in more than 1,000 MBC patients. The primary analysis in this trial is unique in that it uses historical controls in addition to concurrently randomized controls. As a result, we were able to conduct the trial with fewer patients and less expense, and in less time. A disadvantage is the possibility that patients in the concurrent and historical settings could have fundamentally different characteristics. As part of "borrowing" from historical controls, we demonstrated that that they had outcomes similar to those in concurrent controls, once we adjusted for line of therapy.

When trastuzumab was approved for the treatment of HER-2–positive MBC, we faced a critical choice that ultimately made the study more complex. We could either exclude HER-2–positive patients from the trial or treat them with trastuzumab in addition to paclitaxel, recognizing that they would likely have better outcomes than the previous patients with HER-2–positive disease who were treated with paclitaxel alone, generally without knowledge of the HER-2 status. We chose to include trastuzumab for patients with HER-2–positive tumors. At the same time, we took advantage of the opportunity to assess the benefit of trastuzumab in tumors assessed to be HER-2 normal. In effect, this decision created a subtrial with a factorial design. There was the possibility of an interaction between trastuzumab and paclitaxel schedule in the patients with HER-2–normal tumors. Without increasing the sample size, we also had limited ability to assess whether the benefit of weekly paclitaxel was in HER-2–positive tumors than in HER-2–normal or HER-2– unknown tumors. However, in the interest of obtaining timely answers, we deliberately did not increase the sample size and accepted our limited ability to look for interactions or address subsets.

All of the historical controls (3-weekly paclitaxel) and the first 55 concurrent controls had unknown HER-2 status. These patients also differed from the remainder of the population in terms of the proportion of patients treated in the first- versus the second-line setting (25% and 76%, respectively). After adjusting for line of therapy, RR, TTP, and OS were similar among these two groups of patients. In addition, after adjusting for other relevant covariates in multivariate analysis, there were no major differences in our conclusions whether we used the combined sample or just the patients randomly assigned on this study.

Other studies have demonstrated similar results. Weekly paclitaxel yielded more pathologic complete responses in the neoadjuvant setting compared with 3-weekly scheduling.[23] In the adjuvant setting (ECOG 1199), weekly paclitaxel improved disease-free survival over 3-weekly (HR = 1.27; 95% CI, 1.07 to 1.51; $P = .006$) after four cycles of doxorubicin and cyclophosphamide,[24] although this was not a planned, protocol-specified analysis. Recently, the Anglo-Celtic IV trial comparing weekly with 3-weekly paclitaxel reported 42% and 27% RRs ($P = .002$), respectively, in 560 randomly assigned patients with advanced disease.[25] As opposed to CALGB 9840, where treatment lasted until disease progression, in the Anglo-Celtic IV trial, treatment lasted for 6 cycles (18 weeks) in the standard paclitaxel arm and 12 weeks in the weekly arm. It is possible that this asymmetry explains the lack of advantage in TTP observed in the latter trial, despite the higher RR for weekly paclitaxel.

Our study showed no benefit for the addition of trastuzumab in patients whose tumors lacked HER-2 overexpression or gene amplification. Although this result was expected, we know of no other prospective demonstration of this observation. Further, this observation

Table 7. Grade 3-4 Nonhematologic Toxicity by Trastuzumab Use (n = 572)

		Toxicity Grade			
		3 (severe)		4 (life threatening)	
Toxicity	Trastuzumab	No.	%	No.	%
Infection	No trastuzumab*	11	4	1	0
	Trastuzumab	15	5	2	1
Diarrhea	No trastuzumab	8	3	0	0
	Trastuzumab	14	5	0	0
Dyspnea	No trastuzumab	8	3	6	2
	Trastuzumab	17	6	5	2
Cardiac function	No trastuzumab	1	0	0	0
	Trastuzumab	7	2	0	0
Other Heart	No trastuzumab	0	0	0	0
	Trastuzumab	4	1	0	0
Edema	No trastuzumab	14	5	0	0
	Trastuzumab	6	2	2	1
Neurosensory	No trastuzumab	62	22	0	0
	Trastuzumab	49	17	1	< 1
Neuromotor	No trastuzumab	23	8	0	0
	Trastuzumab	16	6	0	0
Malaise/fatigue	No trastuzumab	15	5	1	< 1
	Trastuzumab	16	6	0	0

*There was one lethal infection.

addresses the concern that substantial numbers of patients with HER-2–dependent breast cancers might have been mislabeled as "negative" for this receptor. In our study, HER-2 assessment was performed locally. Patients with either IHC 3+ or IHC 2+ and FISH-amplified tumors were considered HER-2 positive and assigned to trastuzumab; all others were considered HER-2 normal and randomly assigned to trastuzumab versus no trastuzumab. Our findings provide a counterbalance to the recently reported results from National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-31 suggesting an apparent benefit for adjuvant trastuzumab in patients whose tumors tested negative at a central laboratory by both immunohistochemistry and FISH.[29] Weekly paclitaxel served as a foundation for the North Central Cancer Treatment Group (NCCTG)/US Intergroup trial N9831 examining the role of adjuvant trastuzumab.[26] Our study confirms the appropriateness of this approach.

Weekly therapy may be preferable for other taxanes as well as for paclitaxel. A recently reported randomized trial comparing weekly nanoparticle albumin-bound paclitaxel with 3-weekly dosing demonstrated a higher RR and longer TTP in favor of weekly dosing.[27] For paclitaxel, our study establishes the appropriateness of basing future studies, and standard practice, on weekly administration. Comparisons with other schedules, such as every-2-weeks full-dose (dose-dense) paclitaxel, as well as with newer taxanes and formulations, are appropriate.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).