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ORIGINAL REPORT

Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance)

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ABSTRACT

Purpose
We compared nab-paclitaxel or ixabepilone once per week to paclitaxel with bevacizumab as first-line therapy for patients with advanced breast cancer (BC) to evaluate progression-free survival (PFS) for nab-paclitaxel or ixabepilone versus paclitaxel.

Patients and Methods
Eligible patients were age ≥ 18 years with chemotherapy-naive advanced BC. Patients were randomly assigned to bevacizumab with paclitaxel 90 mg/m^2 (arm A), nab-paclitaxel 150 mg/m^2 (arm B), or ixabepilone 16 mg/m^2 (arm C), once per week for 3 of 4 weeks. Planned enrollment was 900 patients, which would give 88% power to detect a hazard ratio of 0.73.

Results
In all, 799 patients were enrolled, and 783 received treatment (97% received bevacizumab). Arm C was closed for futility at the first interim analysis (n = 241), and arm A (n = 267) and arm B (n = 275) were closed for futility at the second interim analysis. Median PFS for paclitaxel was 11 months, ixabepilone was inferior to paclitaxel (PFS, 7.4 months; hazard ratio, 1.59; 95% CI, 1.31 to 1.93; $P < .001$), and nab-paclitaxel was not superior to paclitaxel (PFS, 9.3 months; hazard ratio, 1.20; 95% CI, 1.00 to 1.45; $P = .054$). Results were concordant with overall survival; time to treatment failure was significantly shorter in both experimental arms *v* paclitaxel. Hematologic and nonhematologic toxicity, including peripheral neuropathy, was increased with nab-paclitaxel, with more frequent and earlier dose reductions.

Conclusion
In patients with chemotherapy-naive advanced BC, ixabepilone once per week was inferior to paclitaxel, and nab-paclitaxel was not superior with a trend toward inferiority. Toxicity was increased in the experimental arms, particularly for nab-paclitaxel. Paclitaxel once per week remains the preferred palliative chemotherapy in this setting.

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INTRODUCTION

Metastatic breast cancer (BC) is generally incurable with few patients achieving long-term disease-free survival.[1] Despite a marked increase in the choice of active agents, the impact on overall survival (OS) has been modest.[2,3]

Paclitaxel is a taxane derivative and is among the most active agents in the treatment of BC.[4] Randomized trials based on mathematical modeling compared dosing once per week with dosing once every 3 weeks in advanced disease, demonstrating improved efficacy and reduced hematologic toxicity.[5,6] The Eastern Cooperative Oncology Group (ECOG) 2100 (Paclitaxel With or Without Bevacizumab in Treating Patients With Locally Recurrent or Metastatic Breast Cancer) trial compared paclitaxel alone once per week or in combination with the vascular endothelial growth factor (VEGF) antibody bevacizumab as first-line therapy, with near

doubling of progression-free survival (PFS) in patients receiving bevacizumab[7] and only minimal impact on OS.

One major limitation of paclitaxel is its poor water solubility; thus it requires Cremophor EL as a solvent. Nab-paclitaxel is a solvent-free novel formulation of paclitaxel in albumin-bound nanoparticles, which eliminates the need for premedication to prevent hypersensitivity.[8] Nab-paclitaxel 260 mg/m^2 once every 3 weeks was superior to paclitaxel 175 mg/m^2 with less hematologic toxicity but increased peripheral neuropathy.[9] Once-per-week dosing at 100 and 125 mg/m^2 was found to be efficacious, with minimal toxicity in taxane-resistant disease.[10] A randomized first-line phase II trial reported improved PFS and OS with once-per-week dosing with nab-paclitaxel 150 mg/m^2 compared with nab-paclitaxel 100 mg/m^2, with only slightly higher rates of peripheral neuropathy.[11]

Ixabepilone is a semisynthetic analog of epothilone B that binds to the same beta-tubulin site as paclitaxel and, in preclinical models, is a more potent tubulin polymerizer.[12,13] Ixabepilone once every 3 weeks with capecitabine was superior to capecitabine alone in taxane-resistant disease,[14] and as a single agent, it demonstrated efficacy in multidrug-resistant metastatic BC.[15-17] Its use is complicated by significant peripheral neuropathy and bone marrow suppression. Single-arm trials and randomized phase II studies suggested reduced toxicity with ixabepilone once per week at doses up to 16 mg/m^2.[18-24]

To determine the optimal therapy for patients with chemotherapy-naive advanced BC, we designed a randomized phase III trial comparing either nab-paclitaxel or ixabepilone once per week to paclitaxel once per week. All agents were given in combination with bevacizumab. The paclitaxel and bevacizumab schedule mirrored the schedule in ECOG 2100; the doses for nab-paclitaxel and ixabepilone were chosen on the basis of data from phase II trials. The hypotheses tested were that newer antimicrotubule agents would offer improved PFS with similar or reduced toxicity compared with standard paclitaxel.

PATIENTS AND METHODS

Study Design and Procedures

The Cancer and Leukemia Group B (CALGB) 40502 (Paclitaxel, Nab-Paclitaxel, or Ixabepilone With or Without Bevacizumab in Treating Patients With Stage IIIC or Stage IV Breast Cancer) trial was a three-arm randomized phase III trial comparing paclitaxel once per week to nanoparticle albumin-bound nab-paclitaxel once per week and to ixabepilone as first-line chemotherapy with bevacizumab for locally recurrent or metastatic BC. The study was approved by the National Cancer Institute's Institutional Review Board, and all patients signed approved informed consent before registration and screening. All chemotherapy was administered once per week on days 1, 8, and 15 followed by 1 week of rest with 28-day treatment cycles. Treatment arms were paclitaxel 90 mg/m^2 (arm A), nab-paclitaxel 150 mg/m^2 (arm B), and ixabepilone 16 mg/m^2 (arm C). Bevacizumab was given at 10 mg/kg on days 1 and 15 of each cycle until March 2011, when an amendment allowed optional use to be declared at the time of random assignment. Standard premedications were recommended for paclitaxel and ixabepilone.

Data quality was ensured by review of the data by the Alliance Statistics and Data Center and by the study chairperson who adhered to Alliance policies. This phase III therapeutic trial was monitored at least twice annually by the Data and Safety Monitoring Board, a standing committee composed of individuals from within and outside the Alliance.

Eligibility

Eligibility included patients age ≥ 18 years with histologically documented stage IV or stage IIIC BC not amenable to local therapy, ECOG performance status of 0 to 1, and life expectancy ≥ 12 weeks. No prior chemotherapy for metastatic disease or prior treatment with bevacizumab was allowed; patients could have received any number of prior hormone therapies. Prior taxane therapy in the adjuvant/neoadjuvant setting was allowed if metastatic disease occurred ≥ 12 months after the last dose of taxane. Patients with human epidermal growth factor receptor 2–positive (HER2-positive) disease were eligible if they had previously received trastuzumab or lapatinib. Major surgery must have been completed ≥ 28 days before registration. Patients with a history of resected brain metastases or brain radiation with stable imaging for 3 months were eligible. Measurable disease and adequate bone marrow, renal, and hepatic function were required.

Exclusion criteria included grade ≥ 2 pre-existing peripheral neuropathy, prior grade ≥ 3 hypersensitivity to paclitaxel or Cremophor EL, history of uncontrolled hypertension, recent GI fistula or perforation, recent significant bleeding, a history of significant cardiovascular disease, nonhealing wounds, or bone fracture.

Dose Modifications

Dose levels and selected modifications are outlined in Appendix Table A1 (online only); re-escalation was not allowed. Use of granulocyte colony-stimulating factor was allowed at the physician's discretion. If treatment was delayed for more than 4 weeks, chemotherapy was discontinued. Patients whose disease had not progressed by cycle 7 were allowed to discontinue chemotherapy and continue treatment with bevacizumab alone.

Evaluation of Response

Tumor imaging was repeated every two cycles; responses required 4-week confirmation. Response was assessed by using RECIST 1.0.

Statistics

The primary objective was to test the efficacy of nab-paclitaxel versus paclitaxel (control arm) and ixabepilone versus paclitaxel in combination with bevacizumab in patients with advanced BC. The primary end point was PFS defined as the interval from date of registration until date of first disease progression or death as a result of any cause; patients were censored at the last date they were assessed to be progression free. Secondary objectives included the same comparisons for OS: 12-month rate of progression, objective response rate, duration of response, and time to treatment failure defined as the interval from registration until termination of protocol therapy for any reason. Toxicity end points included adverse events and a comparison of grade greater than 2 sensory neuropathy by using Common Terminology Criteria for Adverse Events version 4.0. Embedded correlative studies of tumor and blood biomarkers, pharmacogenomics, health disparities, and quality of life will be reported in separate analyses.

Target accrual was 900 patients randomly assigned 1:1:1 and stratified by prior use of adjuvant taxane, hormone receptor status, and optional use of bevacizumab. Final analysis after 715 PFS events gave 88% power to detect a prolongation of PFS from 11 months in the control arm to 15 months in each experimental arm.

Interim monitoring for superiority and futility was performed separately for nab-paclitaxel and ixabepilone. Under Lan-DeMets error spending functions,[25] boundaries for superiority required a 99% predictive probability that final analysis would conclude efficacy,[26] and boundaries for futility were defined by Freidlin et al.[27]

The primary assessments of efficacy used stratified log-rank tests[28] with one-sided $\alpha = .0135$ for each comparison established by using the method of Jung.[29] Secondary analysis of efficacy used multivariable Cox proportional hazards models with known prognostic factors. Time-to-event end points were summarized by using Kaplan and Meier estimates.[30] Rates of objective response and adverse events were compared between arms by using Fisher's exact test.[31] For each experimental arm, comparisons with patients concurrently randomly assigned to the control arm were performed under modified intention-to-treat, excluding only those who never began protocol treatment. Statistical analyses were performed by using SAS v9.2 (SAS Institute, Cary, NC) and R 2.15.1 (http://www.r-project.org) and were conducted by the Alliance Statistics and Data Center.

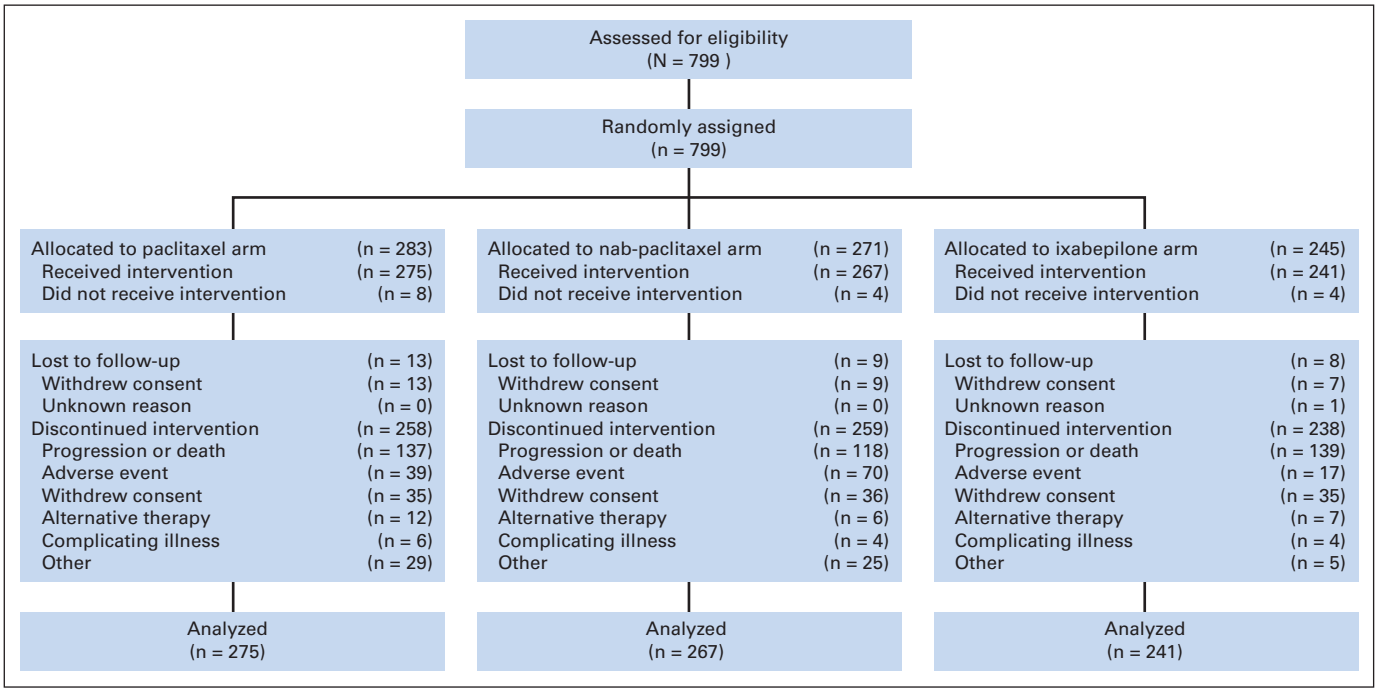

Fig 1. CONSORT diagram for the intent-to-treat analysis of data from the Cancer and Leukemia Group B (CALGB) 40502 (Paclitaxel, Nab-Paclitaxel, or Ixabepilone With or Without Bevacizumab in Treating Patients With Stage IIIC or Stage IV Breast Cancer) trial.

RESULTS

The study was activated in October 2008 and was closed to accrual in November 2011. In March 2011, an amendment allowed optional use of bevacizumab declared before random assignment. After a first planned interim analysis at 165 PFS events, ixabepilone crossed the futility boundary for superiority. On the basis of Data and Safety Monitoring Board recommendations, the ixabepilone arm was closed on July 8, 2011, and accrual continued to the paclitaxel and nab-paclitaxel arms with equally weighted random assignment. At the second planned interim analysis at 236 PFS events, the nab-paclitaxel arm crossed the futility boundary for superiority and was closed on November 30, 2011. Statistical analyses were performed on all data available as of June 4, 2013.

Patient and Disease Characteristics

In all, 799 patients were enrolled and randomly assigned; 16 did not start treatment: eight were randomly assigned to paclitaxel, four to nab-paclitaxel, and four to ixabepilone (CONSORT diagram; Fig 1). In total, 267 patients were treated with nab-paclitaxel, 241 with ixabepilone, and 275 with paclitaxel (246 were concurrently enrolled in the ixabepilone arm). At the time of reporting, 755 (96%) had stopped study therapy; 437 patients (56%) had died, 29 (4%) withdrew consent to be observed, and one (< 1%) was lost to follow-up. The median follow-up for all surviving patients was 25 months, with a maximum of 50 months. The majority of patients received protocol-specified bevacizumab, with only 20 (3%) electing not to receive bevacizumab after the issuance of the amendment allowing optional use. Therefore, strata defined by bevacizumab use were excluded from statistical analyses.

Patient characteristics were well balanced between study arms (Table 1). Median age was 57 years, 99% were female, and 80% were white. Forty-four percent received taxanes as adjuvant therapy, 72% (n = 573) had hormone receptor–positive disease, 25% (n = 201) had triple-negative BC (TNBC) tumors (estrogen receptor–negative/progesterone receptor–negative/HER2-negative), and 2% (n = 20) had HER2-positive disease. Among treated patients, 56% had a disease-free interval (DFI) from diagnosis of primary tumor to diagnosis of metastatic disease of ≥ 2 years. Slightly more patients receiving ixabepilone had bone metastases compared with patients randomly assigned concurrently to paclitaxel (Appendix Table A2, online only).

Efficacy

Tests of superiority of ixabepilone and of nab-paclitaxel to paclitaxel were deemed futile during interim monitoring of the trial. After continued follow-up of all patients, median PFS was 11 months for paclitaxel. In a post hoc analysis, ixabepilone was inferior to paclitaxel with a median PFS of 7.4 months and a hazard ratio (HR) of 1.59 (95% CI, 1.31 to 1.93; $P < .001$; Fig 2A). Nab-paclitaxel trended toward inferiority to paclitaxel with a median PFS of 9.3 months and HR of 1.20 (95% CI, 1.00 to 1.45; log-rank $P = .054$; Fig 2B), but the post hoc test did not reach statistical significance. A multivariable Cox proportional hazards model was used to compare each experimental arm to paclitaxel, adjusting for stratification factors, DFI of ≤ 2 years versus more than 2 years, and presence or not of visceral metastases (Table 2). Results are concordant with log-rank tests and demonstrate the known prognostic relationships of prior taxane use, hormone receptor negativity, shorter DFI, and visceral metastases predicting worse PFS.

An unplanned, exploratory subset analysis of patients with TN (Fig 3A and 3B) and hormone receptor–positive disease (Fig 3C and

Table 1. Patient and Tumor Characteristics

Characteristic	Paclitaxel (n = 283) No. (%)	Nab-Paclitaxel (n = 271) No. (%)	Ixabepilone (n = 245) No. (%)	Total (N = 799) No. (%)	P*
Age, years					
20-49	69 (24)	76 (28)	73 (30)	218 (27)	.30
50-69	183 (66)	163 (60)	154 (63)	500 (63)	
70-80+	31 (11)	32 (12)	18 (7)	81 (10)	
Female sex	277 (98)	268 (99)	243 (99)	788 (99)	.45
Race/ethnicity					
Unknown	7 (2)	4 (1)	3 (1)	14 (2)	
White	220 (78)	214 (79)	206 (84)	640 (80)	.23
Black	42 (15)	45 (17)	26 (11)	113 (14)	
Other/unknown	14 (5)	8 (3)	10 (4)	32 (4)	
Taxane as adjuvant therapy					
Yes	125 (44)	120 (44)	107 (44)	352 (44)	.99
No	158 (56)	151 (56)	138 (56)	447 (56)	
Site of metastases					
Unknown†	11 (4)	6 (2)	4 (2)	21(3)	
Any visceral	217 (77)	205 (76)	199 (81)	621 (78)	.35
Any soft tissue	196 (69)	184 (68)	164 (67)	544 (68)	.60
Any bone	159 (56)	162 (60)	163 (67)	484 (61)	.09
Disease-free interval					
Unknown†	11 (4)	6 (2)	4 (2)	21 (3)	
0 to ≤ 1 month (de novo)	30 (11)	31 (11)	28 (11)	89 (11)	.24
> 1 month to ≤ 2 years	88 (31)	87 (32)	64 (26)	239 (30)	
> 2 years	154 (54)	147 (54)	149 (61)	450 (56)	
Clinical stage					
Unknown	32 (11)	21 (8)	30 (12)	83 (10)	.83
III	25 (9)	21 (8)	21 (9)	67 (8)	
IV	226 (80)	229 (85)	194 (79)	649 (81)	
Tumor subtype					
ER or PgR unknown/missing†	8 (3)	4 (1)	4 (2)	16 (2)	
ER or PgR positive	200 (71)	197 (73)	176 (72)	573 (72)	.97
HER2 missing	6 (2)	6 (2)	3 (1)	15 (2)	
HER2 positive	7 (2)	3 (1)	2 (1)	12 (2)	
HER2 negative	187 (66)	188 (69)	171 (70)	546 (68)	
ER and PgR negative	75 (27)	70 (26)	65 (27)	210 (26)	
HER2 missing	1 (< 1)	4 (1)	0 (0)	5 (1)	
HER2 positive	1 (< 1)	1 (< 1)	2 (1)	4 (1)	
HER2 negative	73 (26)	65 (24)	63 (26)	201 (25)	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor.
*P values are from two-sided Fisher exact tests excluding patients for whom factors were unknown.
†Data on site of metastases, disease-free interval, and tumor subtypes were available for 778 of 783 treated patients.

3D) was conducted. In multivariable Cox proportional hazards models with the covariates mentioned previously, ixabepilone was inferior to paclitaxel (median PFS, 5.6 to 7.4 months; HR, 1.57; 95% CI, 1.08 to 2.29; $P = .020$). No significant difference was found between nab-paclitaxel and paclitaxel (median PFS, 7.4 and 6.5 months, respectively; HR, 0.86; 95% CI, 0.60 to 1.25; $P = .43$).

For patients with hormone receptor–positive disease, the median PFS for paclitaxel was 12.4 months. By using a multivariable Cox proportional hazards model for PFS, ixabepilone (median PFS, 8.0 months; HR, 1.62; 95% CI, 1.29 to 2.04; $P < .001$) and nab-paclitaxel (median PFS, 10.0 months; HR, 1.45; 95% CI, 1.16 to 1.81; $P = .0012$) treatments were inferior to treatment with paclitaxel.

Tumor Response

For 783 patients who began protocol treatment, the overall response rate was 38% for paclitaxel, 34% for nab-paclitaxel, and 27% for ixabepilone (Appendix Table A3, online only). There was no difference in response between nab-paclitaxel and paclitaxel (odds ratio, 0.84; $P = .33$), but response rates were significantly lower with ixabepilone compared with paclitaxel (odds ratio, 0.57; $P = .0038$). Time to treatment failure was significantly shorter in both experimental arms compared with paclitaxel, with a median of 4.9 months versus 6.8 months ($P < .001$) for ixabepilone and 5.2 months versus 6.6 months ($P < .001$) for nab-paclitaxel. On the basis of the lack of benefit in the experimental arms, duration of response was not evaluated.

OS

By using a stratified log-rank test, a post hoc test of inferiority was significant for ixabepilone compared with paclitaxel (median OS, 23.6 to 27.4 months; HR, 1.31; 95% CI, 1.03 to 1.66; $P = .027$; Fig 2C,) but did not reach significance for nab-paclitaxel compared with paclitaxel (median OS, 23.5 to 26.5 months; HR, 1.17; 95% CI, 0.92 to 1.47; $P = .20$; Fig 2D). Multivariable analyses are consistent with univariable tests (data not shown).

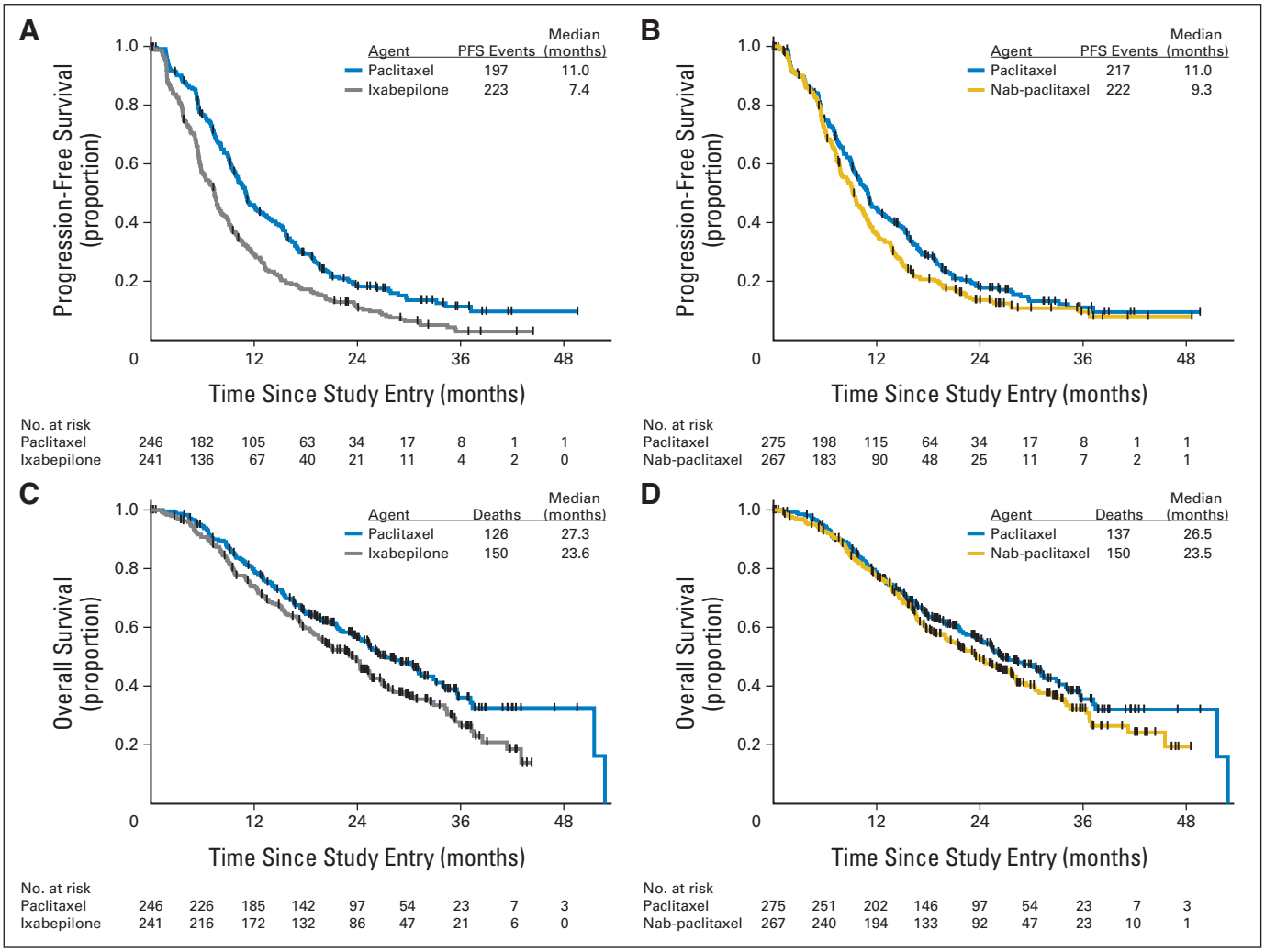

Fig 2. Kaplan-Meier plots of ixabepilone or nab-paclitaxel compared with paclitaxel, respectively, for (A, B) progression-free survival (PFS), and (C, D) overall survival by treatment arm.

Toxicity

Toxicity information was available for 774 patients (99% of treated patients; Table 3; Appendix Table A4, online only). Hematologic toxicity of grade ≥ 3 occurred in 22% of patients receiving paclitaxel, 55% receiving nab-paclitaxel, and 12% receiving ixabepilone. Grade ≥ 3 nonhematologic toxicity was reported in 49% of patients receiving paclitaxel, 65% receiving nab-paclitaxel, and 58% receiving ixabepilone. Compared with paclitaxel, nab-paclitaxel resulted in worse hematologic and

Table 2. Univariable and Multivariable Proportional Hazards Models of PFS

Variable	Comparison of Nab-Paclitaxel With Paclitaxel			Comparison of Ixabepilone With Paclitaxel		
	HR	95% CI	*P*	HR	95% CI	*P*
Univariable model*						
Treatment arm (experimental *v* control)	1.20	1.00 to 1.45	.054	1.59	1.31 to 1.93	< .001
Multivariable factors†						
Treatment arm (experimental *v* control)	1.22	1.01 to 1.48	.035	1.60	1.32 to 1.94	< .001
Prior taxane (yes *v* no)	1.65	1.33 to 2.04	< .001	1.46	1.18 to 1.80	< .001
Hormone receptor status (negative *v* positive)	1.49	1.21 to 1.84	< .001	1.68	1.35 to 2.07	< .001
Disease-free interval (≤ 2 years *v* > 2 years)	1.26	1.02 to 1.56	.036	1.21	0.98 to 1.50	.08
Visceral metastases (any *v* none)	1.46	1.14 to 1.85	.0023	1.17	0.91 to 1.50	.22

Abbreviations: HR, hazard ratio; PFS, progression-free survival.
*Univariable models included all treated patients concurrently enrolled with each experimental arm: n = 542 for nab-paclitaxel *v* paclitaxel; n = 487 for ixabepilone *v* paclitaxel.
†Multivariable models included patients with no missing information: n = 537 for nab-paclitaxel *v* paclitaxel; n = 484 for ixabepilone *v* paclitaxel.

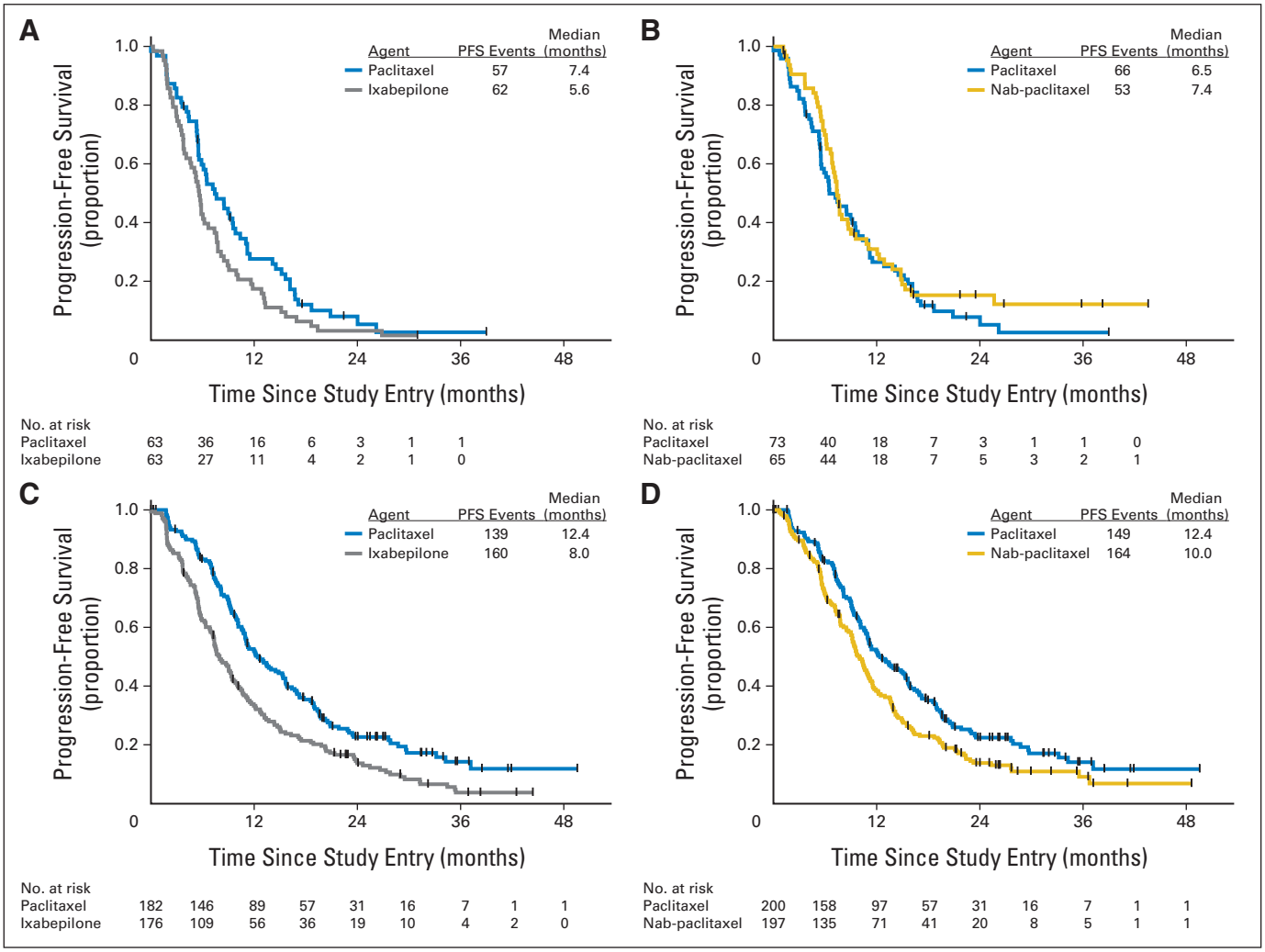

Fig 3. Kaplan-Meier plots of progression-free survival (PFS) for the exploratory analyses in patient subgroups of ixabepilone or nab-paclitaxel compared with paclitaxel, respectively, defined by (A, B) triple-negative disease and (C, D) hormone receptor–positive disease

nonhematologic toxicity ($P < .001$ for both), and ixabepilone resulted in less hematologic toxicity ($P = .0037$) and a nonsignificant trend toward more nonhematologic toxicity ($P = .14$).

The most common grade 3 to 4 hematologic toxicities were neutropenia and anemia, and the most common grade 3 to 4 nonhematologic toxicities were sensory neuropathy, fatigue, hypertension, motor neuropathy, pain, and nausea. The incidence of grade ≥ 2 sensory neuropathy was increased with nab-paclitaxel (54%) compared with paclitaxel (46%; $P = .031$) but was similar when ixabepilone (47%) was compared with paclitaxel.

Dose Reductions and Discontinuations

Dose reductions were more frequent and occurred earlier for patients receiving nab-paclitaxel, with 31% of patients having been dose-reduced by cycle 2, and 45% by cycle 3 compared with 9% (cycle 2) and 15% (cycle 3) for paclitaxel, and 6% (cycle 2) and 15% (cycle 3) for ixabepilone. Only 28% of patients were still receiving full-dose nab-paclitaxel at the start of cycle 5 compared with 76% for paclitaxel and 65% for ixabepilone.

Discontinuation rates for chemotherapy but not for bevacizumab were higher for nab-paclitaxel and ixabepilone compared with paclitaxel. By cycle 5, 80 patients (29%) had discontinued paclitaxel, 131 (49%) nab-paclitaxel, and 120 (50%) ixabepilone.

DISCUSSION

The primary goal of treatment for patients with metastatic BC is to diminish symptoms and control disease progression while maintaining the highest possible quality of life. Improving OS is also a therapeutic goal but one that has been more difficult to demonstrate, particularly in the first-line treatment setting. Although targeted biologic therapy offers promise for some subtypes of metastatic BC, chemotherapy remains the backbone of systemic therapy for hormone-resistant disease. New chemotherapy agents offer the potential for activity in resistant disease, with similar or improved toxicity.

The goal of this phase III cooperative group trial was to compare two newly developed agents for the treatment of metastatic BC with standard paclitaxel, given with bevacizumab. The hypothesis, based on earlier phase II trials, was that one or both of the experimental arms would prove to be superior to paclitaxel given once per week with

Table 3. Toxicity End Points

Toxicity	Paclitaxel (n = 272) No. (%)	Nab-Paclitaxel (n = 263) No. (%)	Nab-Paclitaxel (n = 263) P*	Ixabepilone (n = 239) No. (%)	Ixabepilone (n = 239) P*
Any grade 3+ events	162 (60)	221 (84)	< .001	145 (61)	.93
Any hematologic adverse events	60 (22)	144 (55)	< .001	29 (12)	.0037
ANC/AGC	50(18	134 (51)	< .001	16 (7)	< .001
Leukocytes (total WBC)	21 (8)	48 (18)	< .001	9 (4)	.037
Hemoglobin	8 (3)	13 (5)	.27	8 (3)	.80
Any nonhematologic adverse events	134 (49)	170 (65)	< .001	138 (58)	.17
Sensory neuropathy	48 (18)	70 (27)	.016	60 (25)	.15
Fatigue (asthenia, lethargy, malaise)	27 (10)	43 (16)	.030	35 (15)	.22
Hypertension	25 (9)	20 (8)	.54	28 (12)	.37
Motor neuropathy	9 (3)	26 (10)	.0026	17 (7)	.066
Pain	12 (4)	25 (10)	.026	10 (4)	1.0
Nausea	0 (0)	13 (5)	< .001	14 (6)	< .001
Maximum grade of sensory neuropathy			P†		P†
2	77 (28)	73 (28)	.01	53 (22)	.032
3	47 (17)	67 (25)		54 (23)	
4	1 (< 1)	3 (1)		6 (3)	

Abbreviations: AGC, absolute granulocyte count; ANC, absolute neutrophil count.
*P values are from two-sided Fisher exact tests for patients receiving paclitaxel concurrently enrolled onto each experimental arm.
†P values are from Cochran-Mantel-Haenszel χ^2 tests for ordinal scale data.

similar or reduced toxicity. By using interim analyses for superiority/futility, we were able to limit the total number of patients required to assess the primary end point.

Altering the treatment schedule of paclitaxel has been shown to improve efficacy and reduce toxicity,[32] and once-per-week dosing has become the standard for the treatment of metastatic disease. Randomized phase II data suggested superior efficacy from nab-paclitaxel at 150 mg/m^2,[11] and small phase II studies demonstrated reduced toxicity with ixabepilone once per week.[20] By comparing these three microtubule inhibitors by using once-per-week dosing, we hoped to capitalize on improvements in schedule while assessing the relative efficacy and toxicity of nab-paclitaxel and ixabepilone compared with paclitaxel. The bevacizumab backbone reflected the current best treatment for HER2-negative advanced BC when the study was designed.[7]

In earlier phase II studies, ixabepilone once per week was relatively well tolerated, with less hematologic toxicity than that seen with dosing once every 3 weeks. Here, however, it was inferior to paclitaxel for PFS, response, and OS. The overall rates of nonhematologic toxicity were higher, indicating that it would not be possible to overcome inferior efficacy by increasing ixabepilone dose. Although phase II studies suggested improved efficacy with higher-dose nab-paclitaxel given once per week, in this phase III trial, treatment with nab-paclitaxel resulted in significantly greater hematologic and nonhematologic toxicity compared with paclitaxel, with a trend toward shorter PFS. Early dose reductions were necessary because of toxicity, but the dose was generally maintained within the therapeutic range used in clinical practice.

As noted, virtually all patients received bevacizumab. Usage has since declined because this agent is no longer labeled for the treatment of BC in the United States (although it is still approved in other countries), raising a question regarding the applicability of our results without bevacizumab. Although an interaction is theoretically possible, there are no data to indicate that bevacizumab would preferentially synergize with paclitaxel and not with the other agents or that our results would have been different if bevacizumab had not been included in the treatment regimen.

The dose of nab-paclitaxel used in this study is clearly not feasible, and it resulted in frequent dose reductions and discontinuations. Ongoing trials are evaluating intermediate doses in biologic subsets such as TN disease, although we did not identify differential efficacy in our unplanned analysis. Ixabepilone was approved on the basis of studies that used a once-every-3-weeks dosing schedule in taxane-resistant disease and, although this resulted in significant toxicity,[14-16,27] it remains the standard schedule for ixabepilone use.

In summary, this phase III cooperative group trial failed to demonstrate superiority of either nab-paclitaxel or ixabepilone given once per week compared with paclitaxel in patients with advanced BC, with all drugs given in combination with bevacizumab. Both newer agents were associated with increased overall toxicity, possibly inferior effectiveness, and reduced palliation of disease-related symptoms, even though earlier studies had suggested that either of the investigational arms, particularly nab-paclitaxel, might be more efficacious than standard once-per-week paclitaxel. Without direct evidence, the earlier trials led to widespread use of more costly and higher-dose nab-paclitaxel in many clinical practices. The higher dose used in our phase III trial resulted in early discontinuation and dose reductions, which in turn limited exposure to the drug. On the basis of our data, once-per-week paclitaxel should remain the preferred microtubule inhibitor for treating patients with metastatic BC in the first-line setting, and there is no evidence that either of the newer agents is superior. Our trial illustrates the importance of adequately powered prospective trials to confirm phase II reports. In addition, these results remind clinicians to be cautious when incorporating new agents, particularly those that are more expensive and potentially more toxic, and support the cooperative group mechanism for assessing both better and less expensive therapies.[33]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

bevacizumab: also called Avastin (Genentech, South San Francisco, CA). Bevacizumab is a recombinant, humanized, monoclonal antibody that binds and neutralizes the vascular endothelial growth factor, thus acting as an antiangiogenic agent.

triple-negative breast cancer (TNBC): breast tumors that are negative for estrogen and progesterone receptor expression and that also underexpress *HER-neu*.

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Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance)

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Methods

Data quality was ensured by a review of the data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. This phase III therapeutic trial was monitored at least twice annually by the Data and Safety Monitoring Board, a standing committee composed of individuals from within and outside the Alliance.

Table A1. Dose Modifications for Paclitaxel, Nab-Paclitaxel, and Ixabepilone

Dose Level	Paclitaxel (mg/m^2)	Nab-Paclitaxel (mg/m^2)	Ixabepilone (mg/m^2)
0	90	150	16
−1	75	120	13
−2	60	90	10

NOTE. Chemotherapy was delayed with required dose reduction for absolute neutrophil count (ANC) < 1,000 or platelets < 75,000 on day 1 of a cycle. Chemotherapy was skipped for ANC < 1,000 and platelets < 75,000 on days 8 or 15 with dose reductions required for ANC < 1,000 and platelets < 100,000. Chemotherapy was dose-reduced for intolerable grade 2 peripheral neuropathy, held for grade 3 peripheral neuropathy until improvement to grade < 2 with subsequent mandatory dose reduction, and was discontinued for grade 4 peripheral neuropathy. No dose modifications were allowed for bevacizumab. Bevacizumab was held for uncontrolled hypertension, symptoms of reversible posterior leukoencephalopathy syndrome, venous thromboembolic events, significant proteinuria, wound dehiscence/perforation, and surgery and was discontinued for grade 4 events and any arterial thromboembolism.

Table A2. Patient and Tumor Characteristics for Patients Randomly Assigned to Paclitaxel and Ixabepilone Before Closure of the Ixabepilone Arm

Characteristic	Paclitaxel (n = 246) No. (%)	Ixabepilone (n = 245) No. (%)	*P**
Age, years			
20-49	60 (24)	73 (30)	.20
50-69	159 (65)	154 (63)	
70-80+	27 (11)	18 (7)	
Female sex	243 (99)	243 (99)	1.00
Race/ethnicity			
Unknown	4 (2)	3 (1)	
White	194 (79)	206 (84)	.28
Black	38 (15)	26 (11)	
Other	10 (4)	10 (4)	
Taxane as adjuvant therapy			
Yes	107 (43)	107 (44)	1.00
No	139 (57)	138 (56)	
Site of metastases			
Unknown	3 (1)	4 (2)	
Any visceral	192 (78)	199 (81)	.36
Any soft tissue	176 (72)	164 (67)	.32
Any bone	144 (59)	163 (67)	.06
Disease-free interval			
Unknown	0 (0)	4 (2)	
0 to ≤ 1 month (de novo)	29 (12)	28 (11)	.38
> 1 month to ≤ 2 years	79 (32)	64 (26)	
> 2 years	138 (56)	149 (61)	
Clinical stage			
Unknown	21 (9)	30 (12)	
III	23 (9)	21 (9)	1.0
IV	202 (82)	194 (79)	
Tumor subtype			
ER or PgR unknown/missing	0 (0)	4 (2)	
ER or PgR positive	182 (74)	176 (72)	.84
HER2 missing	5 (2)	3 (1)	
HER2 positive	6 (2)	2 (1)	
HER2 negative	171 (70)	171 (70)	
ER and PgR negative	64 (26)	65 (27)	
HER2 missing	0 (0)	0 (0)	
HER2 positive	1 (< 1)	2 (1)	
HER2 negative	63 (26)	63 (26)	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor.
**P* values are from two-sided Fisher exact tests excluding patients for whom factors were unknown.

Table A3. Secondary Efficacy End Points

End Point	Nab-Paclitaxel (n = 267) No. (%)	HR	95% CI	Paclitaxel (n = 275) No. (%)	95% CI	Paclitaxel (n = 246) * No. (%)	95% CI	Ixabepilone (n = 241) No. (%)	HR	95% CI
Objective response	91 (34)			105 (38)		96 (39)		64 (27)		
Complete	6 (2)			11 (4)		9 (4)		2 (1)		
Partial	85 (32)			94 (34)		87 (35)		62 (26)		
Stable disease	130 (49)			133 (48)		118 (48)		121 (50)		
Progressive disease	22 (8)			26 (9)		23 (9)		34 (14)		
Unevaluable	24 (9)			11 (4)		9 (4)		22 (9)		
Median time to treatment failure, months	5.2	1.37	1.15 to 1.63	6.6		6.8		4.9	1.47	1.22 to 1.77
Median overall survival, months	23.5	1.17	0.92 to 1.63	26.6		27.3		23.6	1.31	1.03 to 1.66
Rate of progression-free survival at 12 months	36%		0.30 to 0.42	45%	0.39 to 0.51	46%	0.39 to 0.52	29%		0.23 to 0.35

*In all, 246 patients were randomly assigned to paclitaxel before closure of the ixabepilone arm.

Table A4. Toxicity End Points for Patients Randomly Assigned to Paclitaxel and Ixabepilone Before Closure of the Ixabepilone Arm

Toxicity	Paclitaxel (n = 243) No. (%)	Ixabepilone (n = 239) No. (%)	P*
Any grade 3+ events	149 (61)	145 (61)	.93
Any hematologic adverse events	54 (22)	29 (12)	.0037
ANC/AGC	45 (19)	16 (7)	< .001
Leukocytes (total WBC)	21 (9)	9 (4)	.037
Hemoglobin	7 (3)	8 (3)	.80
Any nonhematologic adverse events	125 (51)	138 (58)	.17
Sensory neuropathy	47 (19)	60 (25)	.15
Fatigue (asthenia, lethargy, malaise)	26 (11)	35 (15)	.22
Hypertension	22 (9)	28 (12)	.37
Motor neuropathy	8 (3)	17 (7)	.066
Pain	11 (5)	10 (4)	1.0
Nausea	0 (0)	14 (6)	< .001
Maximum sensory neuropathy grade			P†
2	66 (27)	53 (22)	.032
3	46 (19)	54 (23)	
4	1 (< 1)	6 (3)	

Abbreviations: AGC, absolute granulocyte count; ANC, absolute neutrophil count.
*P values are from two-sided Fisher exact tests.
†P value is from Cochran-Mantel-Haenszel χ^2 tests for ordinal scale data.