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ORIGINAL REPORT

Ixabepilone Plus Capecitabine for Metastatic Breast Cancer Progressing After Anthracycline and Taxane Treatment

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ABSTRACT

Purpose
Effective treatment options for patients with metastatic breast cancer resistant to anthracyclines and taxanes are limited. Ixabepilone has single-agent activity in these patients and has demonstrated synergy with capecitabine in this setting. This study was designed to compare ixabepilone plus capecitabine versus capecitabine alone in anthracycline-pretreated or -resistant and taxane-resistant locally advanced or metastatic breast cancer.

Patients and Methods
Seven hundred fifty-two patients were randomly assigned to ixabepilone 40 mg/m^2 intravenously on day 1 of a 21-day cycle plus capecitabine 2,000 mg/m^2 orally on days 1 through 14 of a 21-day cycle, or capecitabine alone 2,500 mg/m^2 on the same schedule, in this international phase III study. The primary end point was progression-free survival evaluated by blinded independent review.

Results
Ixabepilone plus capecitabine prolonged progression-free survival relative to capecitabine (median, 5.8 *v* 4.2 months), with a 25% reduction in the estimated risk of disease progression (hazard ratio, 0.75; 95% CI, 0.64 to 0.88; $P = .0003$). Objective response rate was also increased (35% *v* 14%; $P < .0001$). Grade 3/4 treatment-related sensory neuropathy (21% *v* 0%), fatigue (9% *v* 3%), and neutropenia (68% *v* 11%) were more frequent with combination therapy, as was the rate of death as a result of toxicity (3% *v* 1%, with patients with liver dysfunction [≥ grade 2 liver function tests] at greater risk). Capecitabine-related toxicities were similar for both treatment groups.

Conclusion
Ixabepilone plus capecitabine demonstrates superior efficacy to capecitabine alone in patients with metastatic breast cancer pretreated or resistant to anthracyclines and resistant to taxanes.

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INTRODUCTION

Breast cancer is the most prevalent malignancy in women and metastatic breast cancer is a leading cause of mortality, accounting for more than 400,000 deaths annually worldwide.[1] Even though anthracyclines and taxanes are the most active agents in breast cancer, treatment failure occurs in a substantial number of patients and median survival for metastatic breast cancer remains 2 to 3 years.[2-4] Resistance to antineoplastic agents, and in particular anthracyclines and taxanes, is a limiting factor in breast cancer therapy, either after metastatic or adjuvant treatment.[3,5] With increasing use of anthracyclines and taxanes for early breast cancer, fewer effective options are available for patients with metastatic disease.[3,4] Capecitabine is commonly used for the treatment of anthracycline- and/or taxane-pretreated metastatic breast cancer; however, objective response rates in phase II studies are only 20% to 28%.[6,7] Therefore, there is an unmet need for new treatments of hormone- and chemotherapy-resistant, locally advanced, and metastatic breast cancer.

The epothilones are a new class of antineoplastic agents that stabilize microtubule dynamics leading to apoptotic cell death. They were developed to overcome tumor resistance mechanisms. Ixabepilone (BMS-247550; Bristol-Myers Squibb, New York, NY), a semisynthetic analog of epothilone B, is the first agent in this class and has been specifically designed to provide enhanced antitumor activity relative to other antineoplastic agents. In preclinical models, ixabepilone demonstrated low susceptibility to mechanisms that confer tumor resistance, such as overexpression of efflux transporters (eg,

P-glycoprotein and multidrug-resistance protein-1) and class III isoform of beta-tubulin.[8,9] In phase II studies, single-agent ixabepilone showed clinical activity in metastatic breast cancer, with objective response rates ranging from 12% (in heavily pretreated patients, with disease refractory to anthracyclines, taxanes, and capecitabine) to 42% (in patients with metastatic disease after adjuvant anthracycline-based chemotherapy).[10-13] Furthermore, preclinical data demonstrated synergy between ixabepilone and capecitabine.[14] A phase I/II study identified the recommended dose for additional development and showed promising clinical activity of this combination in anthracycline- and taxane-pretreated metastatic breast cancer.[15]

We conducted a randomized, open-label, phase III study to compare ixabepilone plus capecitabine versus capecitabine alone in patients with anthracycline-pretreated or -resistant and taxane-resistant locally advanced or metastatic breast cancer.

PATIENTS AND METHODS

Patients

Women ≥ 18 years of age with measurable locally advanced or metastatic breast cancer pretreated with or resistant to anthracyclines and resistant to taxanes were eligible. Anthracycline and taxane resistance was defined as tumor progression during treatment or within 3 months of last dose in the metastatic setting, or recurrence within 6 months in the neoadjuvant or adjuvant setting (patients not resistant to anthracyclines were also eligible if they received a minimum cumulative anthracycline dose of doxorubicin 240 mg/m^2 or epirubicin 360 mg/m^2). The definition of taxane resistance was revised after 377 patients were enrolled to align entry criteria with clinical practice, to include recurrence within 4 months of the last dose in the metastatic setting or within 12 months in the adjuvant setting. Patients were allowed to receive up to three prior chemotherapy regimens in any setting, with sequential neoadjuvant/adjuvant treatment counting as one regimen. Karnofsky performance score of 70 to 100 and life expectancy ≥ 12 weeks were required.

Key exclusion criteria included brain metastases; motor or sensory neuropathy grade ≥ 2 based on National Cancer Institute Common Terminology Criteria for Adverse Events version 3 (CTCAE); reduced hematologic or renal function; prior severe hypersensitivity to agents containing polyethoxylated castor oil or hypersensitivity to fluoropyrimidine; known or suspected dihydropyrimidine dehydrogenase deficiency; continued treatment with potent cytochrome P450 3A4 inhibitors; prior epothilone or capecitabine therapy; or patients with liver dysfunction (grade ≥ 2 liver function tests: ALT ≥ 2.5× upper limit of normal [ULN] or bilirubin ≥ 1.5× ULN), with the exception of patients with liver metastases. After consultation with the Drug Safety Monitoring Board, this final criterion was amended after 377 patients were enrolled to exclude patients with grade ≥ 2 liver function tests for ALT, AST, or bilirubin irrespective of liver metastases (see Results). The protocol was approved by the institutional review boards of participating institutions and all patients provided written informed consent.

Study Design

In this international, randomized, open-label, phase III trial, patients were assigned to receive ixabepilone plus capecitabine or capecitabine alone. Four stratification factors were used: presence of visceral metastases in the liver or lung, anthracycline resistance, prior chemotherapy for metastatic disease, and study site.

Patients received ixabepilone 40 mg/m^2 as a 3-hour intravenous infusion on day 1 of a 21-day cycle (diluent/vehicle for constitution: polyethoxylated castor oil and dehydrated ethanol, US Pharmacopeia, as a 50/50 vol/vol solution), plus oral capecitabine 2,000 mg/m^2 administered in two divided doses each day on days 1 through 14 of a 21-day cycle, or capecitabine alone 2,500 mg/m^2 in two divided doses each day on days 1 through 14 of a 21-day cycle. Treatment was continued until disease progression or unacceptable toxicity. Histamine H_1 and H_2 receptor antagonists were administered to patients receiving ixabepilone before infusion to prevent hypersensitivity reactions. Crossover from capecitabine alone to combination therapy was not permitted.

Doses were reduced or discontinued based on tolerability. Events necessitating ixabepilone dose reduction (from 40 to 32 to 25 mg/m^2) included grade 3 neuropathy lasting less than 7 days, grade 2 neuropathy lasting ≥ 7 days, or any other grade 3 nonhematologic toxicity; grade 3 thrombocytopenia accompanied by significant bleeding or requiring transfusion; grade 4 neutropenia lasting ≥ 7 days; or febrile neutropenia. Ixabepilone was discontinued for any other grade 4 toxicity or for grade 3 neuropathy lasting ≥ 7 days. Ixabepilone could be delayed for up to 21 days to allow recovery from treatment-associated toxicities. Capecitabine dose reductions were consistent with those specified by the guidelines for single-agent use.

All randomly assigned patients were assessable for efficacy. Patients were assessed for tumor response every 6 weeks from random assignment until disease progression. Radiologic assessments and photographs of skin lesions were evaluated by independent radiology review (IRR), which was blinded to treatment assignment and investigator, using Response Evaluation Criteria in Solid Tumors. Selection of target lesions by IRR and tumor assessments were done independently of investigator evaluations. Patients who discontinued treatment for reasons other than progression were assessed every 6 weeks up to 24 weeks from random assignment and every 3 months thereafter.

The primary end point was an intent-to-treat analysis of progression-free survival, defined as the time from random assignment to progressive disease or death as a result of any cause. Progressive disease, defined according to Response Evaluation Criteria in Solid Tumors, was determined from tumor assessment by IRR. Secondary end points included tumor response rate, time to response, duration of overall response (also assessed by IRR), overall survival, safety measures, and patient symptoms.

All patients who received study drug were evaluated for safety. Adverse events and laboratory abnormalities were assessed according to CTCAE. Patient symptoms were measured at baseline and before each treatment cycle using the Functional Assessment of Cancer Therapy–Breast Symptom Index 8.

Statistical Analysis

Six hundred fifteen events of IRR-determined progression or death were required to achieve 90% power by two-sided log-rank method ($\alpha = .05$) to detect a hazard ratio (HR) of 0.77 (assuming median progression-free survival of 3 months for capecitabine). The final α level was .0483 when adjusted for an interim analysis based on 344 IRR-determined events in the first 450 randomly assigned patients (O'Brien-Fleming method). Kaplan-Meier methodology was used to estimate progression-free survival and duration of response; the HR was estimated using a stratified Cox proportional hazards model. Statistical comparison between groups for objective response was performed using the Cochran-Mantel-Haenszel test.

Additional secondary (subset) analyses of progression-free survival were performed for the randomly assigned population based on potential prognostic factors.

RESULTS

Patient Population

Seven hundred fifty-two patients were enrolled and randomly assigned between September 2003 and January 2006 at 160 study sites in 22 countries. Of these, 737 patients were treated (369 with ixabepilone plus capecitabine and 368 with capecitabine alone).

Baseline demographics and clinical characteristics across treatment groups were well matched (Table 1). Fifteen percent of patients were human epidermal growth factor receptor (HER-2) positive. The majority of patients (65%) had ≥ three metastatic disease sites determined by IRR and 84% had visceral disease involving the liver and/or lung. Most (75%) had received treatment in the neoadjuvant/adjuvant setting, and nearly half had received ≥ two prior regimens in

Table 1. Baseline Patient Demographics and Disease Characteristics

Characteristic	Ixabepilone Plus Capecitabine (n = 375)*		Capecitabine (n = 377)*	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	53		52	
Range	25-76		25-79	
Race/ethnicity				
White	257	69	247	66
Asian	83	22	87	23
African American/black	11	3	11	3
Other	24	6	32	8
Karnofsky performance score				
90-100	253	67	237	63
70-80	119	32	136	36
< 70	0		1	0.3
Not reported	3	0.8	3	0.8
Hormone receptor status				
ER positive and/or PR positive	177	47	184	49
ER negative, PR negative, HER-2 negative	91	24	96	26
HER-2–positive status†	59	16	53	14
Site of visceral disease				
Liver	245	65	228	61
Lung	180	48	174	46
Extent of disease (No. of disease sites)				
≥ 2	332	89	341	90
< 2	43	11	36	10
Prior regimens in the metastatic setting				
≥ 3	17	5	22	6
2	152	41	138	37
1	179	48	184	49
0	27	7	33	9
Prior chemotherapy and hormonal therapy				
Anthracycline	365	97	365	97
Resistant‡	164	44	165	44
Exceeded minimum cumulative dose	201	54	200	53
Taxanes	367	98	363	96
Resistance in the neoadjuvant/adjuvant setting	40	11	44	12
Resistance in the metastatic setting	327	87	319	85
Progressive disease as best response to prior taxane	144	38	130	35
Progressive disease on therapy	22	6	21	6
Trastuzumab (metastatic setting)	34	9	34	9
Hormonal therapy	196	52	198	53

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.
*Percentages may not add up to 100% due to rounding and/or unknown data for some patients.
†Defined as positive by fluorescent in situ hybridization or 3+ by immunohistochemistry.
‡Resistance is defined as progression during treatment with (or within 3 months of) last dose (metastatic) or recurrence within 6 months of last dose (neoadjuvant).

the metastatic setting. Eight percent of patients were receiving first-line treatment, having relapsed within 1 year of prior anthracycline/taxane therapy in the adjuvant setting; treatment for the remaining 92% of patients was as either second- or third-line therapy. Of the 85% of patients with progression in the metastatic setting after prior taxane, 42% experienced progression while receiving taxane therapy.

Treatment Exposure

Patients receiving ixabepilone plus capecitabine received a median of five treatment cycles (range, one to 37 cycles), whereas patients in the capecitabine group received a median of four cycles (range, one to 33 cycles). In the combination group, 51% and 45% of patients required dose reduction of ixabepilone and capecitabine, respectively. In the capecitabine group, 37% of patients received a reduced dose.

The majority of patients received ≥ 70% of their planned relative dose-intensity. In the combination group, 88% and 62% received ≥ 70% of their relative ixabepilone and capecitabine dose-intensity (2,000 mg/m^2), respectively. In the capecitabine group, 82% received ≥ 70% of their relative capecitabine dose-intensity (2,500 mg/m^2).

Efficacy

Progression-free survival. Ixabepilone plus capecitabine was superior to capecitabine for the primary end point of progression-free survival (HR, 0.75; 95% CI, 0.64 to 0.88; stratified log-rank $P = .0003$),

with a 25% reduction in the estimated risk of disease progression (Fig 1). Median progression-free survival was prolonged to 5.8 months (95% CI, 5.45 to 6.97) for ixabepilone plus capecitabine compared with 4.2 months (95% CI, 3.81 to 4.50) for capecitabine, reflecting a 40% increase in median progression-free survival. Investigator-assessed median progression-free survival provided entirely consistent results (5.3 *v* 3.8 months; $P = .0011$).

Sensitivity analyses of potential confounding factors (including missing data/loss to follow-up, subsequent therapy before progression, and stratification factors at baseline) confirmed the robustness of the primary end point. Predefined subset analyses indicated that benefit was maintained consistently across subgroups (Fig 2). Benefit was evident irrespective of performance status, estrogen receptor, and HER-2 status. Low numbers preclude interpretation for individuals of African American/black race (n = 22), whereas patients with liver dysfunction (grade $\geq$ 2 liver function tests) should not be administered this combination based on safety findings described in Adverse Events. Interestingly, the improvement in progression-free survival for patients with normal or mild hepatic impairment was prolonged to 2.0 months (6.2 *v* 4.2 months; HR, 0.73).

Objective response rate. Ixabepilone plus capecitabine was also superior to capecitabine in terms of IRR objective response rate (35% *v* 14%; odds ratio, 3.2; $P < .0001$; Table 2). Investigator-assessed response rates were consistent (42% [95% CI, 37% to 47%] *v* 23% [95% CI, 18% to 27%], respectively).

IRR-assessed response rates of 33% (95% CI, 26% to 42%) and 14% (95% CI, 8% to 20%) were evident in an exploratory analysis of patients with intrinsic resistance to taxanes (ie, progressive disease as best response to prior taxane usage; Table 1).

Median response duration was 6.4 months (95% CI, 5.6 to 7.1) for ixabepilone plus capecitabine and 5.6 months (95% CI, 4.2 to 7.5) for capecitabine. Time to response was similar for the two treatment groups: 11.7 and 12.0 weeks, respectively. An analysis of overall survival, a secondary end point of the study, is planned after 631 patients have died.

Symptom assessment. Impact of treatment on symptoms measured by Functional Assessment of Cancer Therapy–Breast Symptom Index 8 revealed a statistically significant difference in favor of capecitabine; however, it is noteworthy that there was no clinically meaningful deterioration associated with the combination therapy.[16] These results should be interpreted with caution because approximately 75% of data from both treatment arms were missing.

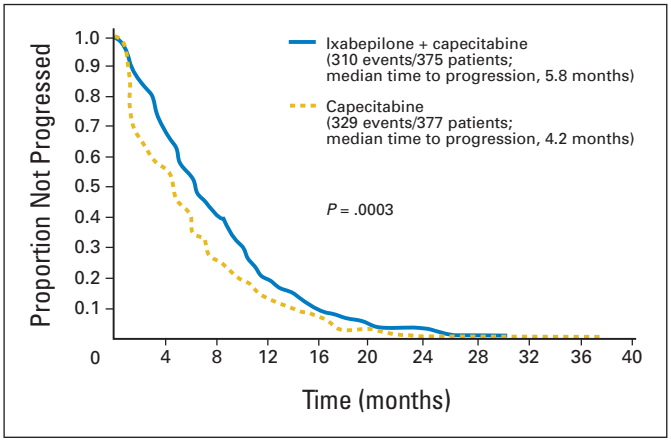

Fig 1. Independent radiology review progression-free survival Kaplan-Meier curves. The proportion of patients free of disease progression in each treatment group, and the stratified log-rank *P* value for the between-group comparison are shown.

Adverse Events

Treatment-related adverse events were mostly grade 1/2 and generally reversible; the toxicity profile of the combination reflected that of the individual agents. Table 3 summarizes the incidences of treatment-related adverse events and hematologic abnormalities by treatment. The most frequently reported grade 3/4 adverse events in the combination group were peripheral sensory neuropathy, hand-foot syndrome, fatigue, myalgia, asthenia, and diarrhea. The most frequent grade 3/4 adverse events in the capecitabine group were hand-foot syndrome and diarrhea, with incidences similar to those for the combination arm.

Thirty-three (9%) patients receiving combination therapy and 39 (11%) from the capecitabine group died within 30 days of last dose (all causes). Among 42 patients with liver dysfunction at baseline (grade $\geq$ 2 liver function tests: AST or ALT $\geq 2.5\times$ ULN or bilirubin $\geq 1.5\times$ ULN), five of 16 (31%) patients receiving combination therapy died compared with five of 26 (19%) from the capecitabine group. These deaths were all related to neutropenia for the combination group and were due to progressive disease for the capecitabine group. Among patients with baseline grade 0/1 liver function tests, neutropenia-related deaths occurred in seven patients (seven of 353 patients; 1.9%) receiving combination therapy and three patients (three of 342 patients; 0.9%) treated with capecitabine.

Peripheral neuropathy was common, primarily sensory, grade 1/2, cumulative, and generally reversible. Peripheral sensory neuropathy occurred in 65% of patients receiving ixabepilone plus capecitabine. Grade 3 sensory neuropathy occurred in 20% of patients and grade 4 sensory neuropathy occurred in 1% of patients. Discontinuation of one or both study drugs due to peripheral neuropathy occurred in 21% of patients receiving combination therapy after a median of six cycles. Events were managed in most cases with dose reduction. Patients with persistent grade 2/3 peripheral neuropathy received a median of three additional cycles (range, one to 16 cycles) after dose reduction. Median time from onset to improvement of grade 3/4 peripheral neuropathy (by one CTCAE grade) was 4.1 weeks, and median time to resolution to baseline or grade 1 was 6.0 weeks (Fig 3).

Myelosuppression was common in patients treated with ixabepilone plus capecitabine and consisted primarily of leukopenia and neutropenia, with a 5% incidence of febrile neutropenia (Table 3). Growth factor support, most frequently filgrastim, was administered to 20% of patients receiving combination therapy and to 3% of patients in the capecitabine group. Anemia and thrombocytopenia were generally grade 1/2 in both treatment groups.

Study drug toxicity led to treatment discontinuation (both study drugs) for 18% of patients receiving combination therapy and for 7% of patients in the capecitabine group.

DISCUSSION

This phase III randomized study compared treatment with ixabepilone plus capecitabine *v* capecitabine alone in patients with locally advanced or metastatic breast cancer resistant to anthracyclines and

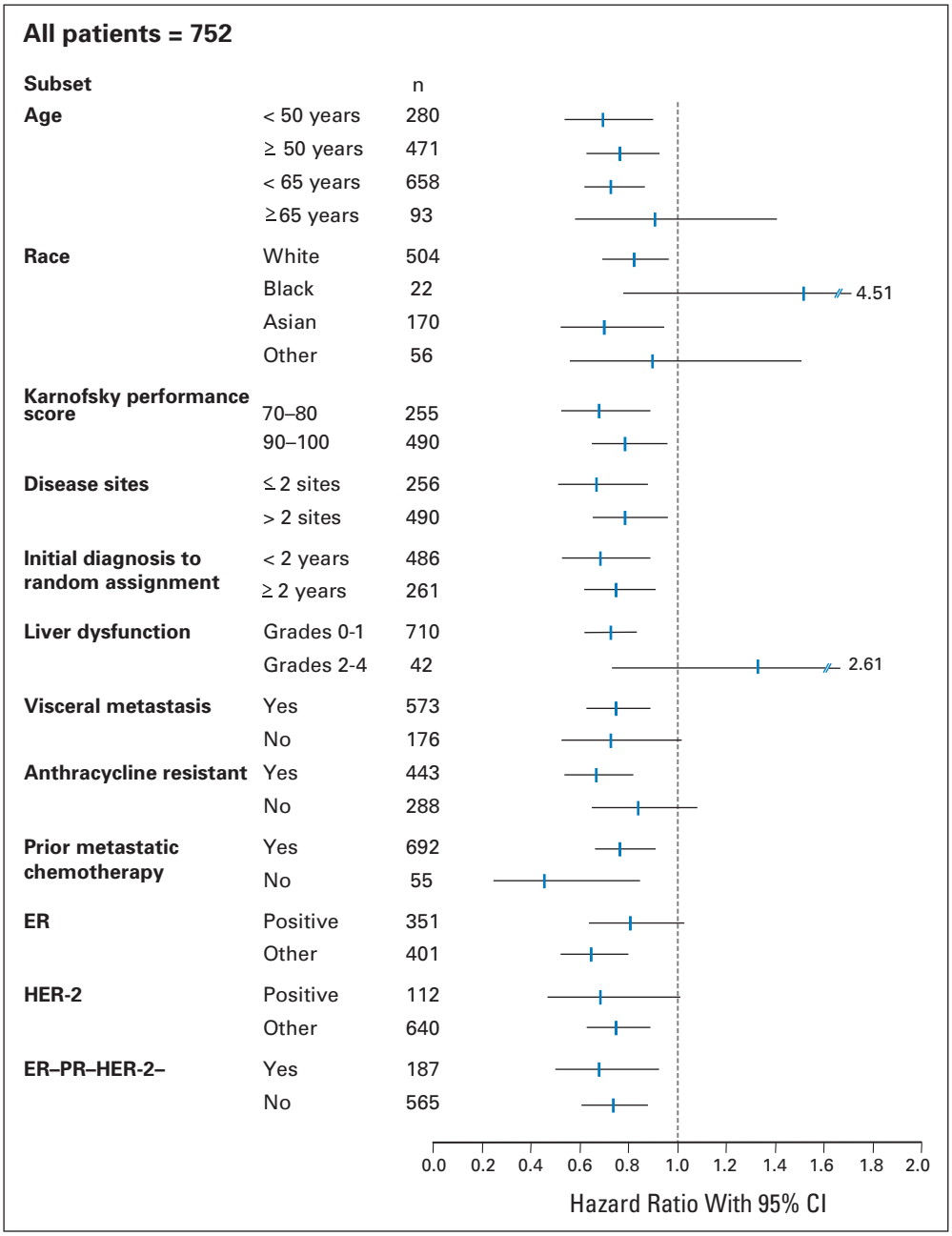

Fig 2. Subset analyses of progression-free survival. Progression-free survival hazard ratios (with 95% CI) for subgroups of patients. Hazard ratios less than 1.00 favor combination therapy. ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; ER–, ER negative; PR–, PR negative; HER-2–, HER-2 negative.

taxanes. Ixabepilone plus capecitabine was associated with a 25% reduction in the estimated risk of disease progression compared with capecitabine alone. The objective response rate was also increased 2.4-fold. The median duration of response was 6.4 months for combination therapy and 5.6 months for the capecitabine group. Assessment of the primary end point of progression-free survival and several secondary end points was determined by independent review under blinded conditions.

This study is the first to our knowledge to demonstrate superior progression-free survival and objective response after the addition of a second agent to capecitabine in patients resistant to anthracyclines and taxanes, irrespective of HER-2 expression. The magnitude of this benefit in progression-free survival is comparable with that observed after first-line chemotherapy in taxane-naïve patients and is therefore clinically meaningful.[17,18] Consistent clinical benefit in favor of combination therapy was maintained across subgroups, including patients with visceral metastases, more than two sites of metastatic disease, age ≥ 65 years, or with HER-2–positive breast cancer. This is also the first phase III study to our knowledge to report a significant improvement in progression-free survival for patients with ER-negative, PR-negative, HER-2–negative breast cancer, a disease subtype traditionally associated with poor prognosis.[19]

Results from the capecitabine arm of this study are consistent with those reported from other recent phase III trials in metastatic breast cancer in which capecitabine was the comparator.[20,21]

Table 2. Objective Tumor Responses in Randomly Assigned Patients (independent radiology review)

Response	Ixabepilone Plus Capecitabine (n = 375)		Capecitabine (n = 377)	
	No. of Patients	%	No. of Patients	%
Objective response rate	130	34.7	54	14.3
95% CI	29.9 to 39.7		10.9 to 18.3	
Difference in response rates (%)	19.5			
95% CI for difference	13.6 to 25.3			
Complete response	1	< 1	0	
Partial response	129*	34	54	14
Stable disease	155	41	175	46
Progressive disease	58	15	102	27
Not determined	32	9	46	12
Clinical benefit†	190	51	113	30

*Includes one patient with a partial response who was assigned to the ixabepilone + capecitabine group but received capecitabine only.
†Complete response + partial response + stable disease ≥ 6 months.

Neuropathy, an event commonly associated with other tubulin-targeting agents, was also observed with ixabepilone. Neuropathy was primarily sensory, cumulative, and reversible (effectively managed by dose reduction or delay enabling a sufficient number of cycles to be administered to attain the observed levels of efficacy). Median time to onset of grade 3/4 peripheral neuropathy was four cycles. Grade 3/4

Table 3. Most Common Treatment-Related Adverse Events and Hematologic Abnormalities

Adverse Event*	Ixabepilone + Capecitabine (n = 369), Grade										Capecitabine (n = 368), Grade									
	1		2		3		4		Any		1		2		3		4		Any	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Peripheral neuropathy	61	17	101	27	82	22	3	0.8	247	67	44	12	15	4	0		0		59	16
Peripheral sensory neuropathy†	62	17	98	27	75	20	3	0.8	238	64	43	12	15	4	0		0		58	16
Peripheral motor neuropathy	16	4	25	7	18	5	0		59	16	1	0.3	0		0		0		1	0.3
Hand-foot syndrome	84	23	86	23	67	18	0		237	64	89	24	77	21	62	17	0		228	62
Nausea	122	33	60	16	12	3	0		194	53	111	30	31	8	6	2	0		148	40
Diarrhea	87	24	53	14	21	6	0		162‡	44	67	18	42	11	31	8	2	0.5	142	39
Fatigue	45	12	70	19	33	9	0		148	40	34	9	28	8	11	3	1	0.3	74	20
Vomiting	70	19	61	17	13	4	0		144	39	51	14	30	8	6	2	1	0.3	88	24
Myalgia	43	12	51	14	29	8	0		123	33	12	3	1	0.3	1	0.3	0		14	4
Anorexia	61	17	44	12	11	3	0		116	31	33	9	16	4	4	1	0		53	14
Alopecia	41	11	75	20	0		0		116	31	5	1	5	1	0		0		10	3
Asthenia	29	8	31	8	24	7	3	0.8	87	24	21	6	13	4	2	0.5	1	0.3	37	10
Constipation	60	16	22	6	0		0		82	22	18	5	3	0.8	1	0.3	0		22	6
Nail disorder	33	9	37	10	5	1	0		75	20	26	7	5	1	0		0		31	8
Arthralgia	25	7	37	10	10	3	0		72	20	6	2	3	0.8	0		0		9	2
Mucositis	34	9	17	5	9	2	1	0.3	61	17	26	7	7	2	7	2	0		40	11
Stomatitis	36	10	19	5	5	1	1	0.3	61	17	27	7	7	2	4	1	0		38	10
Hematologic abnormality§	n = 366										n = 364									
Leukopenia	33	9	88	24	150	41	60	16	331	90	116	32	61	17	17	5	4	1	198	54
Anemia	138	38	157	43	28	8	7	2	330	90	178	49	63	17	13	4	2	0.5	256	70
Neutropenia	23	6	52	14	116	32	133	36	324	89	72	20	45	12	33	9	6	2	156	43
Thrombocytopenia	138	38	28	8	18	5	12	3	196	54	91	25	9	2	6	2	7	2	113	31
Febrile neutropenia¶	0		0		13	4	3	0.8	19‖	5	0		0		2	0.5	0		2	0.5

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities.
*By patients' worse CTCAE (version 3), except hand-foot syndrome, which was graded using Roche criteria.
†Included the MedDRA (version 9.1) terms burning sensation, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, neuritis, neuropathy, neuropathy peripheral, neurotoxicity, painful response to normal stimuli, paresthesia, pallanesthesia, peripheral sensory neuropathy, polyneuropathy, and polyneuropathy toxic.
‡Including one case of grade 5 diarrhea.
§n represents patients for whom on-study laboratory test results were recorded. For neutropenia, results were available for 365 patients in the capecitabine treatment group.
¶Percentages for the adverse event of febrile neutropenia are based on n = 369 patients in the combination therapy group and n = 368 patients in the capecitabine group.
‖Including three cases of grade 5 febrile neutropenia.

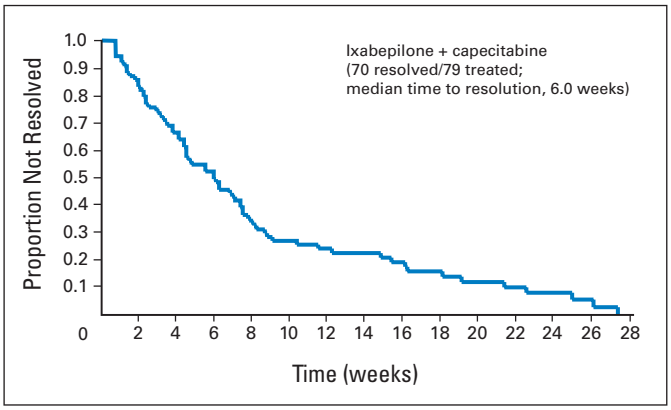

Fig 3. Time to resolution of grade 3/4 ixabepilone-related peripheral neuropathy to baseline or grade 1. Resolution in patients who discontinued treatment was monitored monthly. Analysis included 79 patients with neuropathy occurring within 30 days of last dose of ixabepilone; data from six patients in whom onset was more than 30 days after last dose were excluded.

neuropathy improved by ≥ one CTCAE grade within a median of 4 weeks from onset, or resolved to baseline or grade 1 within a median of 6 weeks after dose reduction. The characteristics and incidence of grade 3/4 neuropathy were consistent with those reported in trials of other tubulin-targeting agents, in which incidences ranged from 0% to 33%.[22] Recent studies have reported rates of grade 3/4 sensory neuropathy of 17% and 19% after weekly dosing with nanoparticle albumin-bound paclitaxel and paclitaxel, respectively.[23,24] Although randomized studies are unavailable, comparison with historical data indicates that recovery from ixabepilone-induced neuropathy may be more rapid than with paclitaxel.[25] Despite the high frequency of discontinuation attributable to sensory neuropathy, most patients received a reasonable course of treatment (median of six cycles) before their withdrawal.

The incidence of adverse events commonly associated with capecitabine, such as hand-foot syndrome, was not exacerbated by the addition of ixabepilone. Leukopenia and neutropenia were more frequent with combination therapy, as was the incidence of neutropenia-related death. In the majority of cases, hematologic toxicity was managed by dose reduction; although growth factor support was permitted, routine use of growth factors is not recommended. A higher rate of neutropenia-related deaths was detected in patients with liver dysfunction through diligent safety monitoring, and eligibility criteria were amended rapidly to exclude these patients; once such patients were excluded, the incidence of death as a result of toxicity was reduced to 2%, with a rate similar to that of single-agent docetaxel.

Dose reduction was common for patients receiving combination therapy; rates were comparable with those reported for docetaxel plus capecitabine.[17] An exploratory analysis evaluating the impact of dose reduction on progression-free survival indicated no detrimental effect for patients who received a reduced dose.

This study demonstrates that ixabepilone in combination with capecitabine possesses superior clinical efficacy to capecitabine alone in metastatic breast cancer that has progressed after multiple prior treatments, including anthracyclines and taxanes. Results provide support for the use of ixabepilone plus capecitabine in patients with metastatic disease pretreated or resistant to anthracyclines and resistant to taxanes, a population with limited effective treatment options. These findings warrant evaluation of the role of ixabepilone in earlier settings of breast cancer.

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®).