

## Phase I Study of Ixabepilone, Mitoxantrone, and Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Therapy: A Study of the Department of Defense Prostate Cancer Clinical Trials Consortium

Jonathan E. Rosenberg, Charles J. Ryan, Vivian K. Weinberg, David C. Smith, Maha Hussain, Tomasz M. Beer, Christopher W. Ryan, Paul Mathew, Lance C. Pagliaro, Andrea L. Harzstark, Jeremy Sharib, and Eric J. Small

### A B S T R A C T

#### Purpose

Mitoxantrone plus prednisone and ixabepilone each have modest activity as second-line chemotherapy in docetaxel-refractory castration-resistant prostate cancer (CRPC) patients. Clinical noncrossresistance was previously observed.

#### Patients and Methods

Metastatic CRPC patients progressing during or after taxane-based chemotherapy enrolled in a phase I multicenter study of ixabepilone and mitoxantrone administered every 21 days along with prednisone. Ixabepilone and mitoxantrone doses were alternately escalated in a standard 3 + 3 design. Patients were evaluated for toxicity and disease response. Dose-limiting toxicities (DLTs) were defined as treatment related, occurring during cycle 1, and included grade 4 prolonged or febrile neutropenia, thrombocytopenia (grade 4 or grade 3 with bleeding), or  $\geq$  grade 3 nonhematologic toxicity.

#### Results

Thirty-six patients were treated; 59% of patients experienced grade 3/4 neutropenia. DLTs included grade 3 diarrhea ( $n = 1$ ), prolonged grade 4 neutropenia ( $n = 4$ ), and grade 5 neutropenic infection ( $n = 1$ ). Due to prolonged neutropenia, the highest dose levels were repeated with pegfilgrastim on day 2 of each cycle. The maximum tolerated dose in combination with pegfilgrastim was not exceeded. The recommended phase II dose is mitoxantrone 12 mg/m<sup>2</sup> and ixabepilone 35 mg/m<sup>2</sup> every 21 days, pegfilgrastim 6 mg subcutaneously day 2, and continuous prednisone 5 mg twice per day. Thirty-one percent of patients have experienced  $\geq 50\%$  prostate-specific antigen (PSA) declines, and two experienced objective responses. Of 21 patients treated with mitoxantrone 12 mg/m<sup>2</sup> plus ixabepilone  $\geq 30$  mg/m<sup>2</sup>, nine (43%) experienced  $\geq 50\%$  PSA declines (95% CI, 22% to 66%).

#### Conclusion

These results suggest that the combination of ixabepilone and mitoxantrone is feasible and active in CRPC and requires dosing with pegfilgrastim.

*J Clin Oncol* 27:2772-2778. © 2009 by American Society of Clinical Oncology

### INTRODUCTION

Docetaxel improves survival for patients with metastatic castration-resistant prostate cancer (CRPC).<sup>1,2</sup> However, the median progression-free survival with docetaxel is approximately 6 months, and many patients with disease progression after docetaxel treatment remain in otherwise reasonable health with a good performance status.<sup>1</sup> No standard therapy exists for treatment of CRPC patients with progression following docetaxel therapy.

Ixabepilone and mitoxantrone are two agents that may have utility in CRPC patients whose disease has progressed after docetaxel. Ixabepilone (Ixempra; Bristol Myers-Squib, New York, NY) is a semi-synthetic epothilone analog recently approved by the US Food and Drug Administration for the treatment of chemotherapy-refractory metastatic breast cancer. Ixabepilone has demonstrated evidence of activity in taxane-resistant cell lines, as well as substantial activity in the first-line treatment of CRPC.<sup>3,4</sup> Similarly, mitoxantrone

From the Department of Medicine, University of California; Biostatistics Core, University of California San Francisco Helen Diller Family Cancer Center, San Francisco, CA; Department of Medicine, University of Michigan, Ann Arbor, MI; Department of Medicine, Oregon Health and Science University, Portland, OR; and the Department of Genitourinary Medical Oncology, M. D. Anderson Cancer Center, Houston, TX.

Submitted August 22, 2008; accepted December 30, 2008; published online ahead of print at [www.jco.org](http://www.jco.org) on April 6, 2009.

Supported in part by the DOD Physicians Research Training Grant No. W81XWH-05-1-175 from the Cancer Therapy Evaluation Program of the National Cancer Institute (J.R.), the Prostate Cancer Foundation, and the DOD Prostate Cancer Clinical Trials Consortium Grant No. W81XWH-06-01-0256.

Presented in poster format at the 2007 American Society of Clinical Oncology (ASCO) Genitourinary Cancer Symposium, February 14-16 2008, San Francisco, CA; 2007 Prostate Cancer Symposium February 22-24, 2007 in Orlando, FL; and the 44th ASCO Annual Meeting, Chicago, IL, May 30 to June 3, 2008.

Written on behalf of the Department of Defense Prostate Cancer Clinical Trials Consortium.

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

Clinical Trials repository link available on [JCO.org](http://JCO.org).

Corresponding author: Jonathan E. Rosenberg, MD, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, 1600 Divisadero St, Box 1711, San Francisco, CA 94115; e-mail: [jonathan\\_rosenberg@dfci.harvard.edu](mailto:jonathan_rosenberg@dfci.harvard.edu).

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

© 2009 by American Society of Clinical Oncology

0732-183X/09/2717-2772/\$20.00

DOI: 10.1200/JCO.2008.19.8002

(plus a corticosteroid) has demonstrated palliative activity in first-line therapy for CRPC.<sup>5,6</sup> We have previously reported the activity of ixabepilone or mitoxantrone and prednisone (MP) in patients with taxane-refractory CRPC.<sup>7</sup> Both regimens demonstrated modest activity (ixabepilone  $\geq$  50% prostate-specific antigen [PSA] decline in 17% of patients, MP  $\geq$  50% PSA decline in 20% of patients). On planned cross-over to the other agent, 11% and 27% of patients demonstrated third-line PSA responses to ixabepilone and MP, respectively, suggesting some clinical noncrossresistance between the two regimens. This has provided the rationale to test the efficacy of ixabepilone administered in combination with MP to patients with disease progression during or after docetaxel-based first-line chemotherapy. While toxicities of these two regimens are somewhat nonoverlapping, concern regarding the use of two potentially myelosuppressive regimens in elderly patients with heavy pretreatment and potential bone marrow involvement mandated cautious dose escalation.

**PATIENTS AND METHODS**

**Study Design**

This study was a multicenter, single arm, phase I dose escalation study testing the safety of ixabepilone and MP in CRPC patients with progression during or after prior docetaxel-based chemotherapy. The study was designed to alternately escalate ixabepilone and mitoxantrone for each subsequent dose cohort. A total of six dose combinations were planned as displayed in Table 1. The standard phase I escalation criteria based on the number of DLTs were applied to each dose cohort. The primary end point of the study was to determine the maximum tolerated dose of the combination. Secondary end points included overall safety and frequency of PSA declines and objective responses.

**Eligibility Criteria**

All patients had histologically confirmed metastatic prostate cancer. Patients were required to have progressive disease despite castrate testosterone levels and at least three cycles of prior taxane-based chemotherapy. Patients were not allowed to have received more than one prior chemotherapy regimen. For patients with measurable disease, progression was defined by Response Evaluation Criteria in Solid Tumors.<sup>8</sup> For patients without measurable disease, a positive bone scan and elevated PSA higher than 5 ng/mL were required. PSA evidence for progressive disease was defined by PSA Working Group 1 Consensus Criteria.<sup>9</sup>

All patients were required to have Eastern Cooperative Oncology Group performance status of 0 to 2, and  $\leq$  grade 1 peripheral neuropathy (National Cancer Institute Common Toxicity Criteria, version 3.0). Hormone therapy other than luteinizing hormone-releasing hormone agonist or a stable dose of

corticosteroid from prior treatment was not allowed within 4 weeks of trial enrollment. Any radiotherapy or radiopharmaceutical treatment must have been completed more than 4 weeks and 8 weeks before enrollment, respectively. All patients were required to have a cardiac ejection fraction greater than the lower limit of institutional normal. Patients with significant cardiovascular disease including congestive heart failure (New York Heart Association class III or IV), active angina pectoris, or myocardial infarction within 6 months were excluded. Patients with known active brain metastases were excluded. Required laboratory values included testosterone lower than 50 ng/dL; creatinine  $\leq$  1.5 $\times$  upper limits of normal (ULN) or calculated creatinine clearance of 40 mL/min; ALT and AST lower than 2.5 $\times$  ULN; granulocytes  $\geq$  2,000/mm<sup>3</sup>; platelets  $\geq$  100,000/mm<sup>3</sup>; total bilirubin lower than 1.5 $\times$  ULN; and, if no bidimensionally measurable disease, PSA  $\geq$  5 ng/mL. Because ixabepilone is a major CYP3A4 substrate, concurrent use of moderate to strong CYP3A4 inhibitors was strongly discouraged.

This clinical trial was sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute, conducted through the Department of Defense Prostate Cancer Clinical Trials Consortium, and approved by the institutional review boards of each participating center. All patients provided written informed consent.

**Treatment Plan**

The dose escalation schema is depicted in Table 1. Patients were treated every 21 days. Patients were premedicated 1 hour before ixabepilone treatment with oral H1- and H2-blockers to prevent hypersensitivity reactions. For patients who developed grade 2 to 4 hypersensitivity reactions to ixabepilone, corticosteroid premedication was used with subsequent cycles. Patients received mitoxantrone intravenously over 30 minutes, followed by ixabepilone intravenously over 3 hours on day 1 of each cycle. Prednisone was given 5-mg twice daily continuously. Patients on dose levels Va and VIa received prophylactic subcutaneous pegfilgrastim on day 2. Patients had complete blood counts tested on days 8 and 15 of each cycle. Patients were treated until disease progression or unacceptable toxicity. Patients underwent imaging with chest x-ray, bone scan, and computed tomography or magnetic resonance imaging of the abdomen and pelvis at baseline and after every 3 cycles. ECG and either multiple gated-acquisition scan or echocardiogram were obtained at baseline and repeated every 3 cycles.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Three patients were enrolled at each dose level. If one of three patients experienced a dose-limiting toxicity (DLT) during the first cycle, three additional patients were enrolled at that dose level. If no additional DLTs were observed, then dose escalation proceeded. If two or more patients in a cohort experienced a DLT, then the maximum tolerated dose would be considered exceeded. DLT was defined as treatment-related toxicity occurring within the first 21 days of therapy that included  $\geq$  grade 3 nonhematologic toxicity (excluding fatigue, alopecia, or toxicity attributed to androgen deprivation), hematologic toxicity defined as grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding, grade 4 neutropenia persisting for more than 7 days, grade 4 neutropenia associated with fever higher than 38.5C, or removal of a patient from toxicity attributable to treatment. Lymphopenia or anemia of any grade, and toxicities related to androgen deprivation therapy were excluded as DLTs.

Dose modifications were defined according to protocol. Dosages were reduced for day 1 neutrophil count lower than 1,500/mm<sup>3</sup> or platelet count lower than 75,000/mm<sup>3</sup>, neutrophil count lower than 500/mm<sup>3</sup> for more than 7 days, neutrophil count lower than 500/mm<sup>3</sup> associated with fever, platelet count lower than 25,000/mm<sup>3</sup>, or platelet count lower than 50,000/mm<sup>3</sup> associated with bleeding, and any  $\geq$  grade 3 nonhematologic toxicity related to therapy. Grade 2 or 3 neurotoxicity required ixabepilone dose reduction. Grade 4 and recurrent grade 3 neurotoxicity required ixabepilone discontinuation. Mitoxantrone was discontinued if the ejection fraction decreased below the institutional lower limit of normal and declined by  $\geq$  15%. For each dose reduction, ixabepilone dose was reduced by 5 mg/m<sup>2</sup>, and mitoxantrone dose was reduced by 2 mg/m<sup>2</sup>. Patients were removed from treatment if more than two dose reductions were required or if there was a treatment delay of longer than 21 days due to toxicity. Patients were not treated with prophylactic

**Table 1.** Dose Escalation Schema

Dose Level	Regimen			
	Mitoxantrone (mg/m <sup>2</sup> )	BMS-247550 (ixabepilone; mg/m <sup>2</sup> )	Prednisone (mg PO BID)	Pegfilgrastim (mg SC on day 2)
I	8	20	5	—
II	8	25	5	—
III	10	25	5	—
IV	10	30	5	—
V	12	30	5	—
VI	12	35	5	—
Va	12	30	5	6
VIa	12	35	5	6

Abbreviations: PO, orally; BID, twice per day; SC, subcutaneously.

antibacterials, and granulocyte growth factor for asymptomatic neutropenia on dose levels I to VI. Secondary prophylaxis with growth factors for recurrent neutropenic infection was allowed in dose levels I to VI.

### Statistical Considerations

Successive cohorts of patients were accrued to determine the maximum tolerated dose that resulted in lower than 33% DLTs with the combination of ixabepilone and MP. At least six patients were treated at the maximum dose to increase the likelihood that the risk of a DLT was lower than 33%. Secondary objectives were to obtain initial estimates of response to study therapy based on PSA Working Group 1 criteria and objective responses by RECIST in patients with measurable disease.<sup>8,9</sup>

## RESULTS

### Patient Characteristics

Between July 2006 and February 2008, 36 patients were enrolled at four participating centers (Table 2). The median age of patients was 66. Seventy-one percent of patients had a Gleason score of 8 to 10. Sixty-four percent of patients had an ECOG performance status of 1 to 2, while 36% had an ECOG performance status of 0. The median lactate dehydrogenase, alkaline phosphatase, and hemoglobin were 313 U/L, 142 U/L, and 11.9 g/dL. The median number of prior chemotherapy cycles was 8.5. Forty-seven percent of patients had experienced a PSA response to prior taxane-based therapy by PSA Working Group 1 criteria. Twenty-three patients (64%) progressed on docetaxel therapy by PSA criteria, nine (25%) progressed on docetaxel therapy in bone and/or soft tissue, two (5.5%) stopped docetaxel therapy for toxicity, and two (5.5%) stopped docetaxel therapy with stable disease after completing a course of chemotherapy. The majority of patients received no intercurrent therapy between docetaxel treatment and enrollment on trial. Two patients received other investigational therapy after docetaxel before enrollment (vorinostat and tandutinib; Millenium Pharmaceuticals, Cambridge, MA), and two other patients received palliative radiotherapy.

### Dose Escalation and DLT

A total of 178 cycles of treatment were administered to 36 patients. No DLTs were observed in the first three cohorts (Table 3). At dose level IV (mitoxantrone 10 mg/m<sup>2</sup>, ixabepilone 30 mg/m<sup>2</sup>) one patient experienced grade 4 neutropenia lasting longer than 7 days leading to cohort dose expansion. No further DLTs were observed at this dose level. At dose level V (mitoxantrone 12 mg/m<sup>2</sup>, ixabepilone 30 mg/m<sup>2</sup>), one patient experienced grade 3 diarrhea, leading to cohort expansion. An additional event of grade 4 neutropenia lasting more than 7 days was identified only after dose escalation had occurred to dose level VI. At dose level VI (mitoxantrone 12 mg/m<sup>2</sup>, ixabepilone 35 mg/m<sup>2</sup>), one patient experienced dose-limiting grade 4 neutropenia lasting longer than 7 days, leading to cohort expansion. In the cohort expansion, a second patient on dose level VI also experienced grade 4 neutropenia lasting longer than 7 days, constituting DLT, and accrual was stopped to this cohort. Based on these toxicities, the study was amended to repeat dose levels V and VI with the addition of pegfilgrastim 6 mg subcutaneously on day 2 (dose levels Va and VIa). No DLTs were observed on dose level Va (mitoxantrone 12 mg/m<sup>2</sup>, ixabepilone 30 mg/m<sup>2</sup>, pegfilgrastim 6 mg subcutaneous). One patient treated on dose level Va was inadvertently treated with the dose level VIa dose of ixabepilone (5 mg higher than planned) for cycle

**Table 2.** Patient Characteristics (N = 36)

Characteristic	No.	%
Median age, years	66	
Range	36-79	
Gleason score	35	
6-7	10	
8-10	25	
ECOG PS		
0	13	
1-2	23	
Median PSA, ng/mL	236.93	
Range	12.8-7,167	
Mean No. of prior chemotherapy cycles	8.5	
Range	3-80	
Prior chemotherapy regimens		
Docetaxel	25	
Docetaxel + bevacizumab/placebo	4	
Docetaxel + sunitinib	2	
Docetaxel + estramustine	3	
Docetaxel + valatinib	1	
Docetaxel + diethylstilbestrol	1	
Prior chemotherapy best response		
PSA decline ≥ 50%	17	
Progressive disease	12	
Stable disease	7	
Reason for discontinuing docetaxel		
PSA progression only	23	
Bone progression	3	
Soft tissue progression	5	
Both bone and soft tissue progression	1	
Toxicity	2	
Completed therapy, stable disease	2	
Interval between docetaxel and study therapy, days		
≥ 60	25	
< 60	11	
Baseline laboratory tests		
Median LDH, U/L	313	
Range	118-1,046	
Median alkaline phosphatase, U/L	142	
Range	37-780	
Median hemoglobin, g/dL	11.9	
Range	8.4-14.1	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; PSA, prostate-specific antigen; LDH, lactate dehydrogenase.

1, and was replaced in the dose escalation. As this dose level had been previously tested without pegfilgrastim, the patient was included in the overall toxicity and response reporting. One patient on dose level VIa (mitoxantrone 12 mg/m<sup>2</sup>, ixabepilone 35 mg/m<sup>2</sup>, pegfilgrastim 6 mg subcutaneous) died of neutropenic infection leading to respiratory and renal failure in the setting of progressive disease during cycle 1 of treatment. That patient was also receiving concomitant therapy with verapamil, a moderate CYP3A4 inhibitor. Dose level VIa was expanded to six patients, and no further DLTs were observed. The maximum tolerated dose with the combination of ixabepilone and mitoxantrone was not exceeded in this study, but further dose escalation was not undertaken, as the study plan was to reach therapeutic dose levels for each drug (mitoxantrone 12 mg/m<sup>2</sup> and ixabepilone 35 mg/m<sup>2</sup>) and not escalate further. Furthermore, the treatment-related

**Table 3.** DLTs (cycle 1 only) and Responses

Dose Level	DLT Frequency	DLTs	PSA Declines $\geq$ 50%/ Total Patients	Objective Responses/ Assessable Patients
I	0/3	—	0/3	0/2
II	0/3	—	0/3	0/1
III	0/3	—	1/3	0/2
IV	1/6	Prolonged grade 4 neutropenia	1/6	1/4
V	2/6	Grade 3 diarrhea; prolonged grade 4 neutropenia	2/6	1/5
VI	2/5	Prolonged grade 4 neutropenia $\times$ 2	3/5	0/3
Va	0/4	—	2/4	0/2
VIa	1/6	Grade 5 neutropenic infection	2/6	0/1

Abbreviation: DLT, dose-limiting toxicities.

death on the highest dose level suggested that further dose escalation was not warranted. Based on the observed DLTs, the recommended phase II dose is mitoxantrone 12 mg/m<sup>2</sup> and ixabepilone 35 mg/m<sup>2</sup> day 1, pegfilgrastim 6 mg on day 2, and prednisone 5 mg twice daily continuously.

### Overall Toxicity

As anticipated, hematologic toxicity was frequently observed (Table 4). Grade 3 neutropenia was observed in 28% of patients, and grade 4 neutropenia was observed in 31% of patients. Grade 4 neutropenia lasting longer than 7 days was observed in 11% of patients. Grade 3/4 neutropenia was observed in 33% of all treatment cycles. Grade 3 thrombocytopenia and grade 3 anemia were infrequent (6% and 8% respectively), and no patients experienced grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding.

Nonhematologic toxicity related to study therapy is detailed in Table 5. Cardiovascular toxicity included two patients with grade 2 asymptomatic decreased left ventricular ejection fraction (to 40% to 50%), and two patients with atrial fibrillation (one grade 2, another grade 3). Grade 3 motor neuropathy was observed in one patient, grade 2 motor neuropathy was observed in one patient, and grade 2 sensory neuropathy was observed in one patient.

### Response Evaluation

Anticancer activity was assessed as a secondary end point of this study. Partial objective RECIST-defined responses were observed in two of 20 patients with measurable disease: one on dose

level IV and one on dose level V. In addition, 11 patients (31%) experienced confirmed PSA declines  $\geq$  50% (Table 3 and online-only Appendix Fig A1). Of the 21 patients who received the US Food and Drug Administration–approved mitoxantrone dose of 12 mg/m<sup>2</sup> (dose levels V, Va, VI, and VIa), nine patients (43%) experienced confirmed PSA declines  $\geq$  50% (Fig 1; 95% CI, 22% to 66%). For responders, the median time to progression was 5.3 months (range, 3.0 to 11.1).

## DISCUSSION

While docetaxel chemotherapy is associated with an overall survival benefit for patients with castration-resistant prostate cancer, the median time to progression remains short, and overall survival remains fewer than 2 years. Recently reported data demonstrated that satraplatin did not provide a survival benefit when compared with prednisone alone in CRPC patients previously treated with chemotherapy.<sup>10</sup> Thus, the exploration of new therapeutic approaches for these patients is clearly warranted.

In a previously reported randomized phase II trial, ixabepilone and MP appeared to have clinical noncrossresistance as second- and third-line therapy for CRPC.<sup>7</sup> Several patients who progressed on one arm and crossed over to the other therapy demonstrated responses. Based on these data, the current study evaluated the safety and tolerability of the combination of ixabepilone and MP as second-line chemotherapy in patients with metastatic CRPC who had progressed during or after a single taxane-based chemotherapy regimen.

This study has demonstrated that mitoxantrone and ixabepilone can generally be safely administered in combination at doses that have demonstrated single-agent activity in CRPC. The recommended phase II dose is mitoxantrone 12 mg/m<sup>2</sup> and ixabepilone 35 mg/m<sup>2</sup> administered intravenously every 21 days, along with prednisone 5 mg orally twice per day continuously. Treatment was well tolerated in most patients. However, treatment at these dose levels required pegfilgrastim to prevent prolonged neutropenia. High rates of neutropenia have been observed with mitoxantrone-based chemotherapy in prostate cancer. For example, grade 3/4 neutropenia was observed in 59% of patients treated with mitoxantrone, without a concomitant high incidence of neutropenic infections or morbidity.<sup>5</sup> The low frequency of febrile neutropenia may be explained by the relatively low frequency of severe mucositis observed with mitoxantrone. In this phase I study, no patients experienced grade 3 or 4 mucositis.

**Table 4.** Frequency of Grade 3 and 4 Hematologic Toxicity Across All Dose Levels and All Cycles

Toxicity	Grade 3		Grade 4	
	No.	%	No.	%
Neutropenia	10	28	11	31
> 7 days	9	25	4	11
Febrile neutropenia	1	3	—	—
Lymphopenia	12	33	2	6
Leukopenia	10	28	6	17
Thrombocytopenia	2	6	—	—
Anemia	3	8	—	—

**Table 5.** Grade 2 and Higher Treatment-Related Maximal Nonhematologic Toxicity, All Dose Levels, and All Cycles

Toxicity	Grade					
	2		3		4	
	No.	%	No.	%	No.	%
Alopecia	1	3	—	—	—	—
Anorexia	2	6	—	—	—	—
ARDS	1	3	—	—	—	—
Atrial fibrillation	1	3	1	3	—	—
Bone pain	2	6	—	—	—	—
Chest pain	1	3	—	—	—	—
Dehydration	—	—	1	3	—	—
Diarrhea	1	3	1	3	—	—
Dizziness	1	3	—	—	—	—
Dyspepsia	1	3	—	—	—	—
Dyspnea	1	3	—	—	—	—
Edema limbs	1	3	—	—	—	—
Fatigue	11	31	—	—	—	—
Febrile neutropenia	1	3	—	—	—	—
Fever	1	3	—	—	—	—
Hot flashes	1	3	—	—	—	—
Infection	1	3	—	—	2	6
Muscle weakness	1	3	1	3	—	—
Nausea	3	8	—	—	—	—
Pain	1	3	—	—	—	—
Peripheral motor neuropathy	1	3	1	3	—	—
Peripheral sensory neuropathy	1	3	—	—	—	—
Phlebitis	1	4	—	—	—	—
Pleural effusion	1	4	—	—	—	—
Pneumonia	1	3	2	6	—	—
Reduced LVEF	2	6	—	—	—	—
Renal failure	—	—	—	—	1	3
Syncope	—	—	1	3	—	—
Taste alteration	2	6	—	—	—	—
Vomiting	2	6	1	3	—	—
Weight loss	2	6	—	—	—	—

Abbreviations: ARDS, adult respiratory distress syndrome; LVEF, left ventricular ejection fraction.

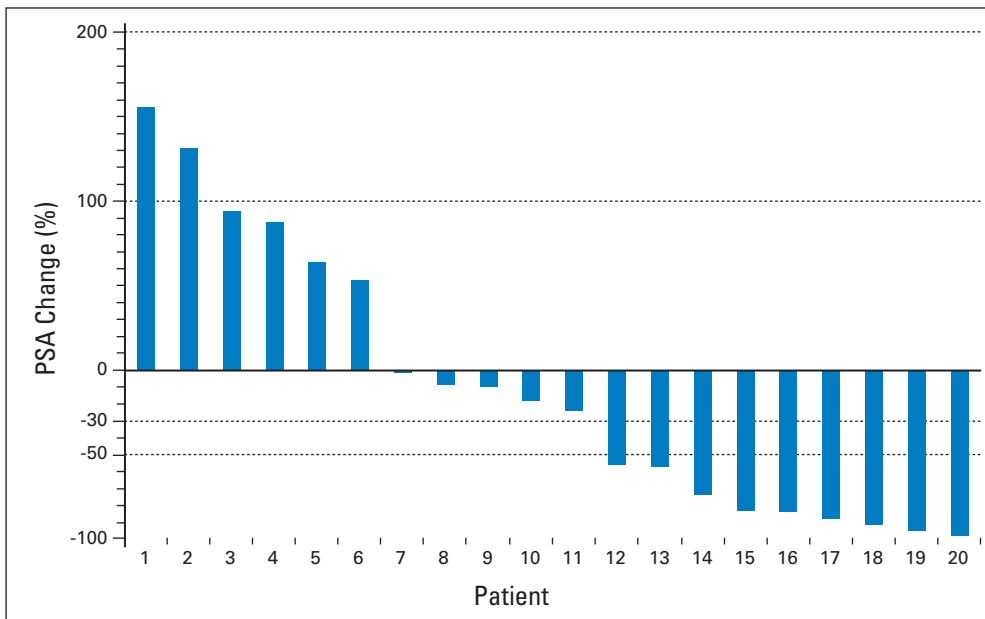
While further dose escalation was formally possible beyond doses of mitoxantrone 12 mg/m<sup>2</sup> and ixabepilone 35 mg/m<sup>2</sup>, due to concerns of broad applicability of the regimen to the general population of CRPC patients, further dose escalation was not pursued.

Neurotoxicity was not frequently observed in this study despite the sequential use of two potentially neurotoxic agents (docetaxel and ixabepilone). Only 12% of patients experienced grade 2 or greater neuropathy. These data are consistent with the previous study of ixabepilone monotherapy after taxanes in CRPC.<sup>7</sup> Patients with pre-existing grade 2 or higher neuropathy were excluded from participation in this trial. These data are also similar to what has been observed in taxane-refractory metastatic breast cancer patients treated with ixabepilone.<sup>11,12</sup> As a result, it may be that these criteria selected for a patient population less susceptible to neuropathy. Furthermore, variations in assessment of toxicity between different physicians and different institutions may result in under-reporting of grade 3 neuropathy.

Although efficacy was not a primary end point of this study, the frequency of PSA declines observed with the combination is intriguing. In patients who received treatment on this study with the US Food and Drug Administration–approved doses of mitoxantrone, the PSA

response frequency was 42%, while the PSA response rate for salvage mitoxantrone and prednisone has been reported to be 20%.<sup>7</sup> The PSA response frequency in first-line mitoxantrone studies ranges from 19% to 32%.<sup>1,2,5</sup> While the numbers of patients in this study are small, these results indicate that the addition of ixabepilone to MP may result in at least additive efficacy. While PSA declines are an intermediate end point and not a direct measure of clinical benefit, the PSA Working Group Consensus Criteria were developed precisely to screen for the activity of cytotoxic regimens in men with metastatic CRPC. The preliminary activity demonstrated in this study suggests that this regimen is worthy of further evaluation. The DOD Prostate Cancer Clinical Trials Consortium is testing this regimen in ongoing phase II study.

One potential weakness of this study may result from patient selection resulting in a group of patients not accurately reflecting the distribution of CRPC patients in the community. In fact, in an earlier study of mitoxantrone versus ixabepilone, such selection was mandated by virtue of an eligibility requirement of progression while on docetaxel or within 60 days of the last docetaxel dose. This study had no such restrictions, and, in fact, 31% of patients accrued to this study developed progressive disease more than 60 days after



**Fig 1.** Prostate-specific antigen (PSA) waterfall plot of maximum PSA declines of the 21 patients who received the US Food and Drug Administration–approved mitoxantrone dose of 12 mg/m<sup>2</sup> (dose levels V, Va, VI, and VIa). Nine patients (43%) experienced confirmed PSA declines of at least 50% (95% CI, 22% to 66%).

the last docetaxel dose. It is possible that some of these patients might have responded to rechallenge with docetaxel. While this difference may result in inadvertent selection of “better” patients for this study, it also reflects the broad distribution of taxane pretreated patients in the community.

A second potential weakness involving careful patient selection at a single specialized center is somewhat addressed by the multicenter participation in this trial. Nevertheless, this study, conducted in four high volume prostate cancer tertiary referral centers, demonstrates that combination chemotherapy for second-line chemotherapy for CRPC is feasible with these agents.

In summary, the combination of ixabepilone and mitoxantrone with pegfilgrastim is safe and feasible in metastatic CRPC patients who have developed progressive disease despite docetaxel-based therapy. Furthermore, this regimen has demonstrated sufficient activity to warrant phase II testing.

**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The author(s) indicated no potential conflicts of interest.

**REFERENCES**

1. Petrylak DP, Tangen CM, Hussain MH, et al: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 351:1513-1520, 2004
2. Tannock IF, de Wit R, Berry WR, et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 351:1502-1512, 2004
3. Hussain M, Tangen CM, Lara PN Jr, et al: Ixabepilone (Epothilone B Analogue BMS-247550) is active in chemotherapy-naïve patients with hormone-refractory prostate cancer: A Southwest

Oncology Group trial S0111. *J Clin Oncol* 23:8724-8729, 2005

4. Galsky MD, Small EJ, Oh WK, et al: Multi-institutional randomized phase II trial of the epothilone B analog ixabepilone (BMS-247550) with or without estramustine phosphate in patients with progressive castrate metastatic prostate cancer. *J Clin Oncol* 23:1439-1446, 2005
5. Kantoff PW HS, Conaway M, Picus J, et al: Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: Results of the CALGB 9182 study. *J Clin Oncol* 17: 2506-2513, 1999
6. Tannock IF, Osoba D, Stockler MR, et al: Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-

resistant prostate cancer: A Canadian randomized trial with palliative end points. *J Clin Oncol* 14:1756-1764, 1996

7. Rosenberg J, Weinberg V, Kelly W, et al: Activity of second-line chemotherapy in docetaxel-refractory hormone-refractory prostate cancer patients. *Cancer* 110:556-563, 2007
8. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organisation for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 92:205-216, 2000
9. Bubleby GJ, Carducci M, Dahut W, et al: Eligibility and response guidelines for phase II clinical

**AUTHOR CONTRIBUTIONS**

**Conception and design:** Jonathan E. Rosenberg, Vivian K. Weinberg, Eric J. Small  
**Financial support:** Eric J. Small  
**Administrative support:** Jonathan E. Rosenberg, Jeremy Sharib, Eric J. Small  
**Provision of study materials or patients:** Jonathan E. Rosenberg, Charles J. Ryan, David C. Smith, Maha Hussain, Tomasz M. Beer, Christopher W. Ryan, Paul Mathew, Lance C. Pagliaro, Eric J. Small  
**Collection and assembly of data:** Jonathan E. Rosenberg, Charles J. Ryan, Vivian K. Weinberg, David C. Smith, Maha Hussain, Tomasz M. Beer, Christopher W. Ryan, Paul Mathew, Andrea L. Harzstark, Jeremy Sharib, Eric J. Small  
**Data analysis and interpretation:** Jonathan E. Rosenberg, Charles J. Ryan, Vivian K. Weinberg, Christopher W. Ryan, Paul Mathew, Lance C. Pagliaro, Andrea L. Harzstark, Jeremy Sharib, Eric J. Small  
**Manuscript writing:** Jonathan E. Rosenberg, Vivian K. Weinberg, Christopher W. Ryan, Lance C. Pagliaro, Jeremy Sharib, Eric J. Small  
**Final approval of manuscript:** Jonathan E. Rosenberg, Charles J. Ryan, Vivian K. Weinberg, David C. Smith, Maha Hussain, Tomasz M. Beer, Christopher W. Ryan, Paul Mathew, Lance C. Pagliaro, Andrea L. Harzstark, Jeremy Sharib, Eric J. Small

trials in androgen-independent prostate cancer: Recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol* 17:3461-3467, 1999

**10.** Sartor AO, Petrylak DP, Witjes JA, et al: Satraplatin in patients with advanced hormone-refractory prostate cancer (HRPC): Overall survival

(OS) results from the phase III satraplatin and prednisone against refractory cancer (SPARC) trial. *J Clin Oncol* 26:250s, 2008 (suppl; abstr 5003)

**11.** Denduluri N, Low JA, Lee JJ, et al: Phase II trial of ixabepilone, an epothilone b analog, in patients with metastatic breast cancer previously untreated with

taxanes. *J Clin Oncol* 25:3421-3427, 2007

**12.** Thomas E, Tabernero J, Fornier M, et al: Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in patients with taxane-resistant metastatic breast cancer. *J Clin Oncol* 25:3399-3406, 2007

---

■ ■ ■

### **Acknowledgment**

We thank the staff at the Department of Defense Prostate Cancer Clinical Trials Consortium (Mary Ellis, Mary Warren, and Kevin Regan) for the extensive work with data management for this multicenter study.