

## Ixabepilone (Epothilone B Analogue BMS-247550) Is Active in Chemotherapy-Naive Patients With Hormone-Refractory Prostate Cancer: A Southwest Oncology Group Trial S0111

Maha Hussain, Catherine M. Tangen, Primo N. Lara Jr, Ulka N. Vaishampayan, Daniel P. Petrylak, A. Dimitrios Colevas, Wael A. Sakr, and E. David Crawford

From the University of Michigan Comprehensive Cancer Center, Ann Arbor; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Southwest Oncology Group Statistical Center, Seattle, WA; University of California at Davis, Cancer Center, Sacramento, CA; Columbia University, New York, NY; National Cancer Institute, Bethesda, MD; and University of Colorado, Denver, CO.

Submitted April 20, 2005; accepted August 19, 2005.

Supported in part by the following United States Public Health Service Cooperative Agreement Grants No. awarded by the National Cancer Institute, Department of Health and Human Services: CA38926, CA32102, CA27057, CA46441, CA14028, CA68183, CA42777, CA12644, CA58861, CA63845, CA20319, CA45450, CA45560, CA74647, CA35178, and CA67663.

Presented in part at the Prostate Cancer Oral Session of the 40th Annual Meeting of the American Society of Clinical Oncology, June 5-8, 2004, New Orleans, LA.

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

Address reprint requests to Southwest Oncology Group (SWOG-S0111) Operations Office, 14980 Omicron Dr, San Antonio, TX 78245-3217; e-mail: mahahuss@med.umich.edu.

0732-183X/05/2334-8724/\$20.00

DOI: 10.1200/JCO.2005.02.4448

### A B S T R A C T

#### Purpose

The epothilones are a new class of tubulin-polymerizing agents with activity in taxane-sensitive and resistant tumor models. We evaluated ixabepilone (BMS-247550) in patients with metastatic hormone-refractory prostate cancer (HRPC).

#### Methods

Eligible patients had chemotherapy-naive metastatic HRPC, a Zubrod performance status of 0 to 2, and adequate organ function. All patients received BMS-247550 at 40 mg/m<sup>2</sup> over 3 hours every 3 weeks. The primary end point was proportion of patients achieving a prostate-specific antigen (PSA) response.

#### Results

Forty-eight patients with metastatic HRPC were registered. Forty-two patients were eligible, with a median age of 73 years and a median PSA level of 111 ng/mL; 78% had bone-only or bone and soft tissue metastases, and 88% had objective radiologic disease progression at registration. Grade 3 and 4 adverse events (AEs) occurred in 16 and three patients, respectively. All grade 4 toxicities were neutropenia or leukopenia. The most frequent grade 3 AEs were neuropathy (eight patients), hematologic toxicity (seven patients), flu-like symptoms, and infection (five patients each). There were no grade 3/4 thrombocytopenia or grade 5 AEs. There were 14 confirmed PSA responses (33%; 95% CI, 20% to 50%); 72% of PSA responders had declines greater than 80%, and two patients achieved an undetectable PSA. The estimated median progression-free survival is 6 months (95% CI, 4 to 8 months), and the median survival is 18 months (95% CI, 13 to 24 months).

#### Conclusion

Ixabepilone has demonstrated activity in patients with chemotherapy-naive metastatic HRPC. Major toxicities were neutropenia and neuropathy. Further testing to define its activity relative to standard therapy is warranted.

*J Clin Oncol* 23:8724-8729.

### INTRODUCTION

The microtubules seem to be a relevant therapeutic target in hormone-refractory prostate cancer.<sup>1-3</sup> Of the antimicrotubule agents, the taxanes have demonstrated single-agent activity in phase II trials.<sup>2,3</sup> This activity, particularly with docetaxel, led to

two randomized phase III trials, both of which demonstrated significant survival improvement for docetaxel-based therapy over mitoxantrone-based therapy.<sup>4,5</sup> This led to the approval of docetaxel and prednisone by the US Food and Drug Administration as standard first-line therapy in patients with metastatic hormone-refractory prostate cancer.

The benefit of docetaxel, however, is modest, and it has no curative potential.

The epothilones are a new class of nontaxane tubulin polymerization agents obtained by fermentation of the myxobacteria *Sorangium cellulosum*. The cytotoxic activities of the epothilones have been linked to stabilization of microtubules, resulting in mitotic arrest at the G<sub>2</sub>/M transition.<sup>6,7</sup> Aza-epothilone B (BMS-247550; ixabepilone) is a semi-synthetic analog of the natural product epothilone B.<sup>8</sup> In preclinical models, BMS-247550 is more active than paclitaxel in paclitaxel-sensitive tumors, and paclitaxel-resistant tumor xenografts were also highly susceptible to the antitumor action of BMS-247550.<sup>9</sup> It has a broad-spectrum antineoplastic activity as demonstrated against several human cancer xenografts (consisting of eight breast cancers, four non-small-cell lung cancers, four pancreatic cancers, eight ovarian cancers, four prostate cancers, four colon cancers, and one each gastric and squamous cell carcinoma; unpublished data, BMS). Phase I trials of ixabepilone have been conducted for a cremophor-based formulation in a variety of schedules, including one 60-minute infusion every 21 days, a weekly schedule, a daily-times-five every 21 days schedule, and daily-times-three every 21 days schedule. Antitumor responses were seen in patients with melanoma, ovarian cancer, non-small-cell lung cancer, and breast cancer, many previously treated with paclitaxel or docetaxel-containing regimens.<sup>8</sup> A dosing schedule of 40 mg/m<sup>2</sup> once every 3 weeks as a single agent was recommended and adopted for phase II testing.

The Southwest Oncology Group investigated ixabepilone therapy in patients with chemotherapy-naïve metastatic hormone-refractory prostate cancer.

## METHODS

### Eligibility Criteria

Eligible patients were required to have a histologic diagnosis of adenocarcinoma of the prostate, metastatic disease, either measurable and/or nonmeasurable, that has progression on androgen deprivation therapy and antiandrogen withdrawal if applicable, as reflected by one or more of the following: progression of measurable or nonmeasurable metastatic disease by radiologic imaging or metastatic disease associated with an increasing prostate-specific antigen level (PSA), defined as at least two consecutive increases in PSA at least 7 days apart documented over a reference value and a minimum PSA of  $\geq 5$  ng/mL. Patients had to have a Zubrod performance status of 0 to 2, continuation of luteinizing hormone-releasing hormone agonists, and discontinuation of all nonsteroidal antiandrogens (flutamide, bicalutamide, or nilutamide) or other hormonal treatment (such as ketoconazole) for at least 28 days before enrollment for flutamide or ketoconazole and at least 42 days before enrollment for bicalutamide or nilutamide. Prior radiation therapy to less than 30% of the bone marrow only was allowed, but prior radiopharmaceuticals or chemotherapy was not allowed. Patients could have had one prior biologic therapy (non-cytotoxic). No concomitant chemotherapeutic, biologic response

modifiers, radiation therapy, corticosteroid, hormonal concomitant therapy (other than continuing luteinizing hormone-releasing hormone agonist treatment), or unconventional therapy (eg, St John's Wort or PC-SPES or any other herbal remedies taken for the purpose of prostate cancer) were allowed. Patients on bisphosphonates therapy were eligible, provided they have documented progressive disease while on therapy, whereas those not receiving bisphosphonates were not allowed to begin bisphosphonates. Recovery from major infections and/or surgical procedures was required, and in the opinion of the investigator, patients must not have significant active concurrent medical illness precluding protocol treatment. Men of reproductive potential had to agree to use an effective contraceptive method. No other prior malignancy was allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cancer of any site, adequately treated stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years. Patients had to consent to providing serum for the correlative studies, but submission of tissue for the correlative studies was optional (tissue was first mandated but because of slow accrual the protocol was amended to make it optional). All patients were informed of the investigational nature of this study and signed a written informed consent in accordance with institutional and federal guidelines. The protocol was approved annually by the institutional review board for each treating institution.

### Baseline Radiologic and Laboratory Assessments

A computed tomography scan of the abdomen and pelvis and a bone scan were required at baseline. Radiologic assessments for measurable disease were done within 28 days before registration. Bone scans were performed within 42 days before registration.

Baseline laboratory tests included PSA, testosterone, CBC with differential and platelets, creatinine or calculated creatinine clearance, AST or ALT, and bilirubin. Patients had to have an absolute granulocyte count of  $\geq 1,500/\mu\text{L}$ , a platelet count of  $\geq 100,000/\mu\text{L}$ , a serum bilirubin less than or equal to the institutional upper limit of normal, AST or ALT  $\leq 2.5 \times$  institutional upper limit of normal, and serum creatinine  $\leq 2.0$  mg/dL or calculated creatinine clearance of  $\geq 40$  mL/min. All laboratory tests had to be obtained within 7 days before registration.

### Treatment Plan

All patients were premedicated 1 hour before ixabepilone with diphenhydramine 50 mg orally and H<sub>2</sub> blocker to prevent hypersensitivity (either ranitidine 150 mg administered orally or famotidine 40 mg administered orally or nizatidine 150 mg administered orally). Ixabepilone was administered at 40 mg/m<sup>2</sup> intravenously over 3 hours every 21 days. Prespecified dose reductions were as follows: -1 dose level was 32 mg/m<sup>2</sup> and the -2 dose level was 25 mg/m<sup>2</sup>. Corticosteroids were not used unless needed for the acute management of grade 3 or 4 hypersensitivity reaction. Patients were evaluated clinically and by laboratory tests before each course of therapy and interim CBC, differential, and platelets were done at day 14. Patients were otherwise evaluated in between courses of therapy as clinically indicated.

### Dose Reductions

Dose was reduced for absolute granulocyte count less than 500/ $\mu\text{L}$  and/or platelet count of less than 50,000/ $\mu\text{L}$ . Granulocyte colony-stimulating factor was allowed at the discretion of the treating physician.

Therapy was delayed for general nonhematologic toxicities (excluding nausea, vomiting, and hypersensitivity) that were

grade 3 or higher until recovery to grade  $\leq 1$ , and dose was reduced by one dose level. Dose reduction was required to  $-1$  dose level for grade 2 neurotoxicity. Therapy was held for grade 3 or higher neurotoxicity and restarted at  $-1$  dose level after recovery to  $\leq$  grade 2. No more than two dose reductions were allowed. Patients who required dose reductions beyond the  $-2$  dose level were removed from protocol treatment.

### **Duration of Therapy, Monitoring and Response Assessment**

In the absence of unacceptable toxicity or progression, patients were to receive a minimum of two cycles. Patients were removed from protocol treatment if progression was documented after two cycles. Otherwise therapy was continued until progression, unacceptable toxicity, patient's choice to withdraw, treatment delay for more than 3 weeks from planned date of therapy, or two cycles beyond a complete response. All patients were evaluated clinically before each cycle and as medically indicated. The CBC/differential and platelet counts were done on the day of therapy and repeated on day 14, whereas PSA, serum creatinine, and liver tests were repeated before each course on the day of therapy. Positive scans were repeated every 6 weeks (after every two cycles). If a scan was negative at baseline, it was not required to be repeated unless clinically indicated. All patients were followed for a maximum of 3 years after registration.

### **Response Definition**

The PSA response definition was based on the PSA Working Group Consensus Criteria.<sup>10</sup> There was not a defined PSA complete response. PSA partial response was defined as  $\geq 50\%$  reduction in PSA as compared with baseline levels. A confirmed PSA partial response required two successive evaluations fulfilling the definition of a partial response a minimum of 4 weeks apart and a minimum objective disease response status of stable disease. Patients who did not qualify for a PSA partial response status were considered nonresponders. Inadequate assessment/response unknown occurred when best response for objective disease was inadequate or unknown or when the PSA had been inadequately assessed. These individuals were also assumed to be nonresponders. Objective disease response was defined using Response Evaluation Criteria in Solid Tumors Group. A complete response required the disappearance of all measurable and nonmeasurable disease, including bone lesions. For a partial response, there must have been a 30% or greater decrease under baseline of the sum of longest diameters of all target measurable lesions and no unequivocal progression of nonmeasurable disease.

Progression for the purpose of this study was defined as follows: measurable disease progression was defined as a 20% increase in the sum of longest diameters of target measurable lesions over smallest sum observed using the same techniques as baseline, a 25% increase in PSA over nadir or baseline (whichever is lower) and an absolute minimum increase of 5 ng/mL (which must be confirmed 4 weeks later), unequivocal progression of nonmeasurable disease in the opinion of the treating physician (explanation must be provided), appearance of any new lesion or site, or death from disease without prior documentation of progression and without symptomatic deterioration.

Radiologic response confirmation was required for a best response status, otherwise without a confirmation, response was considered unconfirmed. Progression-free survival was defined from time of registration to time of first documentation of progression, symptomatic deterioration, or death due to any cause.

### **Statistical Methods**

The primary end point was to assess the proportion of patients that had a PSA response to ixabepilone. A response rate of 40% or greater would be of interest, whereas further testing would not be pursued if the PSA response rate was 20% or less, given that toxicity and survival were also supportive. Initially, 25 patients were to be accrued. If five or more responses were observed, an additional 20 patients were to be accrued. This two-stage design had a type II error rate of 5.2% and a power of 91%.

Secondary end points were to assess the overall survival and progression-free survival rate in patients with hormone-refractory prostate cancer treated with ixabepilone and to estimate the objective response rate (confirmed complete and partial response) among those patients with measurable disease. Kaplan-Meier methods were used to estimate the survival and progression-free survival curves.

## **RESULTS**

Between June 15, 2001, and November 15, 2003, 48 patients were registered to the protocol. Forty-two patients were eligible. Six patients were ineligible for the following reasons: two had no metastatic disease, and four were disqualified because of prestudy laboratory examinations being done outside of the protocol-specified time frame, incomplete baseline disease assessment, or inadequate hormonal withdrawal.

Table 1 lists patient characteristics. The median age was 73 years, 98% of the patients had a performance status of 0 to 1, 19% were African-American, 78% had bone involvement with or without soft tissue metastases, 8% had significant bone pain, 88% had objective radiologic disease progression at registration, and 64% had prior radiotherapy either to the prostate or other sites. All patients are off protocol therapy with a median number of courses of four (range, one to 17 courses). Eleven patients required a dose reduction to  $-1$  dose level, and one patient had a dose reduction to  $-2$  dose level. There was only one major protocol deviation related to a 2-week delay in starting therapy.

### **Adverse Events**

There were no grade 5 (treatment-related deaths) adverse events, and the only grade 4 toxicities were neutropenia (7%) and leucopenia (2%). The most common grade 3 adverse events were neurologic toxicity (19%), hematologic toxicity (17%), flu-like symptoms (12%), and infection (12%). Therapy was discontinued in 13 patients as a result of toxicity (either patient or physician choice); 10 patients were removed because of peripheral neuropathy and three patients were removed because of fatigue. Table 2 describes in detail the toxicities by type and grade. There was no significant thrombocytopenia or anemia, and the predominant neuropathy observed was sensory neuropathy.

### **Neurotoxicity**

Twenty-five patients experienced some neurotoxicity. The median number of ixabepilone courses received by

**Table 1.** Patient Characteristics (N = 42)

	No. of Patients	%
Age, years		
Median	73	
Range	51-85	
African American	8	19
Performance status		
0	21	50
1	20	48
2	1	2
PSA, ng/mL		
Median	111	
Range	6-1,467	
Sites of metastatic disease		
Soft tissue only	9	21
Bone only	17	40
Soft tissue and bone	16	38
Bone pain $\geq$ grade 2*	3*	8
Progression before entry		
PSA only	5	12
Objective disease	37	88
Method of castration		
Medical	34	81
Surgical	8	19
Any prior RT	27	64
Prior RT to prostate	18	43
Prior prostatectomy	10	24

Abbreviations: PSA, prostate-specific antigen; RT, radiotherapy.  
\*Four patients were missing information.

these patients are as follows: eight patients with a maximum neurotoxicity grade of 3 received a median of six courses, nine patients with a maximum grade of 2 received seven courses, and eight patients with a maximum grade of 1 received a median of four courses. Considering the highest grade neurotoxicity per patient, the median time to onset of grade 2 neuropathy was at a median of three courses (range, one to eight), whereas the median time to onset for grade 3 neuropathy was six courses (range, four to 11). Grade 2 neuropathy decreased to grade 1 in three patients, despite continued therapy. These patients received a total of four, five, and 16 courses each.

### Response and Survival

The primary end point for this study was to assess the proportion of patients who had PSA response after receiving ixabepilone. Per protocol requirement, PSA response is determinable only for patients who otherwise had adequate objective disease assessment. PSA response required a minimum of stable or better objective disease status. Fourteen (33%; 95% CI, 20% to 50%) of the 42 patients had a confirmed PSA response. The PSA response was noted starting at a median of 7 weeks after study entry (range, 3 to 15 weeks), and the median time from PSA response to progression was 28 weeks. The majority of patients (72%) with a

confirmed PSA response had PSA declines of greater than 80%, and two patients achieved undetectable PSA ( $< 0.2$  ng/mL). PSA response was considered not determinable in six patients (14%) for lack of adequate objective disease assessment; these patients are counted as nonresponders (two of these six patients had a confirmed PSA partial response).

There were no confirmed objective complete responses among the 20 patients with measurable disease. One patient (5%) had an unconfirmed complete response and two patients (10%) had an unconfirmed partial response. Response durations were 2.5, 4, and 7 months, respectively, for an overall measurable disease response rate of 15%. Eleven patients (55%) had stable disease, two patients had increasing disease (10%), and assessment was inadequate in 20% of patients.

The median follow-up is 25 months. Twenty-seven patients have died. The estimated median progression-free survival is 6 months (95% CI, 4 to 8 months), and the median survival is 18 months (95% CI, 13 to 24).

## DISCUSSION

Our study evaluated ixabepilone in chemotherapy-naïve patients with hormone-refractory prostate cancer in a cooperative group setting. The primary end point was to assess this agent's activity as reflected by the proportion of patients who achieved PSA declines of  $\geq 50\%$ . Fourteen (33%; 95% CI, 20% to 50%) of the 42 patients had a confirmed PSA response. The median progression-free and overall survivals were 6 and 18 months, respectively. There were no treatment-related deaths, and grade 4 toxicities were neutropenia and leucopenia. By comparison with prior Southwest Oncology Group phase II experience in testing single agents or combination therapy in hormone-refractory prostate cancer, this agent clearly has clinically documented antitumor activity.<sup>11,12</sup> Additional efficacy data comes from a parallel multicenter phase II randomized trial that compared ixabepilone alone or in combination with estramustine.<sup>13</sup> Eligible patients were chemotherapy-naïve with progressive disease defined as increasing PSA, new or progressive soft tissue metastasis, or bone metastasis. Treatment consisted of ixabepilone at 35 mg/m<sup>2</sup> administered intravenously on day 2 with or without estramustine 280 mg orally three times per day on days 1 through 5 every 3 weeks. Low-dose prophylactic warfarin 2 mg per day was administered orally to patients receiving estramustine. There were 45 patients treated in the combination arm and 47 patients in the ixabepilone arm for a total of 92 patients. Objective responses were observed in eight (32%) of 25 patients treated with ixabepilone alone and 11 (48%) of 23 patients in combination arm. A PSA response was observed in 48% of patients on the ixabepilone-alone arm and 69% of

**Table 2.** Adverse Events by Summary Category With Detail Reporting of Hematologic and Neurologic Toxicities (n = 42 at risk)

Toxicity	Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
<b>Hematologic</b>								
Neutropenia	4	10	2	5	4	10	3	7
Leukopenia	5	12	6	14	4	10	1	2
Anemia	17	40	5	12	1	2	0	
Lymphopenia	0		4	10	1	2	0	
Maximum grade per patient of any neurologic toxicity*	8	19	9	21	8	19	0	
<b>Neurologic</b>								
Sensory neuropathy	7	17	9	21	7	17	0	
Motor neuropathy	1	2	1	2	1	2	0	
Neuropathic pain	0		3	7	1	2	0	
Neuro, unspecified	1	2	0		0		0	
Insomnia	6	14	1	2	0		0	
Flu-like symptoms	14	33	6	14	5	12	0	
Infection	0		1	2	5	12	0	
Gastrointestinal toxicity	17	40	16	38	3	7	0	
Cardiovascular toxicity	7	17	1	2	1	2	0	
Dermatologic toxicity	10	24	12	29	1	2	0	
Liver toxicity	5	12	1	2	1	2	0	
Metabolic toxicity	8	19	2	5	1	2	0	
Pain	13	31	8	19	1	2	0	
Max grade any adverse event	4	10	17	40	16	38	3	7

NOTE. No grade 5 toxicity was reported.

\*Includes sensory neuropathy, motor neuropathy, neuropathic pain, unspecified neurotoxicity, and insomnia. Some patients had more than one type of neurotoxicity.

patients on the combination arm. Time to PSA progression was similar in both arms (141 days in the combination arm compared with 145 days in the ixabepilone-only arm). Differences in efficacy of ixabepilone between these two trials likely stem from differences in patient selection and disease burden. Similar to our study, neutropenia and neuropathy were the main adverse events observed in this study. Low-grade neuropathy was common, but grade 3 neuropathy occurred in 13% of patients.

As described in Table 2, the majority of the neuropathy is sensory neuropathy. In our study, the onset of grade 3 neuropathy was relatively delayed, occurring at a median of six courses. Interestingly, data from Galsky et al<sup>13</sup> suggest that the neuropathy is reversible, as demonstrated by the improvement in the severity of neuropathy over time. After a median follow-up of 413 days, grade 2 or 3 neuropathy had improved to grade 0 or 1 in 18 (95%) of 19 patients. Several phase I and II studies have been conducted with ixabepilone across different tumor types at a variety of doses and schedules. Most of the results reported to date have come from trials exploring either a once every 21 days or a daily  $\times$  5 schedule. With the once every 21 days schedule, there seems to be a relationship between neuropathy and dose such that the dose of ixabepilone studied in some of the initial phase II trials<sup>14,15</sup> was adjusted down from the original phase I recommended dose of 50 mg/m<sup>2</sup> to 40 mg/m<sup>2</sup> as was done in our study. Although patients treated with 50

mg/m<sup>2</sup> seem to have more neuropathy than those treated with 40 mg/m<sup>2</sup>, the relationship between dose and neuropathy is less clear at this time for doses of  $\leq$  40 mg/m<sup>2</sup> given the limitations of the clinical data. Grade 3 neurotoxicity was not seen in the phase I study with ixabepilone administered daily for 5 days,<sup>16</sup> and in a recent phase II trial with ixabepilone administered daily for 5 days in patients with breast cancer, the grade 3 peripheral sensory neuropathy was only 3%.<sup>17</sup> This seems to be less than that observed in the every 3 weeks schedule. It is not clear whether this favorable profile is related to the schedule of administration or related to a lower total dose than was administered in most of the phase II trials conducted with the every 21 days schedule. This point is illustrated by the preliminary data from a randomized phase II trial of ixabepilone in non-small-cell lung cancer, which demonstrated similar safety and efficacy results in patients administered a total dose of 30 mg/m<sup>2</sup> administered over 5 consecutive days as those treated with 32 mg/m<sup>2</sup> administered once every 21 days.<sup>18</sup> It is also important to note that with regard to efficacy, the relationship between antitumor activity and dose and schedule is also not completely understood at this time.

To assess the potential efficacy of this agent and that of mitoxantrone as second-line chemotherapy in patients experiencing treatment failure with taxane-based chemotherapy, a multicenter Cancer Therapy Evaluation Program-sponsored randomized phase II trial has recently completed

accrual.<sup>19</sup> The primary end point for the trial was second-line PSA response proportion by Consensus Criteria. Updated preliminary data presented on 67 randomly assigned patients at the 2005 Annual Meeting of the American Society of Clinical Oncology indicated 17% and 14% confirmed PSA response rates for the ixabepilone-treated (n = 30) and mitoxantrone-treated patients (n = 37), respectively. These preliminary data suggest that both agents have some antitumor activity in taxane-treated patients. If these data hold in the face of an acceptable toxicity profile, the logical next step would be to definitively evaluate this agent in a phase III trial against mitoxantrone in patients experiencing treatment failure following docetaxel therapy. Although there is no established second-line therapy in this setting, mitoxantrone is a reasonable control arm

considering that, in practice, this is the agent that is likely to be used in patients experiencing treatment failure with docetaxel therapy.

In summary, ixabepilone has antitumor activity in patients with chemotherapy-naïve hormone-refractory prostate cancer as demonstrated by two multicenter trials. Its level of activity compares favorably with that reported for docetaxel plus prednisone. Although it may be argued that an apparent comparable level of activity is not a justification for a phase III trial in first-line therapy of hormone-refractory prostate cancer, it is our belief that the only way to address the question of whether the epothilones are superior to the taxanes is in a phase III setting.

### Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Maha Hussain			BMS (A)			BMS Research Support (B)		
Dollar Amount Codes (A) < \$10,000 (B) \$10,000-99,999 (C) ≥ \$100,000 (N/R) Not Required								

### REFERENCES

- Hudes G, Einhorn L, Ross E, et al: Vinblastine versus vinblastine plus oral estramustine phosphate for patients with hormone-refractory prostate cancer: A Hoosier Oncology Group and Fox Chase Network phase III trial. *J Clin Oncol* 17:3160-3166, 1999
- Picus J, Schultz M: Docetaxel (Taxotere) as monotherapy in the treatment of hormone-refractory prostate cancer: Preliminary results. *Semin Oncol* 26:14-18, 1999
- Trivedi C, Redman B, Flaherty LE, et al: Weekly 1-hour infusion of paclitaxel: Clinical feasibility and efficacy in patients with hormone-refractory prostate carcinoma. *Cancer* 89:431-436, 2000
- 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
- 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
- Bollag DM, McQueney PA, Zhu J, et al: Epothilones, a new class of microtubule-stabilizing agents with a taxol-like mechanism of action. *Cancer Res* 55:2325-2333, 1995
- Kowalski RJ, Giannakakou P, Hamel E: Activities of the microtubule-stabilizing agents epothilones A and B with purified tubulin and in cells resistant to paclitaxel (Taxol). *J Biol Chem* 272:2534-2541, 1997
- Goodin S, Kane MP, Rubin EH: Epothilones: Mechanism of action and biologic activity. *J Clin Oncol* 22:2015-2025, 2004
- Lee FY, Borzilleri R, Fairchild CR, et al: BMS-247550: A novel epothilone analog with a mode of action similar to paclitaxel but possessing superior antitumor efficacy. *Clin Cancer Res* 7:1429-1437, 2001
- Bubley GJ, Carducci M, Dahut W, et al: Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: Recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol* 17:3461-3467, 1999
- Pienta KJ, Fisher EI, Eisenberger MA, et al: A phase II trial of estramustine and etoposide in hormone refractory prostate cancer: A Southwest Oncology Group trial (SWOG 9407). *Prostate* 46:257-261, 2001
- Klein CE, Tangen CM, Braun TJ, et al: SWOG-9510: Evaluation of topotecan in hormone refractory prostate cancer—A Southwest Oncology Group study. *Prostate* 52:264-268, 2002
- 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
- Thomas E, Tabernero J, Fornier M, et al: A phase II study of the epothilone B analog BMS-247550 in patients (pts) with taxane-resistant metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol* 22:8, 2003 (abstr 30)
- Roche EE, Cure H, Bunnell C, et al: A phase II study of epothilone analog BMS-247550 in patients (pats) with metastatic breast cancer (MBC) previously treated with an anthracycline. *Proc Am Soc Clin Oncol* 22:18, 2003 (abstr 69)
- Abraham J, Agrawal M, Bakke S, et al: Phase I trial and pharmacokinetic study of BMS-247550, an epothilone B analog, administered intravenously on a daily schedule for five days. *J Clin Oncol* 21:1866-1873, 2003
- Low J, Wedam S, Lee J, et al: Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in metastatic and locally advanced breast cancer. *J Clin Oncol* 23:2726-2734, 2005
- Vansteenkiste J, Breton J, Sandler A, et al: A randomized phase II study of epothilone analog BMS-247550 in patients (pts) with non-small cell lung cancer (NSCLC) who have failed first-line platinum-based chemotherapy. *Proc Am Soc Clin Oncol* 22:626, 2003 (abstr 2519)
- Rosenberg J, Kelly WK, Michaelson M, et al: A randomized phase II study of ixabepilone (Ix) or mitoxantrone and prednisone (MP) in patients with taxane (T)-resistant hormone refractory prostate cancer (HRPC). *Proc Am Soc Clin Oncol* 23:394s, 2005 (abstr 4566)