Published in final edited form as:
Clin Genitourin Cancer. 2012 June ; 10(2): 99–105. doi:10.1016/j.clgc.2012.01.009.

Phase II Trial of Weekly Ixabepilone in Men With Metastatic Castrate-Resistant Prostate Cancer (E3803): A Trial of the Eastern Cooperative Oncology Group

Glenn Liu[1], **Yu-Hui Chen**[2], **Robert DiPaola**[3], **Michael Carducci**[4], and **George Wilding**[1]
[1]University of Wisconsin Carbone Cancer Center, Madison, WI

[2]Dana - Farber Cancer Institute, Boston, MA

[3]Cancer Institute of New Jersey, New Brunswick, NJ

[4]Johns Hopkins Kimmel Cancer Center, Baltimore, MD

Abstract

Ixabepilone is an epothilone B analogue with activity in a variety of solid malignancies, including prostate cancer. The main dose-limiting toxicity of ixabepilone is myelosuppression when administered by using an every 3-week schedule. Here we evaluate the activity of a weekly ixabepilone in men with metastatic castrate-resistant prostate cancer to minimize hematologic toxicity.

Purpose—BMS-247550 (ixabepilone) is an epothilone B analogue with activity in taxane-resistant cancer cell lines. Here we report the activity and toxicity of ixabepilone, administered by using a weekly schedule, in men with metastatic castrate-resistant prostate cancer (CRPC).

Experimental Design—Patients with metastatic CRPC received ixabepilone at 20 mg/m^2 intravenous weekly × 3, in 4-week cycles. This noncomparative study stratified patients to either a chemotherapy naive (CN), prior taxane (Tax) only, or 2 prior cytotoxic (TCx) chemotherapy arm. The primary endpoint was prostate-specific antigen response by using PCWG (Prostate Cancer Working Group) 1 criteria. Secondary endpoints included radiographic response when using RECIST (Response Evaluation Criteria In Solid Tumors).

Results—In total, 124 patients were enrolled, of whom, 109 were eligible (35 CN, 42 Tax, and 32 TCx) for the primary response determination in this study. Prostate-specific antigen responses were seen in 12 (34.3%) of 35, 12 (28.6%) of 42, and 7 (21.9%) of 32 patients with the partial objective response in 5 (22.7%) of 22, 2 (8.0%) of 25, and 0 (0.0%) of 24 patients for the CN, Tax, and TCx arms, respectively. Significant (grade 3/4) neutropenia was seen in 6 (15.4%), 7 (14.6%), and 9 (25.0%); and grade 3/4 sensory neuropathy was seen in 8 (20.5%), 12 (25.0%), and 12 (33.3%) for CN, Tax, and TCx, respectively. Grade 3/4 thrombocytopenia was infrequent and seen in only one patient on the CN and the TCx arm.

Conclusion—Ixabepilone was found to have an acceptable toxicity profile when administered by using a weekly schedule with less myelosuppression compared with prior studies when using

Address for correspondence: Glenn Liu, MD, Carbone Cancer Center, 1111 Highland Ave, Wisconsin Institute for Medical Research, Room 7051, University of Wisconsin, Madison, WI 53705, Fax: +1-608-265-0614; gxl@medicine.wisc.edu.

Previous Presentations: American Society of Clinical Oncology 2007, American Society of Clinical Ophthalmology 2008, American Society of Clinical Ophthalmology 2011

Disclosure
The authors have stated that they have no conflicts of interest.

the every 3-week schedule. Single-agent activity was observed and met prespecified activity levels for the Tax treated arm.

Keywords

BMS-247550; Chemotherapy; Epothilone; Microtubule-inhibitor

Introduction

Prostate cancer will be diagnosed in approximately 240,890 men in the United States for the year 2011 alone, which resulted in 33,720 deaths.[1] In the past, cytotoxic chemotherapy was administered for palliative purposes in men with symptomatic, castrate-resistant prostate cancer (CRPC);[2] however, the use of cytotoxic chemotherapy expanded with the understanding that microtubule inhibitors modestly improve median survival. The regimen of every 3-week docetaxel with prednisone was approved in 2004 after showing a 2.5-month improvement in median overall survival over mitoxantrone with prednisone in metastatic CRPC.[3] Of note, despite the lack of a proven survival benefit, weekly docetaxel was noted to have an improved hematologic toxicity profile in this disease, which suggests that, in elderly patients, a weekly schedule may be better tolerated and safer.[4,5]

Advances in tumor biology have led to an increased understanding of chemoresistance mechanisms in prostate cancer,[6] which has resulted in the discovery of newer microtubule inhibitors that can overcome these resistance mechanisms. Cabazitaxel is a tubulin-binding taxane that differs from docetaxel in that it has poor affinity for P-glycoprotein, a key adenosine triphosphate dependent drug efflux pump encoded on multidrug resistance (MDR)1 associated with docetaxel resistance.[7,8] Cabazitaxel was approved for use in taxane-resistant metastatic CRPC in 2010, after showing an improvement in median overall survival of 15.1 vs. 12.7 months for mitoxantrone. Despite its benefits, concerns were raised about the high incidence of neutropenia (82% for cabazitaxel vs. 58% with mitoxantrone) and toxic deaths (5% for cabazitaxel vs. 1% with mitoxantrone).[9]

Ixabepilone (BMS-247550; Ixempra, Bristol-Meyer-Squibb Company, Princeton, New Jersey) is a member of the nontaxane microtubule stabilizing compounds called epothilones. Mechanistically, ixabepilone induces polymerization of tubulin dimers into stable microtubules, which leads to mitotic arrest and apoptosis. Preclinical data show strong antitumor activity in paclitaxel sensitive and paclitaxel-resistant tumor models, including MDR and non-MDR resistance models.[10] Ixabepilone has been developed with various treatment schedules.[11–13] When administered on day 1 every 21 days, the recommended phase 2 dose was determined to be 40 to 50 mg/m^2, with the main toxicities being neuropathy, myalgias, arthralgias, and neutropenia. [14,15] Single-agent activity in CRPC has been reported with prostate-specific antigen (PSA) response rates of 33% in patients who were CN[16,17] and 17% in patients previously treated with docetaxel[17] when ixabepilone was administered once every 3 weeks. A feasibility study of BMS-247550 with estramustine in metastatic CRPC was completed and showed that BMS-247550 at 35 mg/m^2 day 1 could be combined with estramustine at 280 mg 3 times daily on days 1–5.[18] A subsequent randomized phase II trial by using this regimen in patients with chemotherapy-naive metastatic CRPC showed a PSA response rate of 48% for ixabepilone alone arm vs. 69% for the ixabepilone/estramustine arm.[19] Neutropenia remained the main adverse event, with grade 3/4 events reported in 22% for ixabepilone and 29% in the ixabepilone/estramustine arm.

The most common dose-limiting toxicity seen with microtubule inhibitors is hematologic (eg, neutropenia). To minimize neutropenia, weekly schedules of taxanes have been studied

and have been shown to have lower incidences of neutropenic events compared with the every 3-week schedule.[5,20,21] A phase I trial of weekly ixabepilone has established a safe dose of 25 mg/m^2 when infused weekly in a continuous 21-day cycle, or 20 mg/m^2 when administered weekly for 3 weeks, repeated in a 28-day cycle.[22] The dose-limiting toxicity was fatigue, with no significant myelosuppression observed. The incidence of neuropathy also was improved with the use of a prolonged ixabepilone infusion with the recommended phase 2 dose being 20 to 25 mg/m^2 administered weekly. Given that microtubule inhibitors have proven activity in CRPC and treatment-limiting myelosuppression, this trial was initiated to determine the single-agent activity and tolerability of weekly ixabepilone in men with metastatic CRPC who were either chemotherapy naive (CN), had previously received 1 taxane-based chemotherapy regimen only, or had already received 2 prior cytotoxic (TCx) chemotherapy regimens.

Patients and Methods

This study was conducted by the Eastern Cooperative Oncology Group (ECOG) with accrual from 31 participating sites in the United States.

Eligibility

Patients with histologically proven adenocarcinoma of prostate cancer with radiographic evidence of metastases and castrate-resistant disease were enrolled. Progressive castrate-resistant prostate cancer was defined as serum testosterone level ≤50 ng/mL and one of the following: 3 consecutively rising PSA levels; new metastatic lesions on bone scan with the last PSA level ≥10 ng/mL, and/or new or enlarging measurable lesions on computed tomography (CT). Patients receiving antiandrogens were required to show disease progression after antiandrogen withdrawal (≥4 weeks after prior flutamide; ≥6 with bicalutamide or nilutamide). For patients who have not been treated with a bilateral orchiectomy, ongoing treatment with gonadotropin-releasing hormone analogues was required. Bisphosphonate use was allowed if initiated ≥4 weeks before registration with evidence of tumor progression while on the bisphosphonate therapy as defined above. Patients were required to continue bisphosphonate therapy while in the study but were not allowed to initiate new bisphosphonate therapy while receiving protocol therapy. Additional eligibility criteria included adequate hematologic criteria (leukocytes ≥ 4000/mm^3; absolute neutrophil count (ANC) ≥ 1500/mm^3; platelets ≥ 100,000/mm^3), hepatic function (alanine aminotransferase level ≤2 times the institutional upper limit of normal, bilirubin level ≤1.5 ng/dL), and renal function (serum creatinine level ≤ 1.5 mg/dL or calculated creatinine clearance ≥50 mL/ min), age ≥ 18 years and ECOG performance status of 0–2. Depending on the treatment stratification arm, the patients can have received only up to TCx chemotherapeutic regimens for CRPC ≥4 weeks before registration. Up to 1 prior experimental (noncytotoxic) regimen was allowed, provided that it was given at least 4 weeks before registration.

Excluded from the study were radiation therapy within 4 weeks of registration, any prior radioisotope therapy (eg, samarium-153 or strontium-89), active angina pectoris or New York Heart Association Class III–IV congestive heart failure, myocardial infarction within 6 months, ventricular dysrhythmia (except atrial fibrillation if rate controlled), peripheral neuropathy higher than grade 1, carcinomatous meningitis or brain metastases, and other malignancy within 5 years (except nonmelanomatous skin cancer treated with curative intent). All the patients provided written informed consent. This study was approved by the ethics committee or the institutional review board at each center and complied with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations.

Study Design

This multi-institutional phase II study was conducted through the ECOG. The primary endpoint was a 50% decline in PSA value when using Prostate Cancer Working Group(PCWG1) criteria[23] stratified to patients who never received cytotoxic chemotherapy, received 1 prior taxane (Tax) based regimen, or received 2 prior cytotoxic (TCx) chemotherapy regimens (including Tax) for metastatic CRPC. Secondary objectives included evaluation of the objective response rate in patients with measurable disease when using RECIST (Response Evaluation Criteria In Solid Tumors)1.0[24] and duration of treatment response, as well as to describe toxicity and tolerability of weekly ixabepilone in this patient population. Adverse events were recorded by using Common Terminology Criteria for Adverse Events version 3.0.

Treatment Plan

All patients received ixabepilone starting at 20 mg/m^2 intravenously (I.V.) over 1 hour on days 1, 8, and 15 (±1 day) in 28-day cycles. Patients were premedicated 30 to 60 minutes before ixabepilone with diphenhydramine 50 mg (orally [p.o.]/I.V.) and ranitidine 50 mg IV or 150 mg p.o. (or equivalent H2 receptor blocker except cimetidine). Treatment was continued until disease progression or the development of unacceptable toxicity. Treatment was held for ANC < 1000/mm^3 or platelets < 75,000/mm^3. Prophylactic use of granulocyte-colony stimulating factors was not allowed but subsequent use for prior febrile neutropenia was permitted. Treatment was also held for creatinine >2 mg/dL or grade >2 neurotoxicity (or subjectively intolerable grade 2 neurotoxicity) until recovery to grade 1 or baseline. For all other adverse events, treatment was held for grade ≥3 nonhematologic toxicity if the event was considered possibly related to the ixabepilone. If a patient recovers to grade 1 (or baseline) within 1 week, then treatment was reinitiated at the current dose; recovery within 2 weeks necessitated a dose reduction. Failure to recover counts within 14 days required treatment discontinuation. For patients who required a dose reduction, the first dose reduction was 15 mg/m^2. The second dose reduction was 10 mg/m^2. Any patient who required further dose reductions were discontinued from the treatment protocol.

Patient Evaluations

The patients were assessed at the beginning of each cycle of therapy (every 28 days) with a history, physical examination, basic chemistry and hematologic laboratories, and values. Between cycles, a weekly complete blood cell count with ANC was obtained before each ixabepilone infusion. Radiographic disease assessments occurred after every 2 cycles and consisted of a bone scan and/or a CT of the abdomen-pelvis for patients with measurable metastasis.

Response Evaluation

PSA values were collected monthly. A PSA response was defined by a ≥50% reduction in PSA value (or normalization of PSA value to <0.2 ng/mL) compared with baseline, confirmed by a repeated PSA test at least 4 weeks later. PSA progression was defined as an increase in PSA value ≥25% baseline value, confirmed by a second PSA test ≥4 weeks later, with an absolute increase at least 5 ng/mL. The date of PSA progression was defined as the date that the initial PSA value increased ≥25% over baseline at a minimum of 5 ng/mL. For patients with a PSA value decline from baseline, PSA progression was defined as an increase in PSA value ≥50% over nadir values, confirmed by a second PSA test ≥4 weeks later, with an absolute increase at least 5 ng/mL. The date of PSA progression was defined as the date that the initial PSA level increased ≥50% over nadir at a minimum of 5 ng/mL. Stable disease was defined as neither meeting response nor progressive disease criteria for at least 90 days.

Bone scans were performed at baseline and at 8-week intervals if skeletal disease was present. New symptomatic lesions were considered progressive disease at all times; however, new asymptomatic lesions on the week-8 bone scan associated with a drop in PSA value from baseline was not considered progressive disease. Subsequent assessments used the week-8 scan for future comparison. Any new lesions on bone scan seen after week 8 was considered progressive disease. For patients with RECIST measurable disease, RECIST 1.0 response guidelines[24] were followed. Progression-free survival (PFS) was defined as the time from study entry to first progression of any type (clinical, radiographic, or PSA) or death. Overall survival was measured starting from date of study entry.

Statistical Analysis

The primary endpoint of interest was the proportion of patients with a PSA response. This study had separate accrual goals for 3 strata (CN, Tax regimen only, or up to TCx chemotherapeutic regimens). Weekly ixabepilone would be considered a promising regimen if a true response rate of 30% was observed for patients in the Tax or TCx regimen strata. By contrast, if the true response rate was 10% or less, then the regimen would not be of further interest. With this design, the probability of concluding that the treatment is effective was 0.9 if the true PSA response rate was 30% and 0.1 if the true response rate was 10%. For patients without prior chemotherapy, the treatment would be considered promising if a true response rate of 50% or more was observed and would not be of further interest if the true response was 25% or less. With this design, the probability of concluding that the treatment is effective was 0.91 if the true PSA response rate was 50% and 0.09 if the true response rate was 25%.

If the regimen demonstrated a PSA response rate of at least 30% for patients with Tax or TCx chemotherapy regimens or at least 50% for patients without prior chemotherapy and if the number of patients with measurable disease entered to either stratum during this part of the study was <25 in each stratum, then we would enter additional patients such that the total number of eligible patients with measurable disease in each stratum was 25. However, the PSA response rate was calculated among the first cohort of patients, not including the additional patients with measurable disease. Measurable disease response rate was calculated among all patients with measurable disease, including the additional patients.

Descriptive statistics were used to characterize patients at study entry. Exact binomial confidence intervals were used to describe PSA response rate and overall response rate. The method of Kaplan and Meier was used to characterize the duration of PSA response, duration of overall response, PFS and overall survival. Differences in the distribution of worst-degree toxicities by stratum were evaluated by using the Kruskal-Wallis test. All *P* values are 2-sided.

Results

The study was activated in limited ECOG institutions on September 16, 2004, and was terminated on February 4, 2009, after reaching its accrual goal. Final accrual to this study was 124 patients.

Patient Characteristics

Patient demographics and disease characteristics are shown in Table 1. Most patients were white (11 [10%] African Americans). Most patients (62 [57%]) received prior bisphosphonate therapy.

Treatment-Related Toxicities

Anemia, fatigue, and leukopenia were the most frequently occurring toxicities. Only one grade 5 event was observed and was classified as cerebrovascular ischemia, which resulted in death. Grade 3 or 4 toxicities observed during treatment, regardless of cycle, grouped by treatment strata, are shown in Table 2. There was no statistically significant difference in the distribution of worst-degree toxicities by stratum ($2P = .42$). Allergic reactions were seen in 4 patients (3 grade 1 or 2, one grade 3 reaction).

Disease Response

PSA Response and Kinetics—Among the patients accrued in the first stage, the PSA response rates were 33% (90% CI, 19%–50%), 24% (90% CI, 12%–38%), and 18% (90% CI, 6%–37%) for the CN, Tax only, and TCx chemotherapy, respectively. The total PSA response (both stages) for all eligible patients when using PCWG1 criteria was 34% (12/35), 29% (12/42), and 22% (7/32) for the CN, Tax, and TCx chemotherapy strata, respectively. Eighteen patients total were not evaluable for PSA response because they had either died or progressed radiographically before meeting any prespecified PSA endpoints. The duration of PSA response (defined as the time from the date of onset of PSA response until the date when progression criteria was met was 6 months for the CN stratum and 7.6 months for the Tax stratum. The median duration for the TCx chemotherapy stratum was not reached due to insufficient evaluation of PSA endpoints as summarized above. The maximal PSA posttherapy change from baseline per stratum as per PCWG 2 criteria[25] is shown in Figure 1.

RECIST Response—No complete responses were seen. Of the patients with RECIST measurable disease, the objective response rate was 23% (5/22) in the CN stratum, 8% (2/25) in the Tax stratum, and 0% (0/24) in the TCx chemotherapy stratum.

Overall and PFS—At the time of this analysis, 107 of 109 patients had died. The median overall survival was 12.8 months (90% CI, 11.0–15.8 months). The overall survival for the 3 strata is shown in Figure 2. The median overall survival per strata was 17.1, 11.0, and 12.1 months for the CN, Tax, and TCx chemotherapy stratum, respectively. The PFS per strata is shown in Figure 3. The median PFS was 5.1 months (90% CI, 3.3–6.4 months), 3.4 months (90% CI, 2.3–4.3 months), and 3.8 months (90% CI, 3.2–5.5 months) for the CN, Tax, and TCx chemotherapy stratum, respectively.

Discussion

Ixabepilone is an epothilone B analogue with activity in taxane-resistant cell lines. When administered by using an every 3-week infusion schedule in men with CN metastatic CRPC, grade 3 or 4 neutropenia was observed in 22%, with grade 3 or 4 neuropathy reported in 13% of patients.[19] Because ixabepilone is believed to have antitumor activity in patients who were taxane refractory, alternative schedules to minimize neutropenia and neurotoxicity may be necessary in men previously treated with docetaxel chemotherapy. This study evaluated the single-agent activity of ixabepilone when administered on a weekly schedule in men with metastatic CRPC and stratified outcomes to those men who were either CN, had received prior docetaxel-based chemotherapy only, or had received TCx chemotherapy regimens (including docetaxel).

Weekly ixabepilone was found to be safe and tolerable in this patient population. Antitumor activity was shown with changes in PSA when seen in each strata and evidence for radiographic responses in both theCNand prior docetaxel chemotherapy strata. Overall, the PSA response rate (34%) did not meet the prespecified level of activity for patients who

were CN. The weekly schedule of ixabepilone did have a lower incidence of significant (grade 3 or 4) neutropenia (15.4%) in the patients who are CN compared with every 3-week ixabepilone; however, the incidence for grade 3 or 4 sensory neuropathy was higher (20.5%) than that observed when ixabepilone was administered when using the every 3-week schedule. The PSA response rate in the prior docetaxel-alone stratum met the prespecified level of activity to justify additional studies.

Since our study has been completed, cabazitaxel, another novel tubulin-binding taxane, was approved for the treatment of men with docetaxel-refractory metastatic CRPC.[9] For comparison, the PSA response rate for cabazitaxel in the Tax state was 39.2%, which is in comparison with the 29% observed in our small study, which supports the fact that patients who have received prior docetaxel-based chemotherapy can still benefit with other microtubule inhibitors. Nevertheless, the toxicity rate with cabazitaxel was substantial, with grade 3 or 4 neutropenia found in 82% of patients with 5% toxic death arguing why alternative schedules need to be considered to minimize toxic effects.

In conclusion, newer microtubule inhibitors have clinical activity in prostate cancer, including in patients refractory to docetaxel. The challenge in these older men with marrow compromise from skeletal metastases and prior chemotherapy is to identify additional agents in which one can achieve clinical benefit with reasonable toxicity. Although cabazitaxel is now one standard of care after docetaxel chemotherapy, the pursuit of additional microtubule-targeting agents in this patient population remains ongoing. Current trials include “lower dose” cabazitaxel (20 mg/m^2) (NCT01308580) to minimize hematologic toxicities or other novel agents, eg, Tesetaxel (Genta Incorporated, Berkeley Heights, New Jersey) (novel oral targeted tubulin inhibitor).[26]

Acknowledgments

We thank all participating ECOG members and patients who participated in this study. In addition, special thanks to Mary Jane Staab, Jane Straus, Dottie Horvath, Janna Bergum, and Kelly Simmons who coordinated this multi-institutional study through the University of Wisconsin Carbone Cancer Center (UWCCC) Genitourinary Oncology Research Program.

Research support: UWMO33JK-00, frontier science and technology research.

Sources of support: This study was conducted by the ECOG (Robert L. Comus, MD) and supported in part by Public Health Service grants CA23318, CA66636, CA21115, CA21076, CA107868, CA16116, CA80775 and from the National Cancer Institute, National Institutes of Health, and the Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

References

1. Society, AC. Cancer Facts and Figures. 2011. Atlanta, GA: American Cancer Society; 2011.
2. Berry W, Dakhil S, Modiano M, et al. Phase III study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer. J Urol. 2002; 168:2439–2443. [PubMed: 12441935]
3. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004; 351:1502–1512. [PubMed: 15470213]
4. Beer TM, Berry W, Wersinger EM, et al. Weekly docetaxel in elderly patients with prostate cancer: efficacy and toxicity in patients at least 70 years of age compared with patients younger than 70 years. Clin Prostate Cancer. 2003; 2:167–172. [PubMed: 15040860]
5. Beer TM, Pierce WC, Lowe BA, et al. Phase II study of weekly docetaxel in symptomatic androgen-independent prostate cancer. Ann Oncol. 2001; 12:1273–1279. [PubMed: 11697840]

6. Sullivan GF, Amenta PS, Villanueva JD, et al. The expression of drug resistance gene products during the progression of human prostate cancer. Clin Cancer Res. 1998; 4:1393–1403. [PubMed: 9626455]
7. Bradshaw DM, Arceci RJ. Clinical relevance of transmembrane drug efflux as a mechanism of multidrug resistance. J Clin Oncol. 1998; 16:3674–3690. [PubMed: 9817290]
8. Mita AC, Denis LJ, Rowinsky EK, et al. Phase I and pharmacokinetic study of XRP6258 (RPR 116258A), a novel taxane, administered as a 1-hour infusion every 3 weeks in patients with advanced solid tumors. Clin Cancer Res. 2009; 15:723–730. [PubMed: 19147780]
9. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010; 376:1147–1154. [PubMed: 20888992]
10. 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. 2001; 7:1429–1437. [PubMed: 11350914]
11. Zhuang SH, Agrawal M, Edgerly M, et al. A phase I clinical trial of ixabepilone (BMS-247550), an epothilone B analog, administered intravenously on a daily schedule for 3 days. Cancer. 2005; 103:1932–1938. [PubMed: 15800893]
12. 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. 2003; 21:1866–1873. [PubMed: 12721265]
13. Gadgeel SM, Wozniak A, Boinpally RR, et al. Phase I clinical trial of BMS-247550, a derivative of epothilone B, using accelerated titration 2B design. Clin Cancer Res. 2005; 11:6233–6239. [PubMed: 16144926]
14. Aghajanian C, Burris HA 3rd, Jones S, et al. Phase I study of the novel epothilone analog ixabepilone (BMS-247550) in patients with advanced solid tumors and lymphomas. J Clin Oncol. 2007; 25:1082–1088. [PubMed: 17261851]
15. Mani S, McDaid H, Hamilton A, et al. Phase I clinical and pharmacokinetic study of BMS-247550, a novel derivative of epothilone B, in solid tumors. Clin Cancer Res. 2004; 10:1289–1298. [PubMed: 14977827]
16. Hussain M, Tangen CM, Lara PN Jr, et al. Ixabepilone (epothilone B analogue BMS-247550) is active in chemotherapy-naive patients with hormone-refractory prostate cancer: a Southwest Oncology Group trial; S0111. J Clin Oncol. 2005; 23:8724–8729. [PubMed: 16314632]
17. Rosenberg JE, Weinberg VK, Kelly WK, et al. Activity of second-line chemotherapy in docetaxel-refractory hormone-refractory prostate cancer patients: randomized phase 2 study of ixabepilone or mitoxantrone and prednisone. Cancer. 2007; 110:556–563. [PubMed: 17577218]
18. Smaletz O, Galsky M, Scher HI, et al. Pilot study of epothilone B analog (BMS- 247550) and estramustine phosphate in patients with progressive metastatic prostate cancer following castration. Ann Oncol. 2003; 14:1518–1524. [PubMed: 14504052]
19. 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. 2005; 23:1439–1446. [PubMed: 15735119]
20. 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. 2000; 89:431–436. [PubMed: 10918176]
21. Berry W, Dakhil S, Gregurich MA, et al. Phase II trial of single-agent weekly docetaxel in hormone-refractory, symptomatic, metastatic carcinoma of the prostate. Semin Oncol. 2001; 28(suppl 15):8–15. [PubMed: 11685723]
22. Awada A, Piccart MJ, Jones SF, et al. Phase I dose escalation study of weekly ixabepilone, an epothilone analog, in patients with advanced solid tumors who have failed standard therapy. Cancer Chemother Pharmacol. 2009; 63:417–425. [PubMed: 18446338]
23. 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. 1999; 17:3461–3467. [PubMed: 10550143]

24. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92:205–216. [PubMed: 10655437]

25. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008; 26:1148–1159. [PubMed: 18309951]

26. Syed SK, Beeram M, Takimoto CH, et al. Phase I and pharmacokinetics (PK) of DJ-927, an oral taxane, in patients (Pts) with advanced cancers. J Clin Oncol. 2004; 22:2028.

Clinical Practice Points

- Microtubule inhibitors have proven clinical activity in prostate cancer, both in the front-line setting and in patients who were refractory to docetaxel.
- The challenge in these older men with marrow compromise from skeletal metastases and prior chemotherapy is to identify additional agents in which one can achieve clinical benefit with reasonable toxicity.
- Here we assess the activity of ixabepilone in men with metastatic CRPC, administered in a weekly schedule to minimize hematologic toxicity.

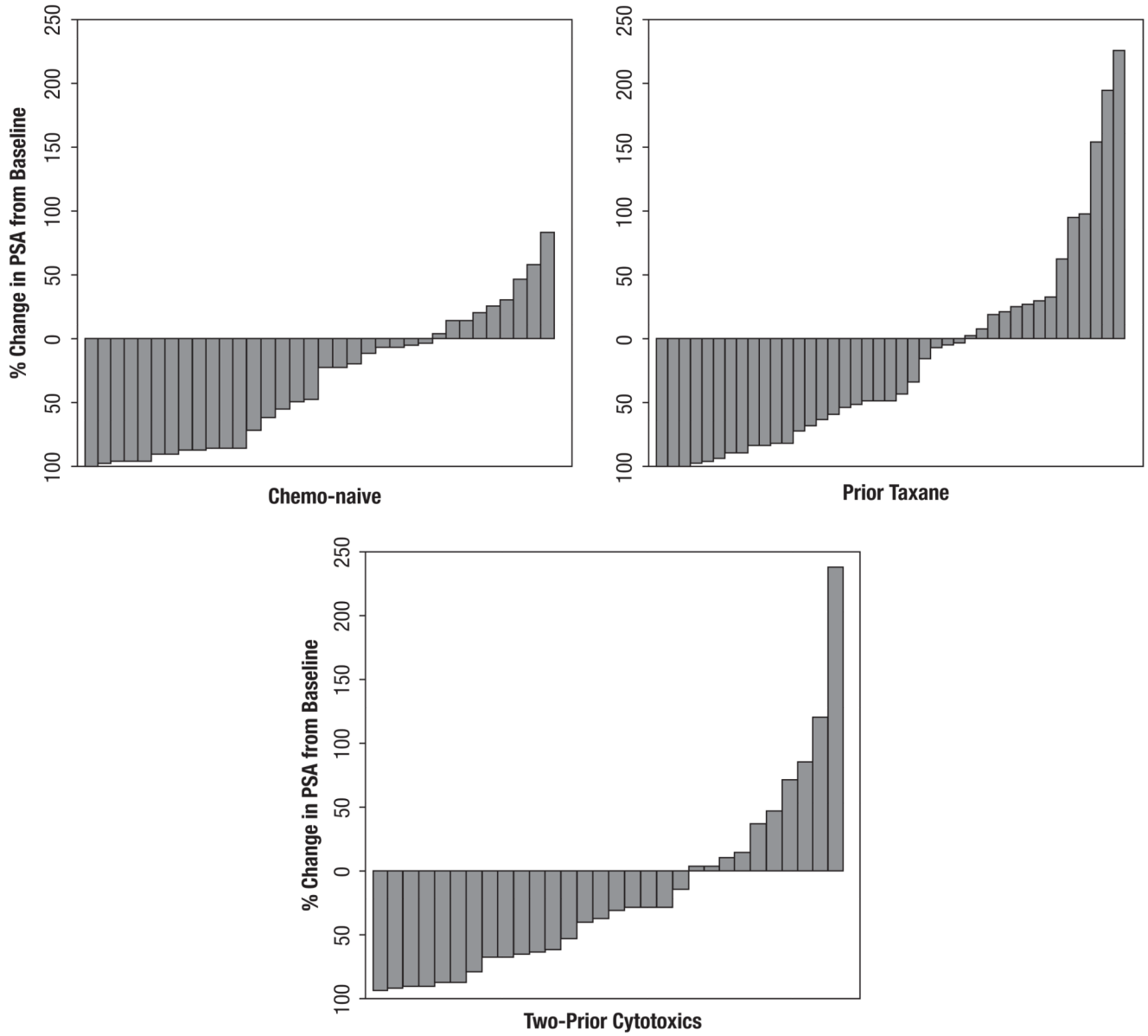

Figure 1.
Maximal Change in Prostate-Specific Antigen Levels From Baseline in Patients Per Strata (Chemotherapy Naive, Prior Taxane, or 2 Prior Cytotoxic Chemotherapy) Treated With Weekly Ixabepilone

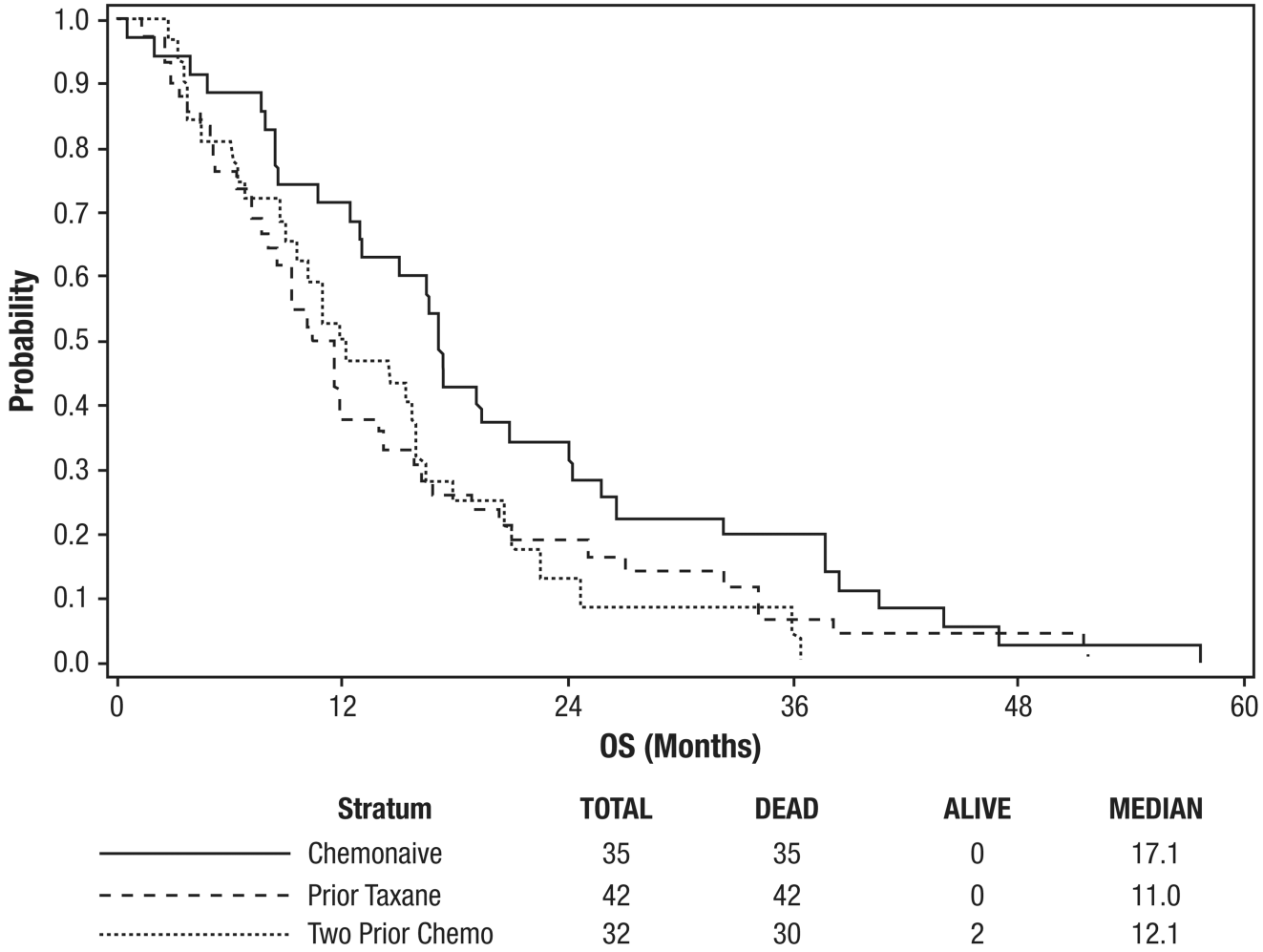

Figure 2.
Median Overall Survival in Each Strata (Chemotherapy Naive, Prior Taxane, or 2 Prior Cytotoxic Chemotherapy) Treated With Weekly Ixabepilone

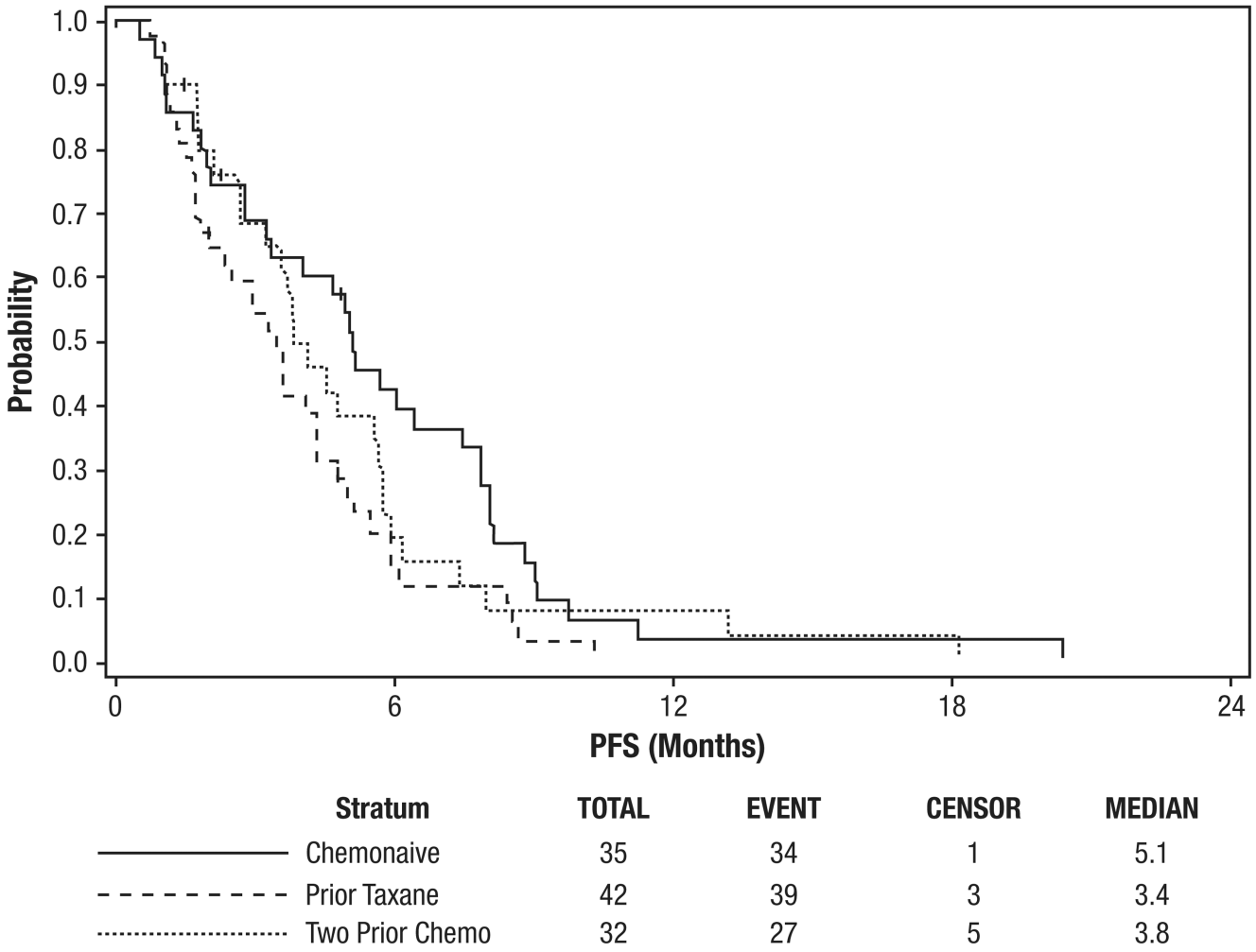

Figure 3.
Progression-Free Survival in Each Strata (Chemotherapy Naive, Prior Taxane, or 2 Prior Cytotoxic Chemotherapy) Treated With Weekly Ixabepilone

Table 1

Patient Demographics and Characteristics

Stratum (No. Eligible Patients)	No Prior Chemotherapy (n = 35)	Prior Taxane (n = 42)	Two Prior Cytotoxic (n = 32)
Median (Range) Age, y	72 (45–82)	69 (50–81)	67.5 (49–90)
ECOG PS (0,1,2), n°, n,[1] n[2]	20,14,1	19,17,6	9,19,4
Gleason Score, <7, 7, >7, Unknown	6,10,17,2	5,16,19,2	4,8,17,3
Baseline PSA (ng/mL), Median (Range)	91 (0.2–8923)	113 (9.3–6252)	168 (0.3–3967)
Sites of Metastasis n (%)			
Bone	31 (89)	40 (95)	29 (91)
Lymph nodes	16 (46)	14 (33)	17 (53)
Liver	3 (9)	8 (19)	4 (13)
Lungs	3 (9)	9 (21)	6 (19)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; n° = number of patients with 0 prior treatment; n^1 = number of patients with 1 prior cytotoxic; n^2 = number with 2 prior cytotoxic; PSA = prostate-specific antigen.

Table 2

Treatment-Related Toxicities

Stratum (No. Treated Patients)	No Prior Chemotherapy, n (%) (n=39)		Prior Taxane, n (%) n = 48)		Two Prior Chemotherapy, n % (n = 36)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Anemia			1 (2.1)	1 (2.1)	5 (13.9)	1 (2.8)
Neutropenia	3 (7.7)	3 (7.7)	5 (10.4)	2 (4.2)	7 (19.4)	2 (5.6)
Thrombocytopenia		1 (2.6)				1 (2.8)
Fatigue	9 (23.1)		10 (20.8)		9 (25.0)	
Diarrhea	6 (15.4)		1 (2.1)			
Dehydration	3 (7.7)		2 (4.2)		1 (2.8)	
Sensory Neuropathy	7 (17.9)	1 (2.6)	11 (22.9)	1 (2.1)	10 (27.8)	2 (5.6)
Motor Neuropathy	4 (10.3)		4 (8.3)	1 (2.1)	4 (11.1)	
Nausea	4 (10.3)		2 (4.2)		1 (2.8)	
Vomiting	1 (2.6)		2 (4.2)			
Ileus	1 (2.6)		1 (2.1)			
Syncope	1 (2.6)		2 (4.2)		1 (2.8)	
Pleural Effusion			2 (4.2)			
Ataxia			2 (4.2)		2 (5.6)	
Anorexia	5 (12.8)		3 (6.3)		4 (11.1)	