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Phase II Trial of Eribulin in Patients With Metastatic Hormone Refractory Prostate Cancer

A Trial of the ECOG-ACRIN Cancer Research Group (E5805)

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Background: Eribulin mesylate, a synthetic analog of halichondrin B, is a novel tubulin-binding agent that inhibits cancer cell proliferation at low-nanomolar levels.

Methods: In a multicenter ECOG trial, patients with progressive metastatic CRPC, ECOG 0-2 were treated with eribulin 1.4 mg/m^2 as an IV bolus over 5 minutes on days 1 and 8 of a 21-day cycle. This noncomparative study stratified points to either a chemonaive (CN), prior-taxane (Tax) only, or 2 prior cytotoxic (TCx) chemotherapy arm. The trial was powered to detect a 50% PSA reduction using Consensus Criteria in at least 40% versus 20% (90% power, one-sided $\alpha = 0.10$) for the CN stratum and 25% versus. 10% (power 87%, one-sided $\alpha = 0.10$) for the Tax and TCx strata.

Results: In total, 119 pts received treatment of which 116 were eligible for the primary response determination in this study. Median age 70 years (range, 45 to 88); median number of treatment cycles 4 (range, 1 to 20+); ECOG 0-1 90%. Confirmed PSA response rates (50% decline from baseline) were 29% (90% [18.2%, 41.2%]; $P = 0.20$), 10% (90% [5.2%, 27.1%]; $P = 1.00$), and 4% ([0.2%, 18.3%]; $P = 0.59$) in the chemonaive stratum, the prior-taxane stratum, and the 2-prior-chemotherapy stratum, respectively. Median progression-free survival was 3.5 months (95% CI, 2.0, 5.9), 2.3 months (95% CI, 2.0, 2.9) and 3.7 months (95% CI, 2.1, 4.2) for the chemonaive stratum, the prior-taxane stratum and the 2-prior-chemotherapy stratum, respectively. Nonhematological toxicities of any grade (mainly grade 1 and 2) were fatigue (74%), neuropathy (40%), alopecia (39%), nausea (35%), and anorexia (34%). Common hematological toxicities were decreased leukocytes (75%), decreased neutrophils (72%), and decreased hemoglobin (66%). The most common grade $\geq$ 3 toxicities were decreased neutrophils (55%), decreased leukocytes (42%), sensory neuropathy (13%), and fatigue (11%). Overall, there was a 4% rate of febrile neutropenia.

Conclusions: In summary, per the prespecified study endpoints, eribulin did not have adequate activity in chemotherapy naïve or chemotherapy pretreated patients with metastatic CRPC to support further study in this setting.

Key Words: eribulin, castrate resistant prostate cancer, microtubule inhibitor

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Metastatic castrate resistant prostate cancer (mCRPC) continues to be a significant source of morbidity and mortality with 29,430 prostate cancer related deaths expected to occur in 2018.[1] Androgen deprivation therapy (ADT) to suppress gonadal synthesis of testosterone represents standard first-line therapy for patients with metastatic hormone sensitive prostate cancer. In recent years, the addition of novel androgen signaling inhibitors has improved overall survival in both hormone-sensitive and castration resistant advanced prostate cancer.[2–5] Nevertheless, chemotherapy remains an important part of the palliative treatment of patients with advanced metastatic prostate cancer. The microtubule inhibitors docetaxel and cabazitaxel have both been demonstrated to improve overall survival in patients with advanced prostate cancer.[6,7] Furthermore, in men with hormone sensitive metastatic prostate cancer, a substantial survival benefit has been seen when docetaxel is given with initiation of ADT rather than once resistance to castration has developed.[8,9] With earlier use of docetaxel in this patient population there is a need for additional chemotherapy agents in patients with castrate resistant prostate cancer that is docetaxel resistant.

Eribulin mesylate (eribulin) is a structurally simplified synthetic analog of halichondrin B, a nontaxane inhibitor of microtubule dynamics with high affinity for the growing plus end of the microtubule.[10,11] Preclinically eribulin has activity against a wide variety of tumors including LNCaP human prostate cancer cells and has effects on angiogenesis, vascular remodeling and epithelial mesenchymal transformation that make it distinct from other microtubule inhibitors.[12,13] A phase III trial of eribulin versus treatment of physician's choice in previously treated patients with metastatic breast cancer demonstrated an overall survival benefit with eribulin treatment leading to regulatory approval for eribulin in the United States in 2010.[14] Eribulin is also approved for treatment of metastatic

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liposarcoma, resulting from an improvement in overall survival compared with dacarbazine.[15] On the basis of the unique efficacy profile of eribulin, preclinical activity in prostate cancer, and clinical efficacy of other microtubule inhibitors in prostate cancer, we conducted a phase II trial of eribulin in men with CRPC. In order to assess drug activity in relevant clinical settings, subjects were assigned to one of three strata based having no prior chemotherapy treatment, prior docetaxel or 2 prior chemotherapies for metastatic CRPC.

METHODS

Study Design

This open label, multisite, single arm, phase II trial evaluated eribulin in men with metastatic CRPC. Subjects were enrolled into one of 3 strata based on prior therapy: chemotherapy naïve, prior taxane therapy or ≥ 2 prior chemotherapies. The trial was conducted in member institutions of the Easton Cooperative Oncology Group (ECOG, now part of ECOG-ACRIN). The study was approved by the institutional review board of each participating institution. Patients provided written informed consent before study participation. The primary objective of the study was to determine the proportion of patients with a ≥ 50% decrease in the PSA of at least 4 weeks duration in patients with metastatic castrate resistant prostate cancer in each of the treatment strata. Secondary objectives were to estimate the measurable disease response in patients with measurable disease, to determine the duration of PSA response (or decline) and measurable disease response and to characterize the safety and tolerability of eribulin.

Patients

All patients in this study had histologically proven adenocarcinoma the prostate and were receiving treatment with androgen deprivation therapy in the form of bilateral orchiectomy or treatment with an LHRH agonist or antagonist. All patients had a ECOG performance status of 0, 1, and 2. All patients had testosterone level <50 at the time of enrollment. Patients were required to have evidence of progressive metastatic prostate cancer defined by new lesions on bone scan or new/enlarging lesions on CT scan, or have a rising PSA within 4 weeks before registration. In addition, patients with bone metastases only were required to have a PSA level ≥ 5 ng/mL within 1 week before registration. Patients with stable metastatic disease and rising PSA were required to have 2 consecutive rises in PSA measurement at least one week apart with the most recent PSA within 4 weeks of study registration. Discontinuation of flutamide was required ≥ 4 weeks before registration and discontinuation of bicalutamide or nilutamide were required ≥ 6 weeks before registration with confirmation of rising PSA obtained after the washout period.

Depending on the stratum patients could be either chemotherapy naïve, have been treated with one prior taxane regimen, or be treated with up to 2 prior cytotoxic chemotherapeutic regimens as long as the last chemotherapy was given > 4 weeks before registration and evidence of disease progression was met. The use of bisphosphonates was allowed as long they had been given > 4 weeks before registration. No radiation was allowed within 4 weeks before registration. Prior treatment with strontium 89, samarium 153, or other radioisotopes was prohibited. Patients receiving eribulin in the first line setting were required to discontinue steroids before enrollment so as not to confound assessment of eribulin as a single agent, patients receiving eribulin after 1 or 2 prior chemotherapies and who had disease progression while receiving a stable dose of prednisone of ≥ 10 mg were allowed to continue prednisone.

Within 7 days of registration all patients were required to have adequate bone marrow function as defined by granulocytes > 1500/μL and platelet count ≥ 100,000/μL in addition to bilirubin ≤ 1.5 mg/dL, AST and ALT ≤ 2.5 times the upper limit of normal, creatinine ≤ 2.0 mg/dL or calculated creatinine clearance ≥ 40 mL/min.

Patients with active angina, medically significant heart disease, ventricular dysrhythmias, or myocardial infarction within 6 months before registration were excluded. Patients could not be treated with therapeutic anticoagulation using warfarin because of potential inhibition of warfarin metabolism by eribulin. Unfractionated heparin or low molecular weight heparins were allowed. Patient was carcinomatous meningitis, brain metastasis, grade 3 or 4 peripheral neuropathy, prior malignancy within the last 5 years (excluding nonmelanomatous skin cancers treated with curative intent), active infections, prior treatment with eribulin or who require treatment with drugs that were strong inhibitors or inducers of CYP3A4 were excluded.

Treatment

Eribulin was administered as an IV bolus at 1.4 mg/m^2 over 5 minutes on days 1 and 8 of each 21 day cycle. Dose was calculated based on actual body surface area before each cycle. Missed doses on day 8 were not made up. Patients requiring dose reduction as noted below were treated at 1.1 mg/m^2 and then 0.7 mg/m^2 if a second dose reduction was required. Patients who met criteria for a third dose reduction were removed from study. Patients who experienced toxicity requiring dose reduction had treatment delayed (if day 1 of a cycle) until toxicity resolved to ≤ grade 1, or skipped (if day 8) only to resume the next planned dose after recovery to grade ≤ grade 1.

Patients experiencing grade 3/4 nonhematological toxicity felt at least possibly related to the study medication (excluding alopecia and nausea/vomiting unless uncontrolled by antiemetics) required dose reduction. Patients who failed to recover to ≤ grade 1 within 2 weeks required discontinuation of protocol treatment. For hematologic toxicity treatment was required to be held for ANC < 1,000/μL and/or platelets <75,000/μL. If counts recovered within 2 weeks, treatment was resumed at the next lower dose level. Failure to recover counts within 14 days required discontinuation of protocol therapy. Any episode of febrile neutropenia (temperature greater than 38.5°C with an ANC < 1000/μL) required a dose reduction for all subsequent doses. Neutropenia on nontreatment days did not require a dose reduction.

Patients continued on treatment with eribulin until they experienced radiographic disease progression, unacceptable toxicity, voluntarily withdrew from the study, or at the decision of the investigator.

Supportive care with antiemetics, antidiarrheal therapy, and erythropoietin were allowed. Patients are required to come off study if radiotherapy for pain control was required during treatment. Prophylactic use of G-CSF was not allowed. Anticoagulation therapy with warfarin or strong CYP3A4 inducers or inhibitors was prohibited during the study.

Evaluation of Toxicity and Efficacy

PSA levels were measured at baseline and before each cycle. Radiographic assessments of the tumor with CT scan of the abdomen and pelvis, chest x-ray (or CT scan of the chest if metastatic disease is present in the chest or the chest x-rays is abnormal), and bone scan were performed within 4 weeks

before registration and were repeated during the last week of every third cycle until disease progression. CBC with differential was performed within one week of registration and then weekly during treatment. A complete metabolic panel was performed at baseline and on day one of all subsequent cycles.

PSA was evaluated according to the 1999 PSA working group criteria.[16] PSA response was defined as a decline from baseline value by $\geq 50\%$ confirmed by a second measurement ≥ 4 weeks later without evidence of clinical or radiographic progression during this time. The date of response was defined as the first date which PSA decline from baseline by $\geq 50\%$. PSA progression in patients who had no PSA decrease was defined as an increase of serum PSA above the baseline value by $\geq 25\%$ and an increase in the absolute value PSA level by at least 5 ng/mL, and confirmed by a second measurement ≥ 4 weeks later. The date of progression was defined as the first date PSA rose by 25% above baseline and increased by 5 ng/mL. In patients whose PSA decreased from baseline, PSA progression was defined by an increase of serum PSA above the nadir by $\geq 50\%$ with an increase by at least 5 ng/mL confirmed by a second measurement ≥ 4 weeks later. The date of progression was defined as the first date PSA rose by 50% above nadir and increased by 5 ng/mL. Patients who discontinue treatment with clinically stable disease, but with a single, unconfirmed PSA measurement that represents progression as defined above will be considered to have PSA progression.

Evaluation of response in measurable disease in the soft tissue or visceral was defined by RECIST 1.0 criteria.[17] Progression on bone scan was designated as the presence of any new lesions appearing after the first restaging bone scan. New, nonsymptomatic lesions seen on the first scheduled disease assessment were not considered progressive disease to exclude a flare response. Any new symptomatic lesion seen on bone scan was considered progressive disease at all times.

Statistical Analysis

The primary endpoint was PSA response defined as 50% PSA decline or PSA normalization, confirmed by a second measurement ≥ 4 weeks later. This study has separate accrual goals for 3 strata (chemonaive, one prior taxane regimen, or up to 2 prior chemotherapeutic regimens) and a 2-stage design was used in this study.

For patients without prior chemotherapy, we considered eribulin promising if a true response rate of $\geq 40\%$ was observed, and would not be of further interest if the true response rate was $\leq 20\%$. With a 2-stage design, the first stage would accrue 19 patients (17 eligible). If at least 4 responses were observed among the 17 eligible patients, an additional 22 patients (20 eligible) would be entered. If ≥ 11 responses were observed among the 37 eligible patients, the treatment would be considered worthy of further study for this group of patients. With this design, we had 90% power to test the response rate of 40% versus; 20% based on a 0.10 level 1-sided 1-sample binomial test. The probability of stopping early was 0.55 if the true response rate was 20%; whereas, if the true response rate was 40%, this probability was 0.05.

We considered eribulin to be a promising regimen if a true response rate of 25% was observed for patients previously treated with one prior taxane regimen or up to 2 prior chemotherapeutic regimens. In contrast, if the true response rate was $\leq 10\%$, the regimen would not be of further interest in this population. With a 2-stage design, the first stage would accrue 23 patients (21 eligible). If at least 3 responses were observed among the 21 eligible patients, an additional 21 patients (19 eligible) would be entered. If ≥ 7 responses were observed among 40 eligible patients, the treatment would be considered worthy of further study for this group of patients. With this design, we had 87% power to test the PSA response rate of 25% versus; 10% based on a 0.09 level 1-sided 1-sample binomial test for each of these 2 strata. The probability of stopping early was 0.65 if the true response rate was 10%; whereas if the true response rate was 25%, this probability was 0.07.

If the regimen demonstrated a PSA response rate of at least 25% for patients with prior taxane or 2 prior chemotherapy regimens, or at least 40% for patients without prior chemotherapy and if the number of patients with measurable disease entered to either stratum was <25, additional patients with measurable disease would be accrued such that the total number of eligible patients with measurable disease in each stratum was 25. However, the PSA response rate would only be calculated among the first cohort of patients, not including the additional patients with measurable disease.

Secondary endpoints included measurable disease response, duration of PSA response, duration of measurable disease response, progression-free survival, and overall survival. Measurable disease response was evaluated using Solid Tumor Response Criteria (RECIST) among patients with measurable disease at study entry.[17] Duration of measurable disease response was defined as the time from onset of complete response or partial response (whichever status was recorded first) until the first date that recurrent or progressive disease was objectively documented. Duration of PSA response was defined as the time from onset of PSA response to PSA progression. Progression-free survival was defined as the time from registration to PSA progression, radiographic progression or death, whichever occurred first. Overall survival was defined as the time from registration to death from any cause.

Descriptive statistics were used to characterize patients at study entry. The method of Atkinson and Brown was used to compute the confidence intervals of PSA response rates for the strata that had two stages of accrual.[18] Exact binomial confidence intervals were used to describe measurable disease response rates. To examine differences in the distribution of worst degree toxicities, Mehta's exact test for ordered categorical data was used.[19] The method of Kaplan and Meier was used to characterize duration of PSA response, duration of measurable disease progression, progression free survival, and overall survival.[20] Toxicities, evaluated using CTCAE version 3.0, were tabulated in each stratum. All *P*-values are 2-sided. A level of 5% was considered statistically significant. The efficacy analysis includes the eligible patients who started treatment (N = 116), whereas the analysis for toxicities includes all treated patients (N = 119).

RESULTS

Patients

The study was open to accrual from November 2006 to August 2009. Accrual occurred in 26 ECOG centers in the United States. Final accrual to this study was 121 patients. The efficacy analysis included all eligible patients who started treatment (N = 116), whereas the analysis for toxicities included all treated patients (N = 119). Four patients were deemed ineligible (of which 3 patients were treated and 1 did not start therapy) and 1 eligible patient did not start therapy. The efficacy analysis was comprised of 41 chemotherapy naive, 51 prior taxane treated, and 24 two prior chemotherapy-treated patients. The 2 prior chemotherapy stratum did not continue to stage II accrual as it did not meet the prespecified level of activity in stage I.

TABLE 1. PSA Response

Best PSA Response	n (%) Chemonaive	Prior Taxane	Two Prior Chemo
Response	12 (29)	5 (10)	1 (4)
Stable disease	4 (10)	10 (20)	8 (33)
Progression	15 (37)	15 (29)	9 (38)
Unevaluable	10 (24)	21 (41)	6 (25)
Total	41	51	24

Demographics and baseline characteristics of patients enrolled on study are summarized in Supplemental Data Table 1 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A246). The median patient age was 70 years with a range of 45 to 88 years; 91% had ECOG PS of 0 or 1; 81% of patients had progressive metastatic disease at enrollment, whereas 19% had stable metastatic disease and rising PSA. Common sites of metastases were bone (82%), lymph nodes (39%), lung (19%), and liver (14%). The median baseline PSA increased based on disease strata-chemotherapy naïve 35.6 ng/mL (2.2 to 769); prior taxane 78.9 ng/mL (1.2 to 4836); 2 prior chemotherapies 169 ng/mL (15.9 to 4104).

Treatment Delivery

Median duration of treatment by treatment strata is described in Supplemental Data Table 2 (Supplemental Digital Content 2, http://links.lww.com/AJCO/A247). Across all strata median duration of treatment was 2.4 months (range, 0.1 to 20.7). 70% of patients came off treatment due to disease progression; 13% came off treatment because of adverse events, 9% for withdrawal of consent and 6% for symptomatic worsening. There was one death on study during cycle 1. Eleven percent of patients across all cohorts underwent a dose reduction in cycle 1 and 29% of patients underwent at least one dose reduction by cycle 3.

PSA Response

Confirmed PSA response rates (50% decline from baseline) were 29% (90% 2-stage CI: 18.2%, 41.2%; $P = 0.20$), 10% (90% 2-stage CI: 5.2%, 27.1%; $P = 1.00$), and 4% (90% exact binomial CI: 0.2%, 18.3%; $P = 0.59$) in the chemonaive stratum, the prior-taxane stratum, and the 2-prior-chemotherapy stratum, respectively. Table 1 shows the PSA response rates by stratum. PSA response data for all patients are summarized in Figs. 1A-C. Exploratory analysis evaluating the rate of 30% PSA decline was observed in 46%, 35%, and 21% of patients in the chemonaive stratum, the prior-taxane stratum, and the 2-prior-chemotherapy stratum, respectively. Twenty-five patients were unevaluable for PSA response because they died or experienced radiographic progression before determination of PSA response. Eight patients were unevaluable because of insufficient evaluation or lack of follow-up. Four patients were unevaluable because of nonprotocol therapy including new hormonal therapy (n = 1) and nonprotocol chemotherapy (n = 3).

In those patients experiencing a PSA response, the duration of PSA response was defined as the time from the date of onset of PSA response until the date the criteria were met for PSA progression. Median duration of PSA response was 17.0 months (95% CI: 2.3, 25.6) and 4.4 months (95% CI: 3.2, 5.3) for the chemonaive stratum and the prior-taxane stratum, respectively (Fig. 2). The patient with PSA response in the 2 prior-chemotherapy stratum had response lasting for 5.9 months at the time the data was censored.

Radiographic Response

Two complete responses (CR) (8%) were achieved in chemonaive patients and one CR (8%) was achieved in a patient treated with 2 prior chemotherapies. Two chemonaieve patients (8%) and one patient (3%) treated with 1 prior chemotherapy had a partial response (PR) as indicated in Table 2. Median duration of measurable disease response in the chemonaive stratum was 18.9 months (95% CI: 4.2, NA). The duration of measurable disease response was 2.2 months and 4.8 months for the 2 patients with measurable disease response in the prior taxane stratum and the 2-prior chemotherapy stratum, respectively. Unevaluable patients had insufficient evaluation or no follow-up assessments to determine measurable disease response.

PFS and OS

All patients either died or experienced progression on this study. Seven patients who died were censored at the date of last disease assessment as the deaths occurred greater than 3 months after the date last known progression-free. Median progression-free survival was 3.5 months (95% CI: 2.0, 5.9), 2.3 months (95% CI: 2.0, 2.9), and 3.7 months (95% CI: 2.1, 4.2) for the chemonaive stratum, the prior-taxane stratum and the 2 prior chemotherapy stratum, respectively Fig. 3. At the time of final analysis, 112 of the 116 eligible and treated patients have died and median survival was 14.4 months (95% CI: 11.2, 17.8). Median survival was 23.1 months (95% CI: 14.7, 27.0), 11.2 months (95% CI: 8.3, 14.8), and 13.7 months (95% CI: 8.5, 17.6) for the chemonaive stratum, the prior-taxane stratum,

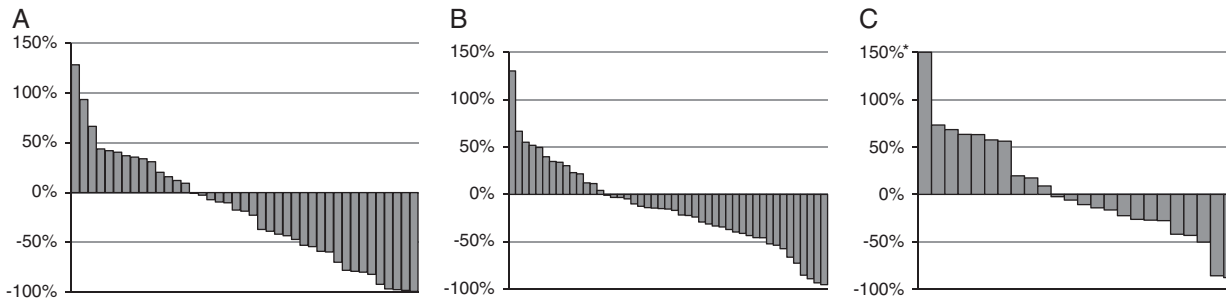

FIGURE 1. Waterfall plot of PSA response by treatment strata. A, Chemonaive cohort 19 patients with at least 30% decrease from baseline 14 patients with at least 50% decrease from baseline. B, Prior Taxane chemotherapy 18 patients with at least 30% decrease from baseline 9 patients with at least 50% decrease from baseline. C, Two prior chemotherapies 5 patients with at least 30% decrease from baseline 3 patients with at least 50% decrease from baseline. "*" indicates 385%.

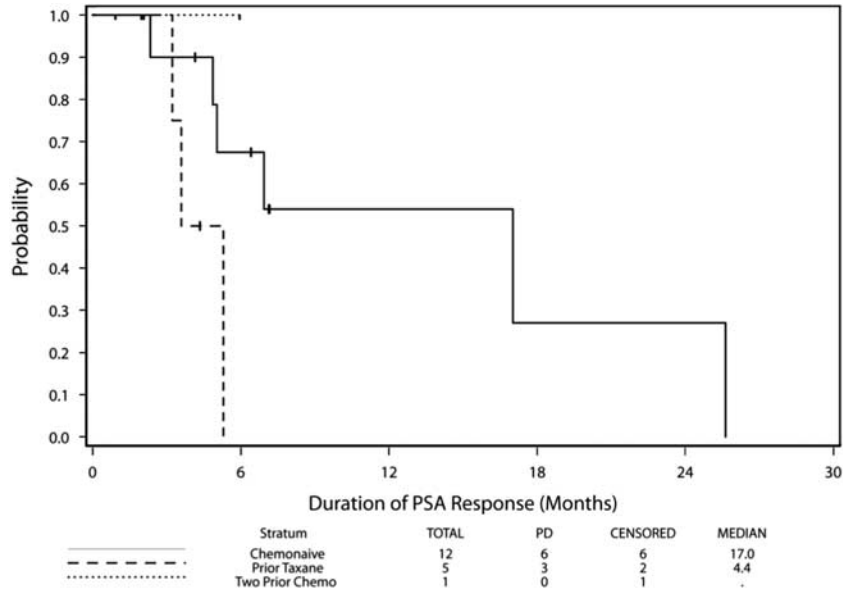

FIGURE 2. PSA response duration.

and the 2-prior-chemotherapy stratum, respectively supplemental data Figure 1 (Supplemental Digital Content 3, http://links.lww.com/AJCO/A248). Fifty percent of patients were removed from study because of PSA progression rather than objective progression on scans (Supplementary data Table 3, Supplemental Digital Content 4, http://links.lww.com/AJCO/A249).

Safety

There were no statistically significant differences in the distribution of worst degree toxicities by stratum ($P = 0.92$). As indicated in Table 3 the most common nonhematological toxicities of any grade (mainly grade 1 and 2) were fatigue (74%), neuropathy (40%), alopecia (39%), nausea (35%), and anorexia (34%). Common hematological toxicities were decreased leukocytes (75%), decreased neutrophils (72%), and decreased hemoglobin (66%). The most common grade ≥ 3 toxicities were decreased neutrophils (55%), decreased leukocytes (42%), sensory neuropathy (13%), and fatigue (11%). Overall, there was a 4% rate of febrile neutropenia.

DISCUSSION

In this phase II study evaluating the activity of eribulin in men with metastatic castrate resistant prostate cancer clinical activity was demonstrated in taxane naïve and previously treated patients. Activity as defined by PSA decline from baseline value by $\geq 50\%$ was observed in 29%, 10% and 4% in the chemonaive stratum, the prior-taxane stratum, and the 2 prior-chemotherapy stratum, respectively. Docetaxel, the current standard of care for chemotherapy naïve patients demonstrated a PSA response rate of 45%.[6] Median progression-free survival was 3.5 months, 2.3 months, and 3.7 months for the chemonaive stratum, the prior-taxane stratum and the 2-prior-chemotherapy stratum, respectively. Despite the evidence of activity in some patients, overall eribulin did not meet a level of activity to justify further evaluation of this agent in an unselected phase II population.

TABLE 2. Measurable Disease Response

Measurable Disease Response	n (%)		
	Chemonaive	Prior Taxane	Two Prior Chemo
Complete response	2 (8)	0 (0)	1 (8)
Partial response	2 (8)	1 (3)	0 (0)
Stable disease	15 (58)	16 (42)	8 (62)
Progression	5 (19)	13 (34)	4 (31)
Unevaluable	2 (8)	8 (21)	0 (0)
Total	26	38	13

The PSA response rate and objective response rate in the current study were commensurate with findings in another study of eribulin in men with metastatic CRPC in which the 50% PSA response rate was 22.4% for taxane naïve patients and 8.5% for taxane pretreated patients.[21] Median duration of PSA response was 17.0 months and 4.4 months for the chemonaive stratum and the prior-taxane stratum, respectively. The long median duration of PSA response in the chemotherapy naïve stratum exceeded the duration of PSA response previously reported with docetaxel (8.2 mo)[6] or eribulin (3.2 mo).[21] This may in part reflect patient selection as patients in the treatment naïve group had lower PSAs at baseline and fewer patients with liver metastasis compared with the patients in the other eribulin prostate study. Alternatively, there may be a select group of patients with exquisite sensitivity to eribulin responsible for this prolonged duration of PSA response.

Presently, multiple agents are approved for use in the treatment of metastatic CRPC. In addition to docetaxel, that was approved at the time this study commenced, the semisynthetic taxane derivative cabazitaxel obtained regulatory approval for the treatment of metastatic castrate resistant prostate cancer after progressing on a docetaxel-containing regimen.[7] In the phase III trial of cabazitaxel versus mitoxantrone in which all subjects were previously treated with docetaxel, cabazitaxel resulted in a notable $\geq 50\%$ PSA decline in 39% of patients, with 14% of patients having an objective tumor response. These results compared favorably to the results seen with eribulin in the current study in which 4 (15%); 1 (2.6%) and 1 (7.7%) subject achieved object response in the

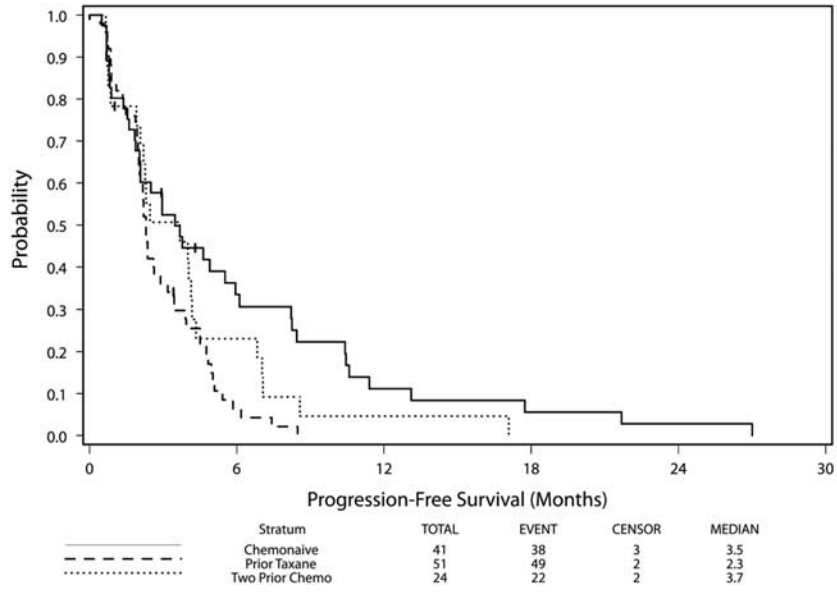

FIGURE 3. Progression free survival.

chemonaive stratum, the prior taxane stratum, and the 2-prior-chemotherapy stratum, respectively. However, median progression-free survival was 2.8 months in the cabazitaxel group and 1.4 months in the mitoxantrone group in this large phase III trial. This PFS was comparable with the PFS seen with eribulin in a comparable disease setting. It is unknown if patients will respond to eribulin after cabazitaxel given these 2 drugs' distinct mechanisms of action with respect to mitotic spindle inhibition.

Additional analysis may also clarify if there is any association between resistance to second generation androgen signaling inhibitors such as enzalutamide and abiraterone and resistance to eribulin. Several groups have described the importance of microtubule mediated AR translocation for AR signaling.[22,23] Although some authors have suggested that resistance to AR inhibitors as a result of cancer cell expression of AR splice variants also confers resistance to taxanes,[24] other authors suggest that taxanes maintain activity even in the presence of AR splice variants, in contrast to AR signaling inhibitors such as enzalutamide.[25] It is not yet known if microtubule inhibitors or stabilizers have differential activity in this clinical setting. Future trials with eribulin in prostate cancer should therefore be designed to account the presence of AR splice variants.

TABLE 3. Toxicity

	Patients [n (%)]	
	All Grades	**Grade ≥3**
Decreased leukocytes	88 (75)	49 (42)
Fatigue	87 (74)	13 (11)
Decreased neutrophils	85 (72)	65 (55)
Decreased hemoglobin	78 (66)	9 (8)
Neuropathy-sensory	47 (40)	15 (13)
Alopecia	46 (39)	0
Nausea	41 (35)	2 (2)
Anorexia	40 (34)	5 (4)
Constipation	33 (28)	0
Hypoalbuminemia	22 (19)	0
Diarrhea	19 (16)	0

Overall treatment with eribulin was associated with manageable toxicity, including in patients with multiple prior treatments. No statistically significant increase in differences in the distribution of worst degree toxicities was seen when evaluated by stratum ($P = 0.92$). Leukocytopenia, fatigue, neutropenia, anemia, and sensory neuropathy were the most common toxicities. Neutropenia was the most common grade ≥3 toxicity with a 4% rate of febrile neutropenia. Unlike docetaxel, eribulin is not given with corticosteroids, which may help to ameliorate some side effects such as anorexia and fatigue which are commonly seen with prostate cancer.

In summary, per the prespecified study endpoints, eribulin did not have adequate activity in chemotherapy naïve or chemotherapy pretreated patients with metastatic CRPC to support further study in this setting. Studies prospectively incorporating relevant biomarkers of resistance such as the presence of AR splice variants that allow us to better understand the characteristics of patients who are exceptional responders to eribulin (as seen in the current study) by incorporating next generation sequencing of tumor biopsies or cell free DNA, may help to establish a role for eribulin or other novel cytotoxic agents in discrete patient populations.

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