

A Phase I-II Study of Docetaxel and Atrasentan in Men with Castration-Resistant Metastatic Prostate Cancer

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Abstract Purpose: The primary aims of this phase I-II study were to determine the maximum tolerated dose, dose-limiting toxicity, pharmacokinetics, and preliminary efficacy of the combination of docetaxel and the endothelin A receptor antagonist atrasentan as first-line treatment for men with metastatic castration-resistant prostate cancer.

Experimental Design: Patients were treated with docetaxel at doses ranging from 60 to 75 mg/m² every 21 days, with daily oral atrasentan 10 mg starting on day 3. Patients were treated until evidence of disease progression or unacceptable toxicity.

Results: Thirty-one patients were enrolled over three docetaxel dose levels (8 at 60 mg/m², 19 at 70 mg/m², and 4 at 75 mg/m²) including dose expansion at 70 mg/m². The maximum tolerated dose of docetaxel was 70 to 75 mg/m². Drug-related grade 3-4 toxicities included neutropenia (50-63%) and febrile neutropenia (16-25%); other grade 1-2 toxicities included fatigue, peripheral edema, diarrhea, headache, rhinitis, anorexia, and nausea. Confirmed prostate-specific antigen (PSA) responses were observed in 23% [95% confidence interval (95% CI), 10-41%]; the rate of >30% declines in PSA was 35% (95% CI, 19-55%). Median overall survival was 17.6 months (95% CI, 13.0-23.2) and median progression-free survival was 4.2 months (95% CI, 2.3-5.8). Significant declines in bone alkaline phosphatase and serum N-telopeptides were observed with therapy.

Conclusions: The maximum tolerated dose of every-3-week docetaxel with 10 mg atrasentan is 70 to 75 mg/m². Overall survival and progression-free survival are comparable to that seen with docetaxel and prednisone, whereas the rates of PSA decline are slightly lower than expected. A phase III study of this combination with prednisone has been initiated and is ongoing.

Despite recent favorable declines in prostate cancer mortality, prostate cancer in 2008 remains a common cause of cancer death worldwide (1). Docetaxel and prednisone was U.S. Food and Drug Administration approved in 2004 for the palliative management of men with castration-resistant metastatic prostate cancer, based on improved survival, pain, and quality-of-life responses and tolerability compared with mitoxantrone and prednisone (2). As a result of this clinical activity in men with metastatic castration-resistant prostate cancer, docetaxel

has become the standard by which experimental therapeutics are being compared against or added to, with the intent of improving on both quantity and quality of life for men with advanced prostate cancer.

Prostate cancer commonly metastasizes to bone, using a number of homing receptors and signaling molecules to interact, adapt to, and grow in this microenvironment (3). One such paracrine and autocrine signaling molecule that plays an important role in metastatic prostate cancer progression is endothelin (4-6). Endothelin-1 levels are increased in advanced prostate cancer and endothelin-1 acts as a mitogen for osteoblasts and prostate cancer cells through its interaction with the endothelin-A receptor (4). In addition to its proangiogenic and vasoconstricting activities important in the maintenance of vasomotor tone, endothelin additionally has a role in the pathophysiology of bone pain (nociception) related to metastatic disease (7, 8). Thus, endothelin-1 and endothelin-A receptor are important in the progression of symptomatic metastatic prostate cancer and likely contribute to the development of osteoblastic bone metastases (5, 9-11).

Atrasentan (Abbott Laboratories) is a highly potent, orally bioavailable selective antagonist of the endothelin-A receptor (4, 11, 12). Recent evidence suggests that endothelin-1 may reduce the rates of apoptosis in prostate cancer cell lines

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Translational Relevance

The bone microenvironment remains a viable target for therapeutic development in advanced prostate cancer, given its role in the promotion of metastatic disease and treatment resistance. Atrasentan is an oral endothelin receptor antagonist that may modify prostate cancer-bone stromal interactions and is under investigation for combination therapy with docetaxel-based chemotherapy for castration-resistant prostate cancer. This phase I/II study provides dose and schedule and safety profile for this combination for further phase III study and suggests a potential independent effect of atrasentan on bone alkaline phosphatase (BAP), a measure of bone turnover. A pharmacokinetic interaction of atrasentan with docetaxel is also suggested based on a higher than expected incidence of neutropenia with or without fever. Further controlled studies are necessary to evaluate the effect of this agent on survival and progression.

exposed to docetaxel, and endothelin-A blockade with atrasentan reduces the rate of tumor growth in preclinical models compared with docetaxel alone (13, 14). Single agent phase III studies have not shown convincing evidence of clinical benefit in castration-resistant prostate cancer; however, given the complexity of the pathogenesis of tumor progression and bone microenvironment interactions, it is likely that combination therapy is needed in this disease (12, 15, 16). Thus, the purpose of this study was to investigate the safety, pharmacokinetics, and preliminary efficacy of combination therapy with docetaxel and atrasentan. Atrasentan 10 mg once daily was chosen as a fixed dose based on single agent studies showing safety and consistent effects on the modulation of bone turnover biomarkers and in reducing rates of metastatic progression (12, 15, 16).

Materials and Methods

Study population. To participate in this study, patients were required to have histologically confirmed metastatic prostate adenocarcinoma with disease progression despite androgen deprivation therapy and a castrate level of testosterone (<50 ng/dL). Progression was defined as radiographic measurable disease progression according to standardized Response Evaluation Criteria in Solid Tumors (RECIST), new bone scan lesions on bone scan, or two consecutive increases in prostate-specific antigen (PSA) levels above the PSA nadir achieved on androgen deprivation therapy, with each PSA measure separated by ≥ 2 wk. Eligible patients were >18 y of age; underwent appropriate antiandrogen withdrawal intervals with continued progression (4 wk for flutamide, 6 wk for bicalutamide or nilutamide); had no other malignancies within 5 y other than nonmelanoma skin cancer; had a Karnofsky performance status >70 ; had a life expectancy >6 mo; had adequate hematologic function (absolute neutrophil count $>1.5 \times 10^9/L$, platelets $>100 \times 10^9/L$, hemoglobin >9.0 g/dL, and no transfusion within 14 d); had adequate liver function (total bilirubin <1.5 times the upper limit of normal, aspartate aminotransferase/alanine aminotransferase <1.5 times the upper limit of normal); and had a baseline calculated creatinine clearance >40 mL/min. All subjects used medically acceptable forms of birth control and provided informed consent. Patients were excluded if they had prior cytotoxic

chemotherapy, radioisotopic therapy, or had received additional hormonally or biologically active therapies other than androgen deprivation therapy within 4 wk. Patients with New York Heart Association Class >2 disability, significant pulmonary comorbidities, HIV positivity, or central nervous system metastases were excluded. This study was approved by the Duke University Institutional Review Board and all subjects signed informed consent documents. All eligible patients who received at least one dose of study medication were included in outcome assessments.

Study design and treatment schedule. This was a phase I/II dose escalation study of docetaxel in combination with oral atrasentan given at a fixed 10 mg daily dose. Docetaxel was administered i.v. over 60 min on day 1 of a 21-d cycle, whereas atrasentan was given by self-administration starting on day 3 of cycle 1. Dexamethasone premedication was given with docetaxel according to standard practice (8 mg twice daily for 3 d starting the day before treatment); prednisone was not given concurrently in this study. Four dose levels were prespecified in the study protocol for every-3-wk docetaxel, with a starting dose level of 60 mg/m². Dose escalation proceeded according to a standard 3 plus 3 design, with escalation to 75 mg/m² (dose level 2) based on the absence of more than one dose-limiting toxicity (DLT) in three to six subjects in this cohort. Cohorts of three were expanded to six if one DLT is experienced in cycle 1. The maximum tolerated dose was defined as the highest dose for which DLT is observed in more than two of three or two of six patients. A third dose level (level 1.5) at 70 mg/m² was opened based on the presence of two or more DLTs at dose level 2. DLT was defined only for the first cycle of treatment as either grade >4 neutropenia or thrombocytopenia lasting ≥ 7 d, nausea, vomiting, or diarrhea grade ≥ 4 lasting >4 d despite adequate supportive measures, other nonhematologic toxicity grade >3 (excluding alopecia), treatment-related hospitalization or death, or toxicity resulting in delay of cycle 2 by >14 d. In this study, a dose expansion cohort of up to 24 additional subjects was permitted to allow greater precision for the estimates of toxicity, pharmacokinetics, and activity of this regimen. Dose modifications to docetaxel were permitted based on grade 3-4 hematologic or nonhematologic toxicity. Atrasentan was held until grade 4 hematologic or grade 3-4 nonhematologic toxicity resolved to grade 1 or 0, with dose reductions permitted for grade 3-4 nonhematologic toxicity such as fluid retention, nausea and vomiting, or cardiovascular events. Pharmacokinetic and pharmacogenomic data are described in a separate article.

Toxicity measures. Descriptive statistics were used to calculate the percentages, medians, ranges, and 95% confidence interval (95% CI)

Table 1. Baseline characteristics of patients in this study

Baseline characteristic, N = 31	Value
Median age (range), y	68 (50-81)
Race	
Caucasian, %	84
African American, %	19
Gleason sum >7 , %	45
Bone metastases (yes), %	81
Measurable metastatic disease	42
Prior secondary hormonal therapies (>2), %	35
Hemoglobin [median (range)], g/dL	12.6 (8.3-14.7)
Alkaline phosphatase [median (range)], IU/L	101 (29-462)
LDH [median (range)], IU/L	546 (409-1332)
PSA [median (range)], ng/mL	80.8 (5.1-403.5)
Baseline pain (any), %	61
Karnofsky performance status (0-1), %	100

Abbreviation: LDH, lactate dehydrogenase.

Table 2. Cumulative toxicity per dose level

	60 mg			75 mg			70 mg		
	Grade 1 and 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 1 and 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 1 and 2 (%)	Grade 3 (%)	Grade 4 (%)
Anemia	100			100			89		
Anorexia	38			100			42		
Back pain	25								
Bone pain	38			50			37	5	
Constipation	38						37		
Diarrhea	50			25			42	5	
Dyspnea	13						26		
Fatigue	88			100			84	11	
Febrile neutropenia						25		5	11
Fever				25			32		
Headache	13			25			32		
Hypotension	25			25			5		
Infection	25			50			11		
Nausea	25			50			42		
Neutropenia	25	50	13		50		16	26	37
Pain	25			25			42	5	
Peripheral Edema	88			50			63	11	
Rash	13						5		
Rhinitis	25			25			32		
UTI				25			16		
Vomiting				25					
Taste changes	38			25			58		
Neuropathy							26		

Abbreviation: UTI, urinary tract infection.

around cycle 1 and cumulative toxicities seen in this study. As DLT was defined for cycle 1 only, this is described separately. Toxicity was scored using the National Cancer Institute Common Toxicity Criteria version 3.0.

Efficacy measures. The greatest degree of PSA decline (percentage decline from baseline) following treatment initiation was described for each patient. A PSA response was defined as a decline in PSA >50% from the baseline pretreatment value and confirmed by a second PSA value 4 wk later. The proportion of men with a ≥30% PSA decline within 3 mo of starting treatment was also described, but without requirements for confirmation. Radiographic response was quantified by an independent radiologist for patients with soft tissue or visceral measurable target lesions (n = 13) using RECIST criteria, not including bone scan lesions (17). Radiologic imaging with computed tomography and bone scan was done at baseline and at the end of every third cycle. PSA was measured at baseline and day 1 of each cycle. Physical examinations and safety assessments were done at baseline and day 1 of each cycle. The time to PSA progression was defined as the time from randomization to a ≥50% increase in the serum PSA from baseline or the average of the two lowest nadir PSA values. The overall progression-free survival was defined as the time from randomization to death or the earliest date of either PSA or radiographic progression using Kaplan-Meier methods. Overall survival was estimated using Kaplan-Meier methods.

Statistical analysis. The sample size for the dose expansion cohort was based on an 86% power to detect an improvement in the PSA response rate from 40% to 65% at a one-sided type I error rate of 0.05. This null hypothesis was conceived before the publication of TAX327, which showed a baseline PSA response rate for every-3-wk docetaxel with prednisone of 45%. Kaplan-Meier estimates were used to calculate progression-free survival and overall survival estimates as well as time-to-progression. Descriptive statistics were used to quantify changes in PSA and bone and total alkaline phosphatase over time. Paired t tests (McNemar's tests) were done for differences in the

mean values over time for bone alkaline phosphatase (BAP) and N-telopeptide levels.

Results

Thirty-two patients were enrolled on this study. However, one patient developed a pulmonary embolism after registration but before study drug administration and was not continued on the study; thus, 31 patients were evaluable based on receipt of at least one dose of study medication. Baseline characteristics are described in Table 1. Patients were predominantly Caucasian (83%) with a median age of 68 years. All patients had metastatic disease, with 81% having bone metastatic

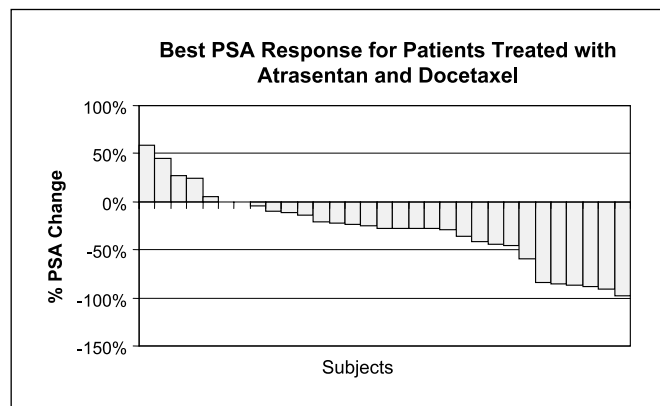


Fig. 1. Waterfall plot of PSA declines per subject in this study, with each bar representing one patient's lowest percent decline following treatment initiation (n = 31).

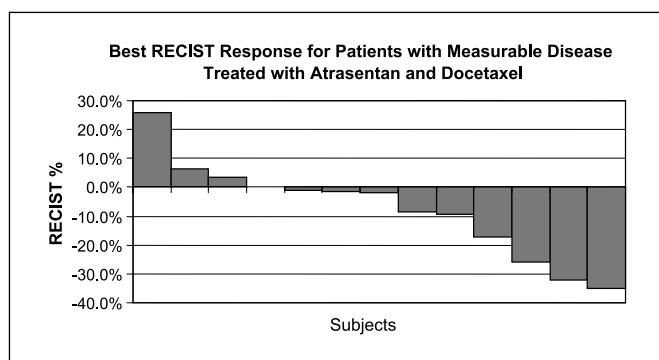


Fig. 2. Waterfall plot of RECIST-defined best radiographic response, among those patients with measurable disease at baseline ($n = 13$). (Data may be published as supplementary online).

disease and 42% having measurable soft tissue metastatic disease. Baseline pain, measured using a patient-determined linear score (0-10) or use of narcotic analgesia, was present in 61% of subjects. The median baseline PSA was 81 ng/mL (range, 5-404). Pretreatment PSA doubling time was not prospectively captured in this study. Twenty-four subjects received zoledronic acid during this study, whereas seven did not.

The median number of cycles completed in this study was 5, and 13% (4 of 31) of patients were able to complete 10 cycles of therapy. The combination of docetaxel and atrasentan in general was well tolerated. At the starting dose level of 60 mg/m², toxicities were predominantly grade 1-2, with a cumulative risk of grade 3 and 4 neutropenia being 50% and 12.5%, respectively, without any dose-limiting toxicities in cycle 1 other than grade 3 neutropenia. The protocol was amended following this cohort to restrict the definition of hematologic DLT to grade ≥ 4 neutropenia or thrombocytopenia lasting ≥ 7 days. Following this amendment, the dose was escalated to 75 mg/m². At this dose level, there was a 25% incidence of cycle 1 hematologic DLT (neutropenic fever) with 2 of 4 (50%) subjects experiencing grade 3 neutropenia. Based on this degree of hematologic toxicity, a third dose level was developed at 70 mg/m². At this dose level, only 1 of 6 (16.7%) experienced a cycle 1 DLT (febrile neutropenia), and this cohort was chosen for dose expansion. The overall incidence of cycle 1 DLT in this dose cohort was 11% (2 of 19), whereas 4 of 19 (21%) of patients had grade 3-4 neutropenia with fever at any time on treatment. The overall incidence of grade 3-4 neutropenia in this cohort was 12 of 19 (63%; 95% CI 38-83%) across all cycles. Other common grade 3 or 4 toxicities at this dose level included fatigue (11%), diarrhea (5%), and peripheral edema (11%). Common grade 1-2 toxicities at this dose level included anemia, taste changes, peripheral edema, fatigue, diarrhea, nausea, bone pain, rhinitis, constipation, fever, and neuropathy. There were no cases of grade 3-4 neuropathy, and the median number of cycles to the development of neuropathy was 4. Hypotension occurred in 5% of subjects at this dose level. There were no documented cases of symptomatic or asymptomatic congestive heart failure. Details of cumulative toxicities seen in this study can be found in Table 2.

The overall proportion of men with a PSA response was 22.5% (95% CI, 9.5-41%), whereas the proportion of men with

a $\geq 30\%$ PSA decline from baseline within 3 months of treatment initiation was 35.4% (95% CI, 19.2-54.6%). PSA declines are graphically displayed in the waterfall chart in Fig. 1. The median time to PSA progression was 168 days, with 13 events.

Using RECIST criteria, 13 subjects had measurable disease at baseline, with the best responses observed being 2 (15%) partial responses, 10 (77%) patients with unconfirmed stable disease, and 1 (8%) patient with progressive disease. The degree of unconfirmed RECIST-defined responses ranged from an increase of 26% to a decrease of 35% in target lesion longest diameter sums and is graphically displayed in the waterfall plot in Fig. 2.

Follow-up in this study is ongoing but extends to 807 days among survivors (median, 776 days) as of an administrative cutoff date of January 8, 2008. The median progression-free survival, including radiologic and PSA progression or death as events, was 125 days (4.2 months; 95% CI, 2.3-5.8 months), including 23 progressive events. Patients were censored at the time of removal from the study due to adverse events but were followed up until death. The Kaplan-Meier estimate for progression-free survival is displayed in Fig. 3. Median overall survival in the entire cohort of treated patients ($N = 31$) was 528 days (17.6 months; 95% CI, 13.0-23.2 months) with 27 mortality events to date. The Kaplan-Meier estimate for overall survival is shown in Fig. 4.

Bone turnover biomarkers were collected on this study at baseline, day 1 of each cycle, and at progression, and included bone alkaline phosphatase (BAP) and serum N-telopeptides (NTx). BAP is an osteoblast-derived measure of bone turnover mediated by osteoclasts or metastatic tumor that may be altered by atrasentan (18). NTx are derived from the NH₂-terminal of cross-linked type I collagen found in bone and is also a measure of neoplastic and physiologic bone turnover mediated by osteoclasts (18). In this study, the median BAP value at baseline was 18 $\mu\text{g/L}$ (mean, 29.9; SD, 26.4; range, 7.6-109; $n = 31$ samples) with the male reference range being $<20 \mu\text{g/L}$. The nadir (typically at the time of best clinical response, around 2-3 months postrandomization) median BAP level was 12.2 $\mu\text{g/L}$, with a mean value of 19.9 $\mu\text{g/L}$ (SD, 19; $P = 0.0003$ using paired t test compared with baseline). At the time of progression, the median BAP increased to 15.1 $\mu\text{g/L}$ (mean,

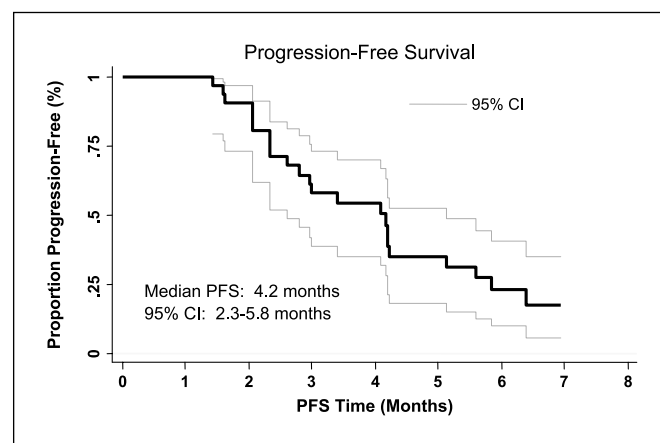


Fig. 3. Kaplan-Meier estimates for progression-free survival (PFS) in this study, with progression defined as the earliest occurrence of death, RECIST-defined progression, new bone scan lesions, or PSA progression.

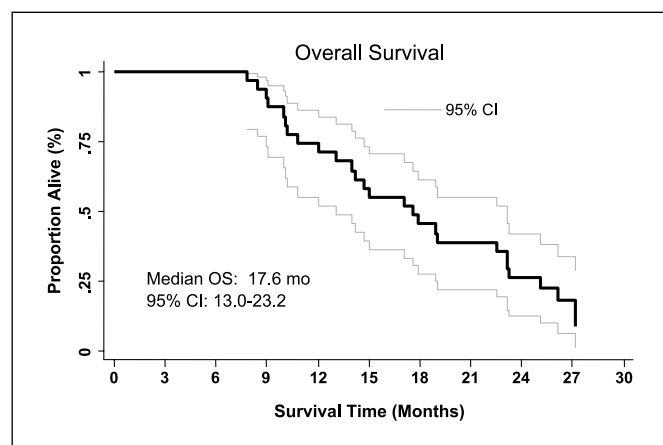


Fig. 4. Kaplan-Meier estimates for overall survival in this study, with follow-up among survivors extending to 807 d (2.21 y).

23.4 $\mu\text{g/L}$; SD, 4.51; $P = 0.009$ versus nadir value). These pharmacodynamic changes are graphically displayed in Fig. 5A. In the six patients who did not receive zoledronic acid on study and had paired bone markers for analysis, BAP was also found to significantly decline with therapy (baseline mean, 16.3 $\mu\text{g/L}$; nadir mean, 12.3 $\mu\text{g/L}$; $P = 0.02$) and increase at the time of progression (mean, 14.4 $\mu\text{g/L}$; $P = 0.02$).

Baseline median NTx levels were 12.8 nmol/L bone collagen equivalent (BCE) with a reference range of 5.4 to 24.2 nmol/L BCE. The mean NTx level at baseline was 16.3 nmol/L BCE (range, 6.4-36.1; SD, 9.2; $n = 29$ samples). The nadir median values for NTx declined to 10.9 nmol/L BCE (mean, 13.0; SD, 6.9; $P = 0.04$ in paired t test versus baseline) and increased to

11.9 nmol/L BCE (mean, 13.4; SD, 6.3; $P = 0.80$ in paired t test versus nadir). This is graphically displayed in Fig. 5B. In the six patients who did not receive zoledronic acid, no statistically significant changes were noted in NTx levels while on therapy (data not shown).

Discussion

In this phase I-II study of docetaxel with a fixed 10-mg oral dose of the endothelin-A receptor antagonist atrasentan, we determined the maximum tolerated dose of docetaxel to be 70 to 75 mg/m^2 on an every-3-week schedule. Toxicities in general were those expected for this combination study, and in general mild to moderate in nature, with no clinical cases of congestive heart failure. However, there was a noticeably higher incidence of grade 3-4 neutropenia (63%) and neutropenic fever (21%) in this study, compared with that seen in the TAX327 study (32% and 3%, respectively; ref. 2). The reasons for this are unclear and are to be discussed in a companion pharmacokinetic article.

The prostate cancer-specific outcomes in this study are notable, in that PSA declines ($\geq 30\%$ or confirmed $>50\%$ declines) were lower than those reported in TAX327 and historic rates seen with docetaxel with prednisone (2, 19). In this study, PSA responses were observed in 23% of men, nearly half of that observed with every-3-week docetaxel and prednisone in TAX327 (45%). Given the small phase II sample size of this study, it is not possible to provide a precise estimate of progression-free survival or overall survival in this trial; however, median overall survival and progression-free survival estimates are within the range expected with docetaxel and prednisone given every 3 weeks. The omission of prednisone, which was often standard practice until the publication of the TAX327 outcomes, may have

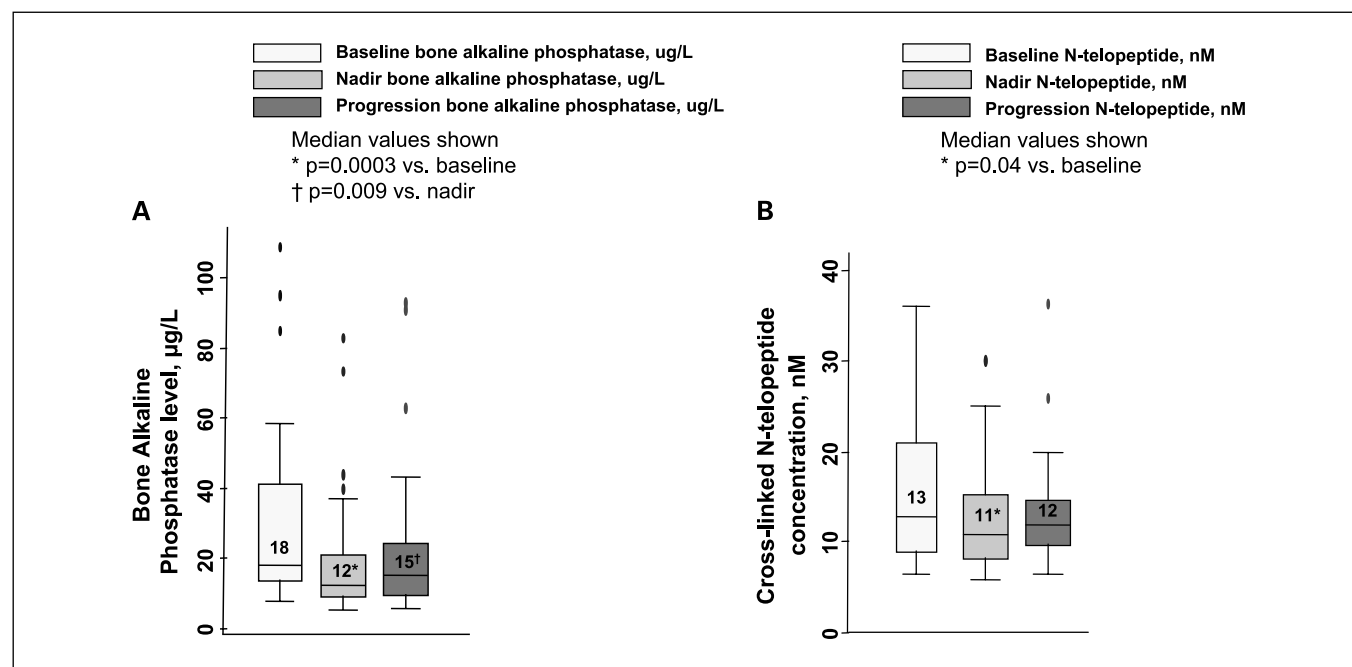


Fig. 5. A, box plots of baseline, nadir, and progression values for BAP. The mean differences are statistically significant for baseline and nadir values ($P = 0.0003$) and for nadir to progression values ($P = 0.009$). B, box plots of baseline, nadir, and progression values for serum N-telopeptides. The mean differences are statistically significant for baseline and nadir values ($P = 0.04$) but not for nadir to progression values.

contributed to lower observed rates of PSA declines. Given that corticosteroids may independently induce transient PSA declines and even pain responses, the use of prednisone in future trials may lead to a higher degree of PSA declines (20). However, this study is underpowered to address this question, and the independent benefit of the addition of atrasentan to docetaxel and prednisone requires a prospective controlled evaluation, which is ongoing in a randomized phase III study. Preclinical models of prostate cancer suggest at least an additive effect of docetaxel and atrasentan on the induction of apoptosis, reduction in proliferation and PSA, and reduction in tumor size (13, 14). Indeed, the combination of atrasentan and docetaxel strongly inhibited the growth of prostate cancer xenografts compared with either agent alone, and the combination significantly reduced serum PSA in these mice compared with either agent alone (13, 14).

Whereas the lack of a docetaxel-only control group limits the interpretation of biomarker changes in this study, markers of osteoblastic bone turnover (BAP) suggest a favorable effect on pathologic bone formation during response to treatment, independent of bisphosphonate use. The lack of reduction in the osteolytic marker NTx in the absence of bisphosphonate use suggests that the osteolytic metastatic process may be relatively unchecked by atrasentan despite docetaxel therapy, whereas the combination of docetaxel with zoledronic acid and atrasentan favorably reduced this biomarker. Both BAP and NTx levels tend to increase to baseline on disease progression, illustrating the need for further efforts to address tumor resistance in this bone microenvironment.

The maximum tolerated dose identified in this study for docetaxel was 70 to 75 mg/m² given the similarities in toxicity at these dose levels and the small sample size used to estimate toxicity. Thus, the full Food and Drug Administration–approved dose of every-3-week docetaxel may be recommended for further studies (2). It is unlikely that the addition of prednisone will modify this conclusion, and its concurrent use may physiologically increase the leukocyte count to allow for fewer dose reductions due to asymptomatic neutropenia (21). Whereas a mild decrease in hemoglobin is commonly reported with atrasentan, myelosuppression has not been observed with this agent in clinical studies, and the higher degree of neutropenia seen in this study suggests pharmacokinetic

interaction, possibly through altered protein binding of docetaxel, and is discussed in the companion article in this issue (12, 16).

The majority of the patients in this study had clinical and demographic features similar to those seen in TAX327, with predominantly bone metastatic disease (80%), approximately half with significant baseline pain and measurable disease, and similar median age and baseline PSA level (2). Our study did have a higher proportion of non-Caucasian patients (19% African-American) and a high degree of good performance status patients. These factors may influence survival and prostate cancer–specific outcomes (22–24). However, given the small sample size of this study, adjustment for known prognostic factors is not feasible. The inclusion of men without bone metastatic disease (20% of subjects) may have attenuated the efficacy of atrasentan in this study, given that endothelin-A receptor inhibition may be more beneficial in men with bone metastases (25, 26). The median overall survival seen in this first line study of men with metastatic castration-resistant prostate cancer is 17.6 months (95% CI, 13.0–23.2), comparable to that seen in TAX327 with every-3-week docetaxel and prednisone (19.2 months; ref. 27). Based on the safety and strong preclinical findings on this combination in the clinic, docetaxel and prednisone at U.S. Food and Drug Administration–approved doses and schedules, with or without 10 mg of oral atrasentan, is currently the subject of an important ongoing phase III study being conducted by the Southwest Oncology Group in men with bone metastatic castration-resistant prostate cancer, with overall survival as the primary end point (28).

Disclosure of Potential Conflicts of Interest

D. Sleep is employed by Abbott Laboratories; D. George has received research support from and is on the speakers' bureau for Sanofi-Aventis; H. Hurwitz has received a research grant from Abbott Laboratories, research support from Sanofi-Aventis, Genentech, and Roche, and is on the speakers' bureau of Genentech and Roche; A. Armstrong is on the speakers' bureau of Sanofi-Aventis.

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