A Phase 3 Randomized Controlled Trial of the Efficacy and Safety of Atrasentan in Men With Metastatic Hormone-refractory Prostate Cancer

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BACKGROUND. The objective of this study was to evaluate the efficacy and safety of atrasentan (Xinlay), a selective endothelin-A receptor antagonist, in patients with metastatic hormone-refractory prostate cancer (HRPC).

METHODS. This multinational, double-blind, placebo-controlled trial enrolled 809 men with metastatic HRPC. Patients were randomized 1:1 to receive either atrasentan 10 mg per day or placebo. The primary endpoint was time to disease progression (TTP), which was determined according to radiographic and clinical measures. Analyses of overall survival and changes in biomarkers also were performed.

RESULTS. Atrasentan did not reduce the risk of disease progression relative to placebo (hazards ratio, 0.89; 95% confidence interval, 0.76–1.04; $P = .136$). Most patients progressed radiographically at the first 12-week bone scan without concomitant clinical progression. In exploratory analyses, increases from baseline to final bone alkaline phosphatase (BAP) and prostate-specific antigen (PSA) levels were significantly lower with atrasentan treatment ($P < .05$ for each). The median time to BAP progression (≥50% increase from nadir) was twice as long with atrasentan treatment (505 days vs 254 days; $P < .01$). The delay in time to PSA progression did not reach statistical significance. Atrasentan generally was tolerated well, and the most common adverse events associated with treatment were headache, rhinitis, and peripheral edema, reflecting the vasodilatory and fluid-retention properties of endothelin-A receptor antagonism.

CONCLUSIONS. Atrasentan did not delay disease progression in men with metastatic HRPC despite evidence of biologic effects on PSA and BAP as markers of disease burden. ***Cancer* 2007;110:1959–66.** © *2007 American Cancer Society.*

KEYWORDS: atrasentan, endothelin-A receptor antagonist, hormone-refractory prostate cancer, time to disease progression, bone metastasis.

Dr. Sleep is an employee of Abbott Laboratories and owns stock in the company.

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Advanced hormone-refractory prostate cancer (HRPC), which is characterized by the development of painful osteoblastic metastases, remains an incurable disease. Despite recent improvements in survival reported with docetaxel-based chemotherapy,[1,2] independent data collected from OncoTrack, a comprehensive patient records database that tracks drug use and patient characteristics, indicates that only approximately 50% of patients with metastatic HRPC ever receive chemotherapy.[3] Effective, well-tolerated agents that delay disease progression, particularly the onset of the often severe and debilitating consequences of bone metastases associated with HRPC, still are needed.

Atrasentan (Xinlay) is a highly potent, selective endothelin-A (ET_A) receptor antagonist that blocks or reverses the biologic effects of endothelin-1 (ET-1).[4] ET-1 is a weak mitogen for prostate cancer cell lines but a significant inhibitor of chemotherapy-induced apoptosis in vitro and in vivo.[5] It is highly secreted by normal prostate epithelial cells and is expressed in all stages of prostate cancer, both within the gland and in all metastatic lesions tested.[6] Moreover, the predominant receptor subtype shifts from ET_B in normal prostate tissue to ET_A in prostate tumors.[7]

Mounting evidence indicates that ET-1 is involved in the osteoblastic bone remodeling response typical of the disease.[8,9] Osteoblasts express ET_A receptors at high density (from 10^5 to 10^6 receptors per cell), and tumor-derived ET-1 drives osteoblast proliferation and new bone formation through this receptor.[10–13] Proliferating osteoblasts generate other growth factors that appear to stimulate local metastatic tumor production reciprocally, creating a positive feedback loop.[14–16] Preclinical studies demonstrate that the effects of ET-1 on prostate cancer cells and osteoblasts can be blocked by selective endothelin receptor antagonists.[5–14,17] Therefore, the ET_A receptor and the endothelin axis are attractive targets for the management of HRPC.

Phase 1 pharmacokinetic studies demonstrated that atrasentan can be administered on a once-daily oral dosing schedule.[18,19] In a randomized, double-blind, placebo-controlled, dose-ranging Phase 2 trial, atrasentan at a dose of 10 mg per day demonstrated a significant effect on prostate-specific antigen (PSA), bone alkaline phosphatase (BAP), and other markers of bone remodeling in men with metastatic HRPC. In an intent-to-treat (ITT) analysis, a nonsignificant trend in delaying clinical disease progression was noted in favor of atrasentan.[20,21] In the current report, we present findings from a larger randomized Phase 3 trial of atrasentan 10 mg per day that was conducted in a similar group of men with metastatic HRPC.

MATERIALS AND METHODS

Eligibility Criteria

This Phase 3 randomized, double-blind, placebo-controlled study was conducted at 180 sites in 21 countries. Patients were recruited between June 25, 2001 and November 25, 2002 and were eligible to participate if they had metastatic prostatic adenocarcinoma that was refractory to androgen-ablation therapy, as defined by standard criteria (rising PSA or PSA >20 ng/mL).[22] A centralized, independent radiologic reviewer confirmed the presence of distant metastases at baseline by computed tomography (CT) scans, magnetic resonance images (MRI), and/or bone scans. Surgical or pharmacologic castration ≥3 months before randomization and a screening testosterone level <50 ng/dL were required. Patients with pharmacologic castration were to continue androgen-suppression therapy during the study. Patients had to be free of disease-related pain that required opioids, and they had to have a Karnofsky performance score between 70 and 100 with a life expectancy >6 months. Patients were ineligible if they had ever received radionuclides or chemotherapy, if they had inadequate withdrawal from antiandrogen therapy (≥4 weeks for flutamide and 6 weeks for nilutamide and bicalutamide), or if they had received bisphosphonates within 4 weeks of randomization. Patients with central nervous system metastases or with New York Heart Association grade ≥2 heart failure were excluded. Only patients who had signed an informed consent form were enrolled, and the study was conducted according to the Declaration of Helsinki under the supervision of institutional review boards.

Study Design

The study consisted of a screening period no longer than 35 days followed by a double-blind treatment period. Enrolled patients were assigned randomly 1:1 to receive once-daily oral atrasentan 10 mg or placebo. Treatment continued until the patient experienced disease progression or discontinued study drug or until the study was stopped. Patients who experienced confirmed disease progression and those who were active at the time the study was stopped were eligible to receive open-label atrasentan in an extension study.

Patients visited the study site on Days 1 and 14; Weeks 4, 8, and 12; and every 12 weeks thereafter until the final visit. Follow-up survival assessments

TABLE 1
Criteria for Disease Progression

Measure	Criteria
Radiographic measures	
New measurable bone lesions	At least 2 new lesions determined by bone scan scheduled every 12 wk
New measurable soft-tissue lesions	One new lesion or changes to existing lesion(s) determined by CT scan or MRI using modified RECIST criteria
Clinical measures	
Metastatic pain	Prostate cancer-related pain as demonstrated by evidence of disease at the site and requiring opiates (oral or transdermal opioids administered for 10 of 14 d or a single dose of intravenous, intramuscular, or subcutaneous opioids), chemotherapy, radiotherapy, radionuclide therapy, or glucocorticoids (≥5 mg oral prednisone for 10 of 14 d or a doubling of the current dose for 10 of 14 d for patients on chronic steroid therapy)
Skeletal-related event	A clinically manifested skeletal-related event with evidence of disease at the site (a pathologic or vertebral compression facture not related to trauma, prophylactic radiation, or surgery for an impending fracture, or spinal cord compression)
New intervention	Progression requiring other intervention, eg, urinary tract obstruction, malignant pleural effusion, brain metastases, or other similar events, and not including an increase in PSA

CT indicates computed tomography; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors; PSA, prostate-specific antigen.

were performed every 12 weeks after discontinuation and during the open-label extension. Serum BAP and PSA values were measured at baseline; at Weeks 4, 8, and 12; and every 12 weeks thereafter. Bone and CT/MRI scans were obtained at screening. All patients underwent follow-up bone scans at 12-week intervals; patients who had evidence of extraskeletal metastases at baseline and, at the investigator's discretion, had CT or MRI scans every 12 weeks. Patients who experienced disease progression by any measure were not followed for subsequent progression events.

Outcome Measures

The primary endpoint was time to disease progression in the ITT population. Disease progression was defined as the first occurrence of any one of the events summarized in Table 1, which included a rigorous composite of clinical and radiographic criteria. An independent radiologist reviewed all scans, and an independent oncologist confirmed all endpoints.

Secondary endpoints included change in BAP values, time to PSA progression, mean rate of change in Bone Scan Index (BSI),[23] and overall survival (OS). The time to PSA progression was defined as the days from randomization to the first of 2 consecutive postbaseline measurements (at least 14 days apart) that demonstrated a rise ≥50% from nadir. Patients with both a baseline measurement and at least 2 postbaseline measurements were included in the analysis. Tertiary analyses included time to BAP progression (defined the same as the time to PSA progression) and longitudinal analyses of PSA.

Safety assessments were performed on all patients who received study drug and included evaluation of adverse events, vital sign measurements, and laboratory analyses. An independent data monitoring committee (IDMC) regularly reviewed safety and efficacy data.

Statistical Analysis

We estimated that 650 events would be needed to achieve 90% power at the 2-sided .05 level of significance to detect a treatment difference of a magnitude similar to that demonstrated in the Phase 2 trial for the ITT population (hazards ratio [HR], 0.77; 95% confidence interval [95% CI], 0.55–1.09).[20]

Demographic and baseline variables were compared between groups. The Fisher exact test was used to compare equality of proportions, and *F* tests were used for equality of means for continuous variables. The primary endpoint was analyzed using the weighted log-rank statistic, $G^{1,1}$.[24] All time-to-event analyses were performed using Kaplan-Meier methodology and the log-rank and $G^{1,1}$ test statistics. Cox proportional hazards modeling also was applied, with HRs <1.00 favoring atrasentan. Ad hoc analyses were conducted on the radiographic and clinical components of the primary endpoint. In these analyses, patients were censored at the time of disease progression for any reason and were not followed for subsequent progression events. Mean changes from baseline in biomarkers were analyzed using analysis of covariance with treatment group and baseline value as covariates. The Fisher exact test was used to compare frequencies of adverse events between treatment arms.

RESULTS

Disposition of Patients

Eight hundred nine patients were randomized to receive either atrasentan (n = 408) or placebo (n = 401) and are included in the ITT cohort. Patients ranged in age from 45 years to 93 years (mean age, 72 years), and 95% of patients were Caucasian. There were no clinically meaningful differences between

TABLE 2
Baseline Characteristics

	Placebo group (n = 401)		Atrasentan group (n = 408)	
Variable	**Median**	**Range**	**Median**	**Range**
Age, y	72.0	45.0–92.0	73.0	45.0–93.0
Hemoglobin, g/dL	13.2	9.1–18.1	13.4	9.3–17.4
LDH, IU/L	188	108–2365	186	97–1318
Bone alkaline phosphatase, ng/mL	24.8	2.0–1599.0	25.5	2.0–1903.8
PSA, ng/mL	79.6	2.2–5424.8	69.8	1.7–5784.0
Total Gleason score	7.0	2.0–10.0	7.0	3.0–10.0
Time since diagnosis, y	4.8	0.1–23.2	5.0	0.3–23.7
Karnofsky PS: no. of patients (%)				
≤70	12 (3)		10 (2)	
80	41 (10)		40 (10)	
90	125 (31)		151 (37)	
100	223 (56)		207 (51)	

LDH indicates lactate dehydrogenase; PSA, prostate-specific antigen; PS, performance status.

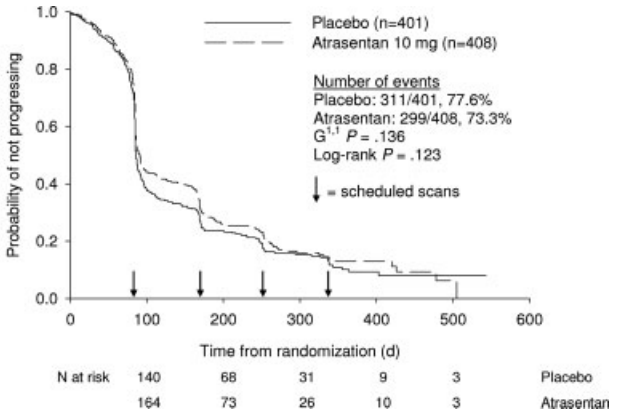

FIGURE 1. This graph illustrates the time to disease progression caused by either a radiographic or a clinical event. $G^{1,1}$ indicates the weighted log-rank statistic.

TABLE 3
Results of Primary and Secondary Endpoint Analyses in the Intent-to-treat Population (N = 809)

Endpoint	HR (95% CI)*	*P*
TTP	0.89 (0.76–1.04)	.136†
OS	0.97 (0.81–1.17)	.775†
TTPSA	0.84 (0.70–1.01)	.366†
Mean change from baseline:	between-group comparison	
BAP, ng/mL	−20.66	.001‡
BSI	−0.003	.723‡

HR indicates hazards ratio; 95% CI, 95% confidence interval; TTP, time to disease progression; OS, overall survival; TTPSA, time to prostate-specific antigen progression; BAP, bone alkaline phosphatase; BSI, Bone Scan Index.

* An HR <1.00 favors atrasentan; an HR >1.00 favors placebo (Cox proportional hazards model).

† Determined by the weighted log-rank statistic ($G^{1,1}$).

‡ Determined by analysis of covariance.

treatment arms in baseline characteristics, including factors with established prognostic importance in prostate cancer (Table 2).[25]

Enrollment ceased at the recommendation of the IDMC in September 2002 because, with 137 events already accrued, they estimated that a sufficient number of patients had been enrolled to achieve the prespecified number of endpoint events. The committee subsequently recommended in February 2003 that the study be stopped, because it was unlikely to achieve statistical significance in the primary analysis. The IDMC based their decision on 343 confirmed events plus additional events not yet adjudicated. Once all patients had completed final study visits and undergone final imaging procedures, 610 disease progression events had occurred.

Primary Endpoint

Protocol-defined disease progression was unexpectedly rapid in both treatment arms, with >50% of patients demonstrating progression within 100 days (Fig. 1). Estimates of progression were based on the dose-ranging study, in which clinical investigators determined progression without mandated radiographic scans every 12 weeks. In this study, the majority of progression events resulted from the acquisition of new lesions on scheduled bone scans, and most were identified on the first scan at Week 12. Atrasentan did not affect the time to disease progression relative to placebo in the ITT population ($G^{1,1}$; P = .136) (Table 3). It is noteworthy that the vast majority of radiographic progression events (433 of 498 events; 87%) occurred

in the absence of any protocol-defined clinical progression event.

Secondary Endpoints

Baseline BAP values were similar in the 2 treatment arms. The mean change at final assessment was an increase of 13.2 ng/mL with atrasentan compared with an increase of 33.9 ng/mL with placebo (P = .001). The time to PSA progression (requiring 2 consecutive increases of 50% from nadir) was longer with atrasentan but did not reach statistical significance (HR, 0.84; 95% CI, 0.70–1.01). However, an additional 26% of patients had a single 50% increase in PSA, and many of those men did not have a confirmatory test because their initial PSA increase occurred at Week 12 or later, coincident with disease progression. Patients were not followed for the next PSA assessment once they experienced disease progression. In an exploratory analysis of the time to first 50% increase in PSA, atrasentan significantly extended the time before PSA progression (HR, 0.86; 95% CI, 0.73–1.00).

The survival analysis did not detect a difference between treatment arms based on initial randomization; the median survival was 20.5 months for patients who were randomized to the atrasentan arm and 20.3 months for patients who were randomized to the placebo arm. Interpretation of these results was confounded by the extension study, in which nearly 65% of patients from both randomized arms received open-label atrasentan.

Tertiary Endpoints

Results for the time to BAP progression and for the mean change from baseline PSA favored atrasentan (Table 3). The median time to BAP progression was nearly twice as long with atrasentan as with placebo (505 days vs 254 days; HR, 0.56; 95% CI, 0.42–0.75). Atrasentan significantly slowed the rise in mean PSA at Weeks 4, 8, 12 and at the final visit compared with placebo. The mean baseline PSA value for the atrasentan arm was 200.1 ng/mL with a mean increase of 199.7 ng/mL at the final assessment; whereas the mean baseline PSA value was 215.0 ng/mL for the placebo arm with a greater mean increase from baseline of 290.7 ng/mL at the final assessment ($P < .023$).

Safety

Treatment with atrasentan was generally well tolerated, with 9% (36 of 404 patients) of atrasentan-treated patients discontinuing from the study primarily because of an adverse event and without disease progression compared with 6% (22 of 397 patients) of placebo-treated patients. The incidence of grade 3 of 4 events (42% placebo, 40% atrasentan) was also similar between treatment arms, as were serious adverse events (placebo arm, 26%; atrasentan arm, 29%) and deaths from treatment-emergent adverse events (placebo arm, 5%; atrasentan arm, 6%) according to the National Cancer Institute Common Toxicity Criteria (NCICTC), version 2.

Bone pain was the most common adverse event and was reported more frequently with placebo (Table 4). The most frequently reported adverse events that were more common with atrasentan were peripheral edema (40%), rhinitis (36%), and headache (21%), which reflect the vasodilatory and/or fluid-retention properties of ET_A receptor antagonism (Table 4). Overall, the incidence of most grade 3 or 4 adverse events was similar between treatment groups. Bone pain was more common with placebo, and heart failure was more common with atrasentan (Table 4).

The incidence of heart failure was higher with atrasentan than with placebo (P = .002). Heart failure likely caused by fluid overload also was observed in the Phase 2 study and has been described in studies of other endothelin antagonists in cardiac disease.[21,26,27] Atrasentan recipients who experienced heart failure generally were older and weighed less at baseline than atrasentan-treated patients who did not develop heart failure (mean age, 78 years vs 72.1 years; mean weight, 74.7 kg vs 84.3 kg). Most men (13 of 18 patients; 72%) had a significant cardiovascular history, including previous congestive heart failure, ischemic heart disease, cardiac arrhythmia, and/or valvular heart disease. Heart failure tended to occur within the first 2 months of dosing with atrasentan (median time to onset, 35 days; range, 4–310 days). Heart failure resolved for 50% of the atrasentan-treated patients, with most continuing or briefly interrupting atrasentan therapy and receiving appropriate medication. Events for 4 patients resolved after atrasentan discontinuation. Six atrasentan-treated patients died from complications related to heart failure, although the clinical presentation was questionable for 3 of those patients, and 5 of them had very advanced cancer at baseline (3 patients had visceral metastases, and 2 had a BSI in the upper quartile).

Myocardial infarction (MI) also was reported more frequently with atrasentan (9 of 404 patients; 2.2%) than with placebo (2 of 397 patients; 0.5%). Five atrasentan recipients had MI concurrent with heart failure. The incidence of fatal MI was similar between treatment arms (2 deaths in the atrasentan arm; 1 death in the placebo arm).

DISCUSSION

The current study did not demonstrate a significant effect of atrasentan on delaying disease progression,

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