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Phase II Study of Single-Agent Orteronel (TAK-700) in Patients with Nonmetastatic Castration-Resistant Prostate Cancer and Rising Prostate-Specific Antigen

Maha Hussain[1], Paul G. Corn[2], M. Dror Michaelson[3], Hans J. Hammers[6], Joshi J. Alumkal[7], Charles J. Ryan[8], Justine Y. Bruce[9], Susan Moran[4], Shih-Yuan Lee[4], H. Mark Lin[5], and Daniel J. George[10] for the Prostate Cancer Clinical Trials Consortium, a program of the Department of Defense Prostate Cancer Research Program and the Prostate Cancer Foundation

Abstract

Purpose: Orteronel (TAK-700) is an investigational, nonsteroidal, oral, inhibitor of androgen synthesis with greater specificity for 17,20-lyase than for 17α-hydroxylase. We investigated orteronel without steroids in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC; M_0).

Experimental Design: Patients with nmCRPC and rising prostate-specific antigen (PSA) received orteronel 300 mg twice daily until PSA progression, metastases, or unacceptable toxicity. The primary endpoint was percentage of patients achieving PSA $\leq$0.2 ng/mL (undetectable levels) at 3 months. Secondary endpoints included safety, PSA response, time to metastases, and correlated endpoints.

Results: Thirty-nine patients with a median baseline PSA doubling time of 2.4 months (range, 0.9–9.2) received a median of fourteen 28-day treatment cycles. PSA decreased >30% in 35 patients and 6 (16%) achieved PSA $\leq$ 0.2 ng/mL at 3 months. Median times to PSA progression and metastasis were 13.8 and 25.4 months, respectively. Kaplan–Meier estimates of freedom from PSA progression were 57% and 42% at 12 and 24 months, and of freedom from metastasis were 94% and 62% at 12 and 24 months, respectively. At 3 months, median testosterone declined by 89% from baseline. Adverse events led to therapy discontinuation in 12 patients and grade $\geq$3/4 adverse events occurred in 22 patients. Most frequent all-cause adverse events included fatigue (64%), hypertension (44%), diarrhea (38%), and nausea (33%), which were primarily grade 1/2.

Conclusions: Single-agent orteronel produced marked and durable declines in PSA in patients with nmCRPC. Orteronel has moderate but manageable toxicities and its chronic administration without steroids appears feasible. *Clin Cancer Res; 20(16); 4218–27. ©2014 AACR.*

Authors' Affiliations: [1]University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan; [2]MD Anderson Cancer Center, Houston, Texas; [3]Massachusetts General Hospital Cancer Center, Boston; [4]Takeda Pharmaceuticals International Co.; [5]Millennium: The Takeda Oncology Company, Cambridge, Massachusetts; [6]Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland; [7]Oregon Health & Science University, Knight Cancer Institute, Portland, Oregon; [8]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California; [9]University of Wisconsin Carbone Cancer Center, Madison, Wisconsin; and [10]Duke University Medical Center, Durham, North Carolina

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Corresponding Author: Maha Hussain, 7314 University of Michigan Comprehensive Cancer Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109. Phone: 734-936-8906; Fax: 734-615-2719; E-mail: mahahuss@umich.edu

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Introduction

A significant percentage of patients with nonmetastatic, biochemical [or prostate-specific antigen (PSA)]-recurrent prostate cancer will progress on androgen deprivation therapy (ADT) to castration resistance (1–4). Patients with nonmetastatic, castration-resistant prostate cancer (nmCRPC; M_0) have a median metastasis-free survival of approximately 25 to 30 months (5, 6); risk of bone metastasis or death has been shown to increase when PSA doubling time (PSADT) decreases below 8 months (7). Baseline PSA and PSA velocity are independent predictors of first bone metastases, overall survival (OS), and bone metastasis-free survival (BMFS; refs. 5–7). Considering the morbidity of bony metastases, several trials evaluated bone-targeted therapy in this disease population, resulting in no or modest effects and no impact on the totality of the disease (i.e., overall disease progression in bone and non-bone sites) or OS (8–11). Thus, delaying all site metastasis in patients with nmCRPC remains an unmet medical need (1, 3–5, 12).

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Translational Relevance

Despite several phase III trials, there is no standard therapy for patients with nonmetastatic castration-resistant prostate cancer (nmCRPC), a heterogeneous population in whom a rapid prostate-specific antigen doubling time (PSADT) and/or high baseline PSA are prognostic for poorer outcomes. Orteronel (TAK-700) is an investigational, nonsteroidal, selective inhibitor of 17,20-lyase, a component of the CYP17A1 enzyme involved in the production of steroidal hormones. Orteronel selectively inhibits 17,20-lyase relative to 17α-hydroxylase, which may reduce the potential for adrenocorticotropic hormone–driven mineralocorticoid excess and the resultant need for concomitant corticosteroids. This phase II study evaluated orteronel, in a steroid-free regimen, in patients with nmCRPC and a median baseline PSADT of <3 months. Orteronel produced marked and durable declines in serum PSA, testosterone, and dehydroepiandrosterone sulfate, with moderate but manageable toxicity. Encouraging metastasis-free survival was observed in this high-risk population. Orteronel is currently being evaluated without steroids in several ongoing phase III studies.

One mechanism contributing to castration resistance is the conversion of adrenal and intratumoral androgen precursors to androgens, which results in tumor progression (1, 3, 4). Inhibition of 17,20-lyase, a key component of the CYP17A1 enzyme that produces steroidal hormones, causes suppression of androgen production in the testes and also inhibits synthesis of adrenal sex steroid hormone precursors (13–16). Data from phase III trials with abiraterone acetate validates the role of this pathway (17, 18).

Orteronel (TAK-700) is an investigational, nonsteroidal, selective inhibitor of 17,20-lyase. In preclinical studies, orteronel more potently inhibited 17,20-lyase relative to 17α-hydroxylase, up to 5.4-fold, with minimal effect on other CYP drug-metabolizing enzymes (16). More selective inhibition of 17,20-lyase by orteronel may result in a lesser effect on 17α-hydroxylase, necessary for cortisol synthesis, reducing the potential for adrenocorticotropic hormone (ACTH)-driven mineralocorticoid excess and the resultant need for concomitant corticosteroids. Thus, orteronel could be an attractive drug for longer duration therapy or where prolonged corticosteroid is not ideal. This phase II study evaluated a steroid-free regimen of orteronel in patients with nmCRPC and rising PSA.

Materials and Methods

Study design and treatment

This open-label, multicenter study evaluated single-agent orteronel 300 mg twice daily (BID) in continuous 28-day treatment cycles in patients with nmCRPC. Orteronel was taken without regard to food. The primary endpoint was percent of patients achieving PSA of ≤0.2 ng/mL (undetectable levels) after 3 months of treatment. Secondary endpoints included safety, PSA response rates at 3 and 6 months [decline in PSA of ≥90%, ≥50%, and ≥30% (PSA90, PSA50, and PSA30)], percentage of patients achieving PSA ≤0.2 ng/mL after 6 months of treatment, time to PSA progression, time to development of metastases, duration of PSA progression-free survival (PFS), and changes in concentrations of endocrine markers, including serum testosterone, dehydroepiandrosterone sulfate (DHEA-S), ACTH, corticosterone, and cortisol. Exploratory objectives included analysis of circulating tumor cells (CTC), changes in biochemical markers of bone turnover and bone mineral density (BMD), and assessment of possible changes in androgen deprivation symptoms. Orteronel was continued until PSA progression, metastases, or unacceptable toxicity.

The study was approved by the local institutional review boards and run in accordance with all applicable regulatory requirements and Good Clinical Practice. All patients provided institutional review board–approved written informed consent.

Patients

Eligible patients had a pathologic diagnosis of prostate cancer, no radiographic evidence of metastasis, a rising PSA despite castrate levels of testosterone (<50 ng/dL) following orchiectomy or ongoing gonadotropin-releasing hormone (GnRH) analog therapy. Patients had to have baseline PSA ≥2 ng/mL and higher risk for metastases (PSADT of ≤8 months, or PSA ≥8 ng/mL if doubling time was >8 months; ref. 5). Other entry criteria included Eastern Cooperative Oncology Group (ECOG) performance status ≤2, serum alanine aminotransferase or aspartate aminotransferase ≤1.5 × upper limit of normal (ULN), total bilirubin ≤1.5 × ULN, serum creatinine < 2 mg/dL and/or creatinine clearance >40 mL/min, and ejection fraction ≥50% at screening. Excluded patients had prior prostate cancer treatment with aminoglutethimide or ketoconazole at any time, anti-androgen therapy within 4 weeks (flutamide) or 6 weeks (others), prior chemotherapy, or radiation ≤30 days before the first dose of orteronel.

Assessments

PSA progression was defined as a 25% increase over the baseline/nadir concentration and an absolute PSA increase of ≥2 ng/mL. PSA response endpoints included PSA90, PSA50, and PSA30. Duration of PSA response was measured from the time of first PSA response to PSA progression or death. Detection of metastases by radiologic progression included bone scans and computed axial tomography scan or magnetic resonance imaging of the abdomen and pelvis at screening and every 3 to 4 cycles per protocol. PFS was defined as the time from first dose of orteronel to first PSA progression, metastasis (≥2 new bone lesions or one new soft-tissue lesion on imaging; refs. 19, 20), or death. Toxicity was evaluated per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

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Hypothalamic–pituitary–adrenal axis function, including plasma ACTH, serum cortisol, DHEA-S, corticosterone, and testosterone and bone biochemical markers, including creatinine-corrected urine *N*-telopeptide, serum parathyroid hormone, 25-hydroxy vitamin D, and serum bone-specific alkaline phosphatase (ALP), were assessed at baseline and at 3 and 6 months. Ultra–low-level quantification of testosterone was measured by liquid chromatography and mass spectrometry. The lower limit of detection for testosterone was 0.2 ng/dL. BMD was evaluated by dual energy X-ray absorptiometry. Blood samples for evaluation of CTCs were collected at baseline and at 3, 6, and 12 months. Cardiac assessments included creatine kinase MB, troponin, left ventricular ejection fraction, and QTc interval.

Health-related quality of life (HRQoL) was assessed using the Aging Males Symptom (AMS) scale, which evaluates changes of symptoms of aging and androgen deprivation over time (21, 22). The AMS includes 18 questions, of which 17 generate a total score classified as: 0–26, no symptoms of androgen deficiency; 27–36, mild symptoms; 37–49, moderate symptoms; and ≥50, severe symptoms. Three subscales covering psychological, somatic, and sexual domains are similarly classified.

Statistical analysis

On the basis of the primary endpoint, 38 patients provided 90% power to give a one-sided significance level of 0.1, assuming 20% achieved a PSA of ≤0.2 ng/mL after 3 months of orteronel treatment versus the null hypothesis of 5%. To be evaluable for the primary endpoint and the secondary endpoints of PSA response and achievement of PSA ≤0.2 ng/mL following 6 months of treatment, patients had to have both a baseline PSA and at least one post-baseline PSA measurement. For PSA response rate calculations, the number and percentage of responders, and the two-sided 80% exact confidence interval (CI), were provided. The Kaplan–Meier method was used to assess time to PSA progression, time to metastasis, and PFS. All patients receiving ≥1 dose of orteronel were evaluable for safety.

Results

Patient demographics and disease characteristics are shown in Table 1. Thirty-nine patients were registered and treated. Median serum PSA at study entry was 12.1 ng/mL (range, 2.6–67.8) and median baseline PSADT was 2.4 months (range, 0.9–9.2). The median number of treatment cycles received was 14 (range 1–34); 26 patients (67%) were on treatment for >6 months and 20 (51%) for >12 months. As of July 22, 2013, 6 patients (15%) remain on treatment and 33 (85%) have discontinued—17 (44%) due to disease progression, 15 (38%) due to PSA progression, 12 (31%) for adverse events (AEs), 2 (5%) by patient choice, and 2 (5%) other reasons.

Table 1. Baseline patient demographics and disease characteristics

Characteristic	$N = 39$[a]
Median age (range), y	71 (53–81)
Race, *n* (%)	
White	35 (90)
Black or African American	4 (10)
ECOG performance status, *n* (%)	
0	33 (85)
1	6 (15)
Gleason score >7, *n* (%)	20 (51)
Median (range)	
PSA	12.1 ng/mL (2.6–67.8)
Testosterone ($n = 38$)	8.5 ng/dL (1.4–17.3)
ACTH ($n = 32$)	19.5 ng/L (0–47)
PSADT	2.4 months (0.9–9.2)
Prior surgery, *n* (%)	
Radical prostatectomy	25 (67)
Bilateral orchiectomy	2 (5)

NOTE: Two patients received prior ketoconazole (protocol deviations).
[a]$N = 39$ represents all 39 treated patients.

Efficacy

PSA response. PSA declined from pretreatment baseline levels in 37 of 38 (97%) evaluable patients and decreased >30% in 35 patients (Fig. 1A). One patient was not evaluable for PSA response because they had only a baseline PSA measurement and no on-study PSA measurement. PSA response rates after 3 and 6 months of treatment are summarized in Table 2 and Fig. 1B. At 3 months, of 34 patients with PSA measurements at this time point, 33 patients (97%) experienced a PSA decline. A PSA decline to ≤0.2 ng/mL (primary endpoint) occurred in 6 PSA-evaluable patients (16%) at 3 months (Fig. 1B) and in 12 PSA-evaluable patients (32%) at any time on study (best response; Fig. 1). At 3 months, declines in PSA30, PSA50, and PSA90 responses occurred in 31 (82%), 29 (76%), and 12 (32%) patients, respectively, and at 6 months in 22 (58%), 19 (50%), and 9 (24%) patients, respectively.

PSA progression. In 38 PSA-evaluable patients, the Kaplan–Meier estimate of median time to PSA progression was 13.8 months (95% CI, 11.1–25.8; Fig. 2A). Estimates of freedom from PSA progression were 88%, 57%, and 42% at 6, 12, and 24 months, respectively. Duration of PSA response to PSA progression or death is shown in Fig. 2B. Kaplan–Meier estimates of median time from PSA50 (or better) response to PSA progression or death was 14.8 months and for patients with PSA90, 24.9 months.

Time to metastasis. As of final data cutoff, 11 of 39 (28%) patients had developed systemic metastasis. Median time to development of first metastasis was 25.4 months (95% CI, 17.6 to not reached). Kaplan–Meier estimates of freedom from metastasis (time from first dose to first occurrence of metastasis) were 94% and 62% of patients at 12 and 24 months, respectively (Fig. 2C).

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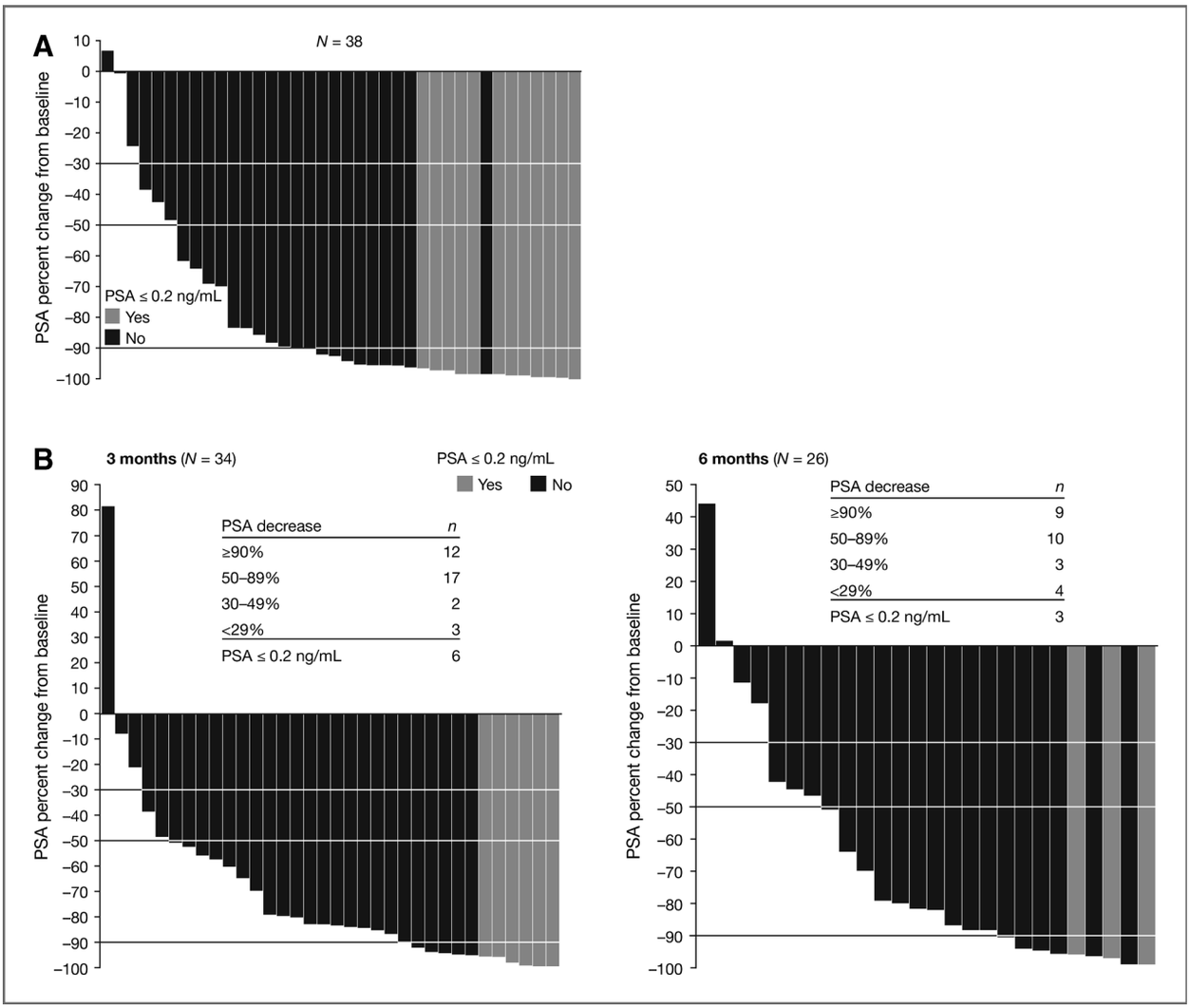

Figure 1. Waterfall plots of PSA response: A, maximum PSA response at any time on treatment for $N = 38$ PSA-evaluable patients; B, responses at 3 and 6 months for $N = 34$ and $N = 26$ PSA-evaluable patients, respectively, with a PSA measurement at the 3- and 6-month time points.

PFS. In all 39 patients, median duration of time from first dose to PSA progression, metastasis, or death was 14.8 months (95% CI, 11.1–24.7). Kaplan–Meier estimates of PFS at 6, 12, and 24 months were 88%, 57%, and 37%, respectively.

CTCs. Seven of 35 patients assessed had ≥1 CTC per 7.5 mL of whole blood at baseline assessment (Supplementary Table S1). One patient had ≥5 CTCs per 7.5 mL at baseline, which converted to <5 cells per 7.5 mL for

Table 2. PSA response rates at 3 and 6 months

	3 mo		6 mo	
***N* = 38**[a]	***n* (%)**	**(80% exact CI)**	***n* (%)**	**(80% exact CI)**
PSA ≤0.2 ng/mL	6 (16)	9–26	3 (8)	3–17
PSA30	31 (82)	71–89	22 (58)	46–69
PSA50	29 (76)	65–85	19 (50)	39–62
PSA90	12 (32)	22–43	9 (24)	15–35

NOTE: PSA response rate: percentage of patients achieving a decline in PSA of ≥90% (PSA90), ≥50% (PSA50), ≥30% (PSA30).
[a]$N = 38$ represents the PSA-evaluable population.

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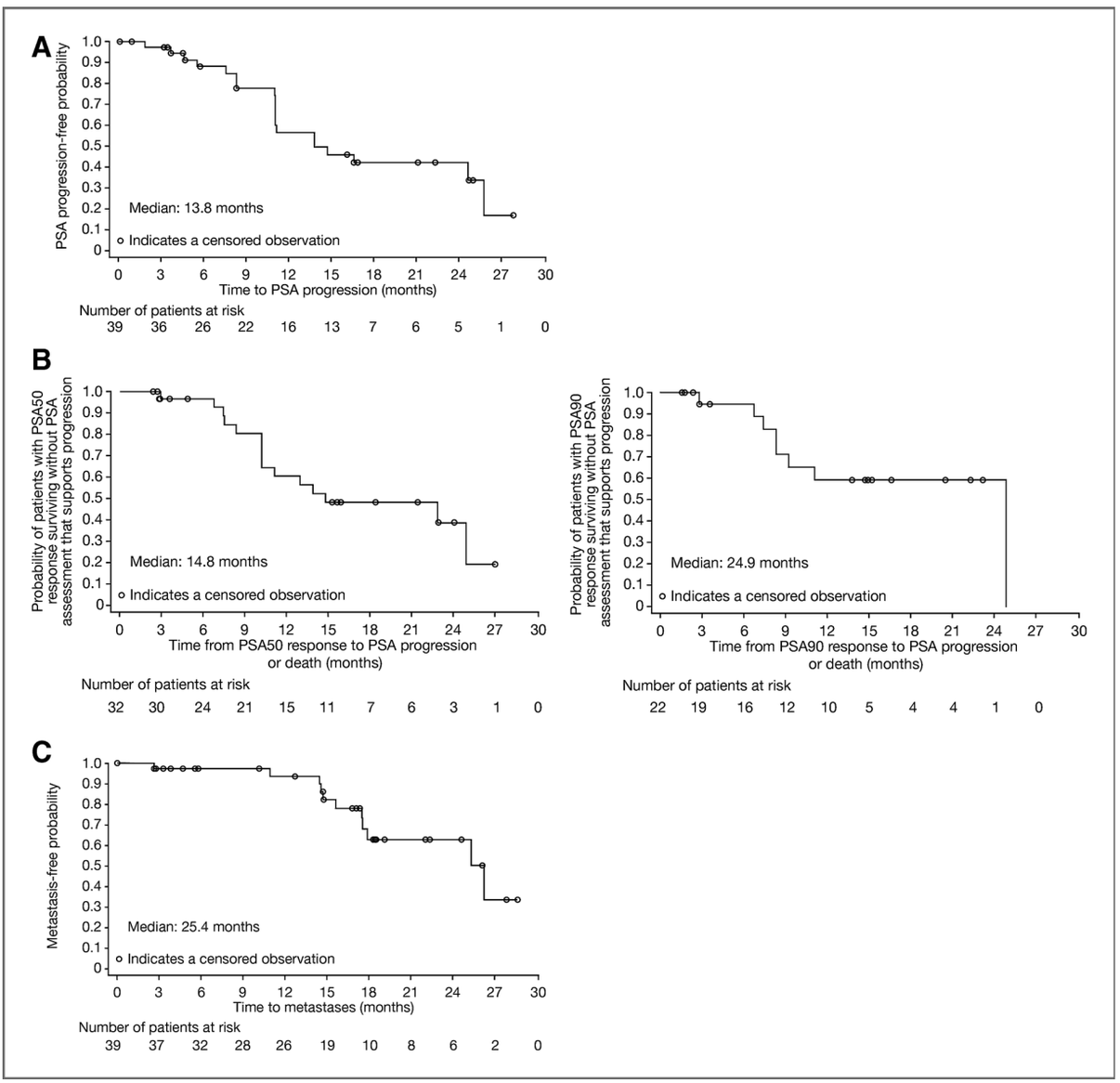

Figure 2. Kaplan–Meier estimates of: A, time to PSA progression for $N = 39$ (non–PSA-evaluable patients censored at time 0); B, duration of PSA response in patients achieving a PSA decline of $\geq$50% or $\geq$90% (PSA50 and PSA90, respectively); C, time to metastasis for $N = 39$.

the ensuing 12 months on treatment; no patient had a CTC count $\geq$5 cells per 7.5 mL blood at any on-treatment visit.

Endocrine—efficacy response. Changes over time for serum testosterone and DHEA-S are shown in Fig. 3A. After 3 and 6 months, respectively, median testosterone declined by 89% and 87% from a baseline of 8.5 ng/dL to 0.78 and 0.84 ng/dL. Median DHEA-S decreased by 85% and 89% to 197 and 188 nmol/L.

HRQoL (AMS scale). Median changes from baseline in androgen deprivation–related symptom scores were generally minimal throughout the study. No clinically significant changes in androgen deprivation–related symptoms were observed (Supplementary Fig. S1). The median total AMS score at baseline, 6 months, and 12 months was 33, 34, and 34, respectively, consistent with mild symptoms. Similar results were observed for psychological, sexual, and somatic scores.

Safety. AEs were reported in 38 of 39 patients (97%; Table 3). Commonly reported treatment-emergent AEs included fatigue (64%) and gastrointestinal events, particularly diarrhea (38%) and nausea (33%). Twenty-two patients (56%) reported grade $\geq$3 AEs, of whom 2 had grade 4 AEs (1 each with pulmonary embolism and bladder cancer, both considered unrelated to orteronel treatment). Serious AEs were reported in 10 patients (26%). There were no on-study deaths. AEs led to study discontinuation in 12 patients (31%) and included hypertension (patients with

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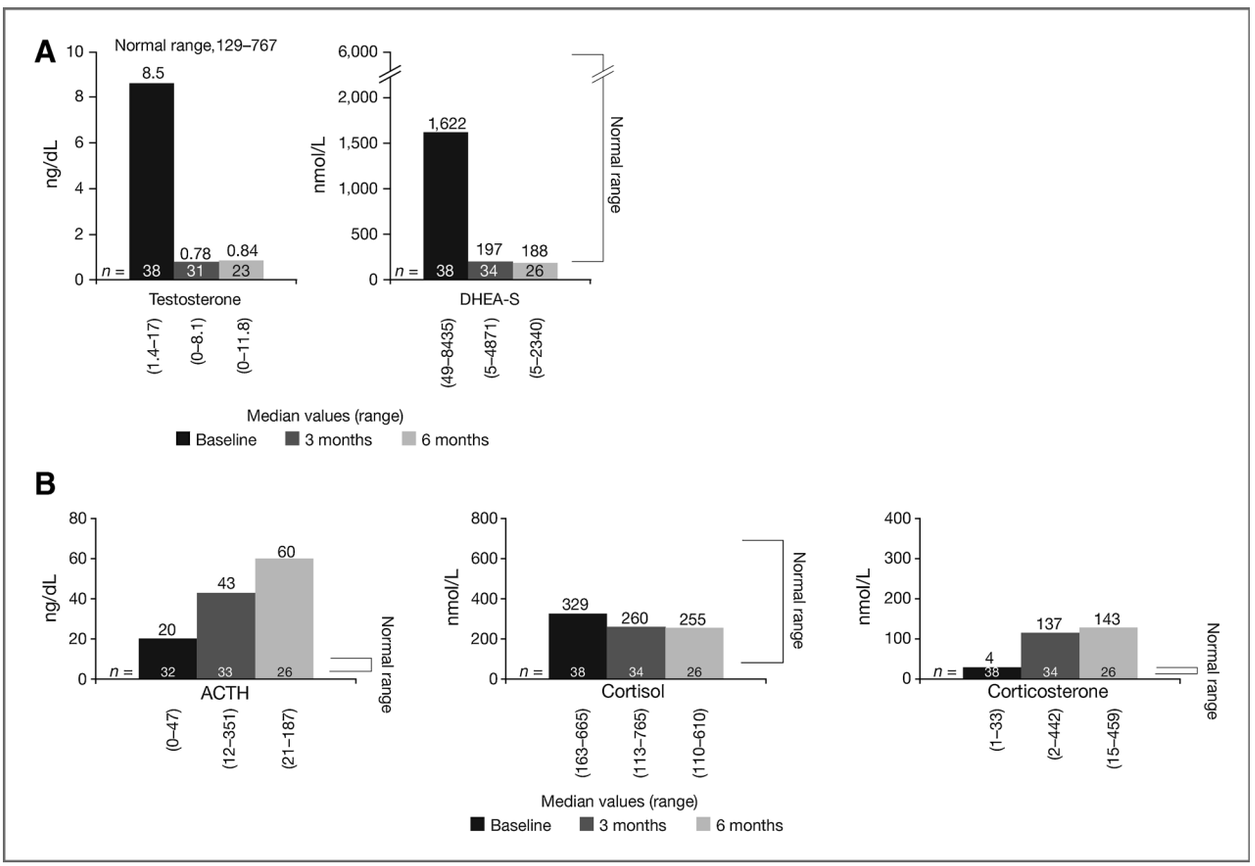

Figure 3. Median pharmacodynamic changes from baseline to assessment at 3 and 6 months: A, testosterone and DHEA-S; B, ACTH, cortisol, and corticosteroid. Percent change from baseline is based on the number of patients with both baseline and post-baseline values at that cycle. Normal ranges are also shown for reference.

prior history of hypertension that worsened), dyspnea, and fatigue (each $n = 2$; 5%).

Consistent with the observed elevations in ACTH and corticosterone (see below and Fig. 3B), hypertension was reported in 17 patients (44%), including at grade 3 in 7 (18%). One patient required a dose reduction and, eventually, discontinuation of orteronel, a second patient also discontinued orteronel due to hypertension; both patients received concomitant hypertension medication. Eight patients had a history of hypertension and experienced worsening of the event, the remaining 9 patients had newly occurring hypertension. Fourteen of the 17 patients with hypertension received antihypertensive medication. Outcome of hypertension was reported as resolved for 7 patients and ongoing for 10. A mixed-effect model analysis did not reveal a correlation between hypertension and cortisol levels. However, the sample size is small for definitive conclusions.

Seven patients (18%) experienced hypokalemia, including grade 3 in 2 patients (5%); 5 patients received concomitant medication, no action was taken in 2, and no patients discontinued because of hypokalemia. Three patients (8%) experienced grade 1 or 2 adrenal insufficiency, 2 were treated with medication (steroid) due to the event. Adrenal insufficiency was reported as a serious AE in the third patient, who discontinued study drug.

Three patients (8%) experienced pneumonitis (1 grade 2, 2 grade 3); all 3 cases were drug-related serious AEs, and all patients ultimately discontinued study drug due to the event. Each patient received medication or a concomitant procedure and pneumonitis resolved in each case. None of the patients had a prior history of pneumonitis, although 1 patient had an ongoing medical history of cough, exertional dyspnea, and bilateral atelectasis.

One patient experienced a grade 1 aspartate aminotransferase increase, no patients had grade >1 elevations in hepatic transaminases. There were no other clinically significant changes in laboratory evaluations, including liver function tests and serum lipids, cardiac markers, ECGs, or measures of ejection fraction.

Laboratory and biomarker indices of safety

Endocrine—safety markers. Associated with the steroid-free dosing regimen, modest changes in the ACTH-adrenal axis occurred (Fig. 3B). Median ACTH increased approximately 2- to 3-fold and median corticosterone increased more than 30-fold. These increases are consistent with modest increases in the ACTH-driven mineralocorticoid

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Table 3. Most common AEs irrespective of causality or drug-relatedness reported in ≥20% of patients overall or in ≥5% at grade 3 and corresponding rates of drug-related AEs

	Orteronel 300 mg BID ($N = 39$[a])					
	Treatment-emergent				Drug-related	
AEs, *n* (%)	All	Grade 1	Grade 2	Grade 3	All	Grade 3
Fatigue	25 (64)	14 (36)	9 (23)	2 (5)	25 (64)	2 (5)
Hypertension	17 (44)	2 (5)	8 (21)	7 (18)	15 (38)	6 (15)
Diarrhea	15 (38)	8 (21)	6 (15)	1 (3)	13 (33)	1 (3)
Nausea	13 (33)	12 (31)	1 (3)	0	11 (28)	0
Decreased appetite	13 (33)	10 (26)	3 (8)	0	12 (31)	0
Constipation	12 (31)	10 (26)	2 (5)	0	10 (26)	0
Cough	10 (26)	9 (23)	1 (3)	0	2 (5)	0
Vomiting	10 (26)	9 (23)	1 (3)	0	6 (15)	0
Dyspnea	9 (23)	5 (13)	1 (3)	3 (8)	6 (15)	2 (5)
Arthralgia	8 (21)	6 (15)	2 (5)	0	1 (3)	0
Dysgeusia	8 (21)	7 (18)	1 (3)	0	8 (21)	0
Dyspepsia	8 (21)	8 (21)	0	0	5 (13)	0
Hypokalemia	7 (18)	4 (10)	1 (3)	2 (5)	7 (18)	2 (5)
Pneumonitis	3 (8)	0	1 (3)	2 (5)	3 (8)	2 (5)
Syncope	2 (5)	0	0	2 (5)	1 (3)	1 (3)

NOTE: Serious AEs were reported in 10 men (26%). Of these, serious AEs in 6 men were considered drug-related: 2 men had pneumonitis; 1 had pneumonitis, dyspnea, and hypoxia; 1 had syncope and atrioventricular block; 1 had atrial fibrillation and atrial flutter; and 1 had adrenal insufficiency. Grade 4 serious AEs were reported in 2 men and were considered unrelated to drug treatment: 1 with bladder cancer and humerus fracture and 1 with pulmonary embolism. There were no grade 5 events.

[a]$N = 39$ represents all 39 treated patients.

and alternative glucocorticoid pathways, which do not require 17α-hydroxylase. Median post-baseline cortisol levels decreased by 21% (260 nmol/L) at 3 months and 36% (255 nmol/L) at 6 months, which is within normal limits and may reflect diurnal variation.

Biochemical markers of bone turnover and BMD. No systematic treatment-related changes in serum bone–specific ALP, urine *N*-telopeptide, 25-hydroxy vitamin D, or serum parathyroid hormone were observed. No clinically significant changes were observed in BMD imaging results (Supplementary Table S2).

Discussion

Many patients with prostate cancer who undergo ADT for biochemical PSA relapse following local therapy (23) will develop castration resistance, manifested by a rising PSA, without radiographic evidence of metastasis and no physical disease-related symptoms (nmCRPC). Four phase III trials were conducted in this population (8–11). Considering the predominance of bone metastasis in this disease and the ensuing morbidity, 3 of these trials tested bone-targeting agents with a primary objective of delaying time to bone metastasis (8, 10, 11), whereas the primary endpoint in the study by Nelson and colleagues was PFS or time to disease progression (not including increase in PSA; ref. 9). Unfortunately, none of these trials improved overall disease PFS or OS. Data from these trials indicate that patients with nmCRPC have a variable clinical course, with median survival of approximately 30 to 48 months but great within-group heterogeneity (6, 24). Disease features such as PSA level or PSADT are prognostic for survival. Baseline PSA ≥8.0 ng/mL and PSADT ≤8 months are predictive for higher risk of progression and consistently associated with time to first bone metastasis and death (6, 25). Currently, there is no standard therapy for this potentially deadly stage of disease.

Orteronel is a nonsteroidal inhibitor of androgen production, and a recent phase II trial showed ≥90% suppression of testosterone and DHEA-S with orteronel 300 mg BID (25). Because orteronel has the potential advantage of steroid-free dosing, we investigated orteronel 300 mg BID without steroids. As previously reported in a phase II study in mCRPC (25), orteronel 300 mg BID monotherapy rapidly and profoundly suppressed the adrenal-derived androgens, testosterone, and DHEA-S.

In this study, the median duration of PFS (time to PSA progression, metastases, or death) was 14.8 months, whereas the median time to PSA progression was 13.8 months (Fig. 2A). The duration of PSA response (time from start of PSA response to PSA progression or death, Fig. 2B) was longer in patients achieving greater PSA decline (PSA90) than in patients achieving lesser decline (PSA50 or better), supporting the use of PSA decrease as an intermediate response biomarker in this setting. Furthermore, median time to

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development of metastasis was more than 24 months in this high-risk population with median baseline PSADT of <3 months (Fig. 2C). Kaplan–Meier estimates of freedom from metastasis were 94% and 62% at 12 and 24 months, respectively. The study of atrasentan in men with nmCRPC reported by Nelson and colleagues demonstrated median time to disease progression (defined as the onset of metastases) in the control arm of 22 months with Kaplan–Meier estimates of freedom from disease progression of approximately 65% and 45% at 12 and 24 months, respectively (9). However, there are differences in the study population (e.g., PSA inclusion criteria) and the primary endpoint metrics between this study and the present study. Although patient numbers in the present study were relatively small, the observed metastasis-free survival in this population appears encouraging.

AEs led to study discontinuation in 12 patients (31%). Whether concomitant steroids would have prevented some of the AEs that led to discontinuation of therapy is unclear. Data from other orteronel trials in different patient populations and disease settings showed rates of discontinuation due to AEs of 42% in a phase II study of orteronel plus docetaxel and prednisone in 24 patients with chemotherapy-naïve mCRPC (26), 21% overall in a phase I/II study of orteronel with or without prednisone in 123 patients with mCRPC, in which the discontinuation rates due to AEs were similar between the 2 treatment groups (27), and 26% in a phase III study of orteronel plus prednisone in 734 patients with mCRPC that progressed post-docetaxel treatment (28).

The most common treatment-related AEs were low-grade fatigue, diarrhea, and hypertension. Of the 17 patients who experienced hypertension, 9 had a prior medical history of hypertension. Only 2 of 9 patients discontinued treatment as a result of hypertension whereas 3 patients (8%) had reports of serious pneumonitis leading to study-drug discontinuation. The pneumonitis resolved in each patient, diagnostic evaluations were inconclusive, and etiology remains unclear. To date, pneumonitis has not emerged as a safety concern in the randomized phase III orteronel trials (ref. 28; NCT01193244). We were encouraged by the apparent lack of hepatotoxicity with orteronel, which has a nonsteroidal structure and, as it is not hepatically metabolized, has no significant interactions with hepatic enzymes (29).

Although orteronel blocks 17α-hydroxylase to a lesser extent than 17,20-lyase, there was concern that decreased plasma cortisol levels with compensatory elevated ACTH concentrations might result in mineralocorticoid excess. Median ACTH and corticosterone levels were increased but median cortisol remained within the normal range. As discussed above, 17 patients experienced hypertension. Other mineralocorticoid toxicities, such as hypokalemia and peripheral edema, were predominantly low-grade. In addition, examination of androgen or sex hormone–related HRQoL, assessed using the AMS scale, showed no further impact of orteronel on patient-reported outcomes associated with conventional ADT (21, 22). However, as the AMS scale is not validated in this population, these results should be interpreted with caution. There were no clinically significant changes in BMD.

Achievement of PSA $\leq$0.2 ng/mL was chosen as a novel endpoint to assess the antitumor effect, as PSA is the only assessable manifestation of the disease and a marker of response in patients with mCRPC (30, 31). Achieving a PSA level of $\leq$0.2 ng/dL has been associated with a significantly reduced risk of death versus PSA $\geq$4 ng/dL ($P < 0.0001$) in hormone-sensitive prostate cancer (32). This did, however, set a higher bar in a proof-of-concept study such as this. The percentage of patients achieving a decline in PSA to $\leq$0.2 ng/mL at 3 months did not achieve the prespecified statistical parameters of the study [16% (80% exact CI: 9–26) vs. alternative hypothesis rate of 20%]. The totality of the data, including secondary endpoints and the overall rate of PSA decline to $\leq$0.2 ng/mL (32%) at any time post-baseline, suggest that orteronel 300 mg BID directly inhibits the androgen synthesis pathway and is effective at this dose and feasible in the absence of prednisone for most patients with nmCRPC.

Orteronel 400 mg plus prednisone has been evaluated in 2 phase III studies in mCRPC, one in chemotherapy-naïve patients (ELM-PC 4; NCT01193244) and the other in the post-docetaxel setting (ELM-PC 5; NCT01193257). The accompanying prednisone may alleviate increased risk of side effects due to 17α-hydroxylase or nonselective inhibition, which is more likely to occur at higher doses of orteronel. In the recently reported ELM-PC 5 study (28), the orteronel plus prednisone group did not meet the primary endpoint of OS ($P = 0.1898$) despite notable improvement in radiographic PFS ($P = 0.0004$) and $\geq$50% decline in PSA ($P < 0.0001$) as well as an apparent OS benefit in patients outside of North America and Europe ($P = 0.019$). Orteronel 300 mg BID is also being evaluated without steroids in several ongoing phase III studies, including in combination with radiation therapy and a GnRH agonist (NCT01546987).

Disclosure of Potential Conflicts of Interest

M.D. Michaelson is a consultant/advisory board member for Medivation and Millennium. J.J. Alumkal, C.J. Ryan, and D.J. George are consultants/advisory board members for Millennium. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

Employees of Takeda Pharmaceuticals International Co. participated in trial design, data collection, data analysis, data interpretation, and writing of the report. The sponsor of the study was involved in the design of the trial and provided grants to trial sites and had no other involvement in conduct of trial. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Authors' Contributions

Conception and design: M. Hussain
Development of methodology: M. Hussain, H.M. Lin, D.J. George
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Hussain, P.G. Corn, M.D. Michaelson, H.J. Hammers, J.J. Alumkal, C.J. Ryan, J.Y. Bruce, D.J. George
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Hussain, M.D. Michaelson, J.J. Alumkal, C.J. Ryan, S. Moran, S.Y. Lee, H.M. Lin, D.J. George
Writing, review, and/or revision of the manuscript: M. Hussain, P.G. Corn, M.D. Michaelson, J.J. Alumkal, C.J. Ryan, J.Y. Bruce, S. Moran, S.Y. Lee, H.M. Lin, D.J. George

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.Y. Lee
Study supervision: C.J. Ryan, S. Moran

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Maha Hussain, Paul G. Corn, M. Dror Michaelson, et al.

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