Phase I/II Trial of Orteronel (TAK-700)—an Investigational 17,20-Lyase Inhibitor—in Patients with Metastatic Castration-Resistant Prostate Cancer

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Abstract

Purpose: The androgen receptor pathway remains active in men with prostate cancer whose disease has progressed following surgical or medical castration. Orteronel (TAK-700) is an investigational, oral, nonsteroidal, selective, reversible inhibitor of 17,20-lyase, a key enzyme in the production of androgenic hormones.

Experimental Design: We conducted a phase I/II study in men with progressive, chemotherapy-naïve, metastatic castration-resistant prostate cancer, and serum testosterone <50 ng/dL. In the phase I part, patients received orteronel 100 to 600 mg twice daily or 400 mg twice a day plus prednisone 5 mg twice a day. In phase II, patients received orteronel 300 mg twice a day, 400 mg twice a day plus prednisone, 600 mg twice a day plus prednisone, or 600 mg once a day without prednisone.

Results: In phase I (n = 26), no dose-limiting toxicities were observed and 13 of 20 evaluable patients (65%) achieved >50% prostate-specific antigen (PSA) decline from baseline at 12 weeks. In phase II (n = 97), 45 of 84 evaluable patients (54%) achieved a >50% decline in PSA and at 12 weeks, substantial mean reductions from baseline in testosterone (–7.5 ng/dL) and dehydroepiandrosterone-sulfate (–45.3 μg/dL) were observed. Unconfirmed partial responses were reported in 10 of 51 evaluable phase II patients (20%). Decreases in circulating tumor cells were documented. Fifty-three percent of phase II patients experienced grade ≥3 adverse events irrespective of causality; most common were fatigue, hypokalemia, hyperglycemia, and diarrhea.


Introduction

Testosterone suppression through medical or surgical castration has been the standard of care in advanced prostate cancer since the seminal work of Huggins and Hodges (1). Androgen deprivation therapy, while highly effective short term, is not curative with the majority of patients eventually developing disease progression (2).

In CRPC, intraprostatic dihydrotestosterone, and testosterone levels remain sufficiently elevated to activate the androgen receptor despite castrate serum levels with...
Translational Relevance

This phase I/II trial of orteronel tests the concept of selective inhibition of the androgen synthesis pathway combined with continued adrenal cortisol synthesis by targeting the 17,20-lyase activity over the 17α-hydroxylase activity of CYP17A1 in the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) and increased sensitivity to low remaining androgens. Alleviating the effects of early castration resistance can contribute to the development of more effective orteronel-based treatment for mCRPC. In this trial, we conducted dose escalation studies to evaluate the clinical benefits and pharmacokinetics of orteronel. This is the first clinical manuscript to report the safety and efficacy of orteronel. Our findings are currently being validated in ongoing phase III trials in patients with mCRPC.

Evidence for persistent expression of androgen-synthesizing enzymes and ongoing androgen synthesis within prostate tumors collected from castrated patients (3, 4). The most common mechanism of early resistance is androgen receptor upregulation, which increases sensitivity to low remaining androgens (5). These findings have fostered an interest in CYP17A1 inhibition to deplete both intratumoral and extragonadal sources of steroid ligands (6, 7). CYP17A1 is an essential enzyme for biosynthesis/production of steroidal hormones, and has both 17,20-lyase and 17α-hydroxylase activities (8–10). This pathway’s importance in CRPC has been reinforced by positive phase III trials with abiraterone acetate (Zytiga; refs. 11 and 12) and androgen deprivation therapy (ADT; refs. 13 and 14). Androgen deprivation may contribute to the development of more effective orteronel.

Patients and Methods

Patients

Patients were recruited from 11 U.S. centers. The study was conducted in accordance with the Declaration of Helsinki/Good Clinical Practice, Institutional Review Boards approved all aspects of the study, and all participants provided written informed consent. Eligibility included pathologically confirmed prostate adenocarcinoma with radiographically confirmed metastatic disease progression despite castrate levels of testosterone (<50 ng/dL), an Eastern Cooperative Oncology Group performance status of 0 to 2, and prostate-specific antigen (PSA) ≥5 ng/mL. Eligibility also required adequate hematologic, cardiovascular, renal, and hepatic function. Patients also had to be free of significant prostate cancer–related symptoms, including opioid requiring bone pain. Patients could have received amino-glutethimide, ketoconazole, or radiation therapy, but not within 30 days before first dose of study drug.

Study design

Phase I dose escalation followed a standard 3 + 3 schema: patients received open-label single-agent orteronel in 28-day cycles (continuous dosing) at 1 of 5 dose levels: 100, 200, 300, 400, or 600 mg twice a day. An additional cohort also received orteronel 400 mg twice a day plus prednisone 5 mg twice a day.

In phase II, patients received open-label orteronel daily without food restrictions in 28-day cycles in 4 parallel dose cohorts: 300 mg twice a day, 400 mg twice a day plus prednisone 5 mg twice a day, 600 mg twice a day plus prednisone 5 mg twice a day, or 600 mg every day in the morning. These regimens were selected for further exploration based on (i) frequency of PSA responses at doses ≥300 mg twice a day; (ii) the determination that any dose regimen ≥400 mg twice a day would likely benefit from concomitant prednisone administration; and (iii) to test whether administration of 600 mg every day was similarly efficacious to an equal but divided daily dose.

Patients continued to receive orteronel until PSA progression (prostate cancer working group 2 [PCWG2; ref. 15], objective disease progression by Response Evaluation Criteria in Solid Tumors [RECIST; ref. 16], bone scan or investigator opinion, or occurrence of unacceptable toxicity. At investigator assessment and request, patients with PSA progression without new symptoms were allowed to remain on study drug.

The primary objective was to assess safety and tolerability. Secondary objectives included assessment of efficacy, as shown by PSA response and/or objective disease response; assessment of endocrine responses to orteronel [testosterone, dehydroepiandrosterone-sulfate (DHEA-S) and adrenocorticotropic hormone (ACTH)-adrenal axis; pharmacodynamics]; and pharmacokinetics of orteronel. Exploratory objectives included enumeration of circulating tumor cells (CTC).

Assessments

Sampling timepoints are shown in Supplementary Table S1. Adverse events were graded using National Cancer Institute Common Terminology Criteria for adverse events (NCI-CTCAE) v3.0. During phase I, maximum-tolerated dose (MTD) was defined as the dose level immediately below that at which ≥2 of up to 6 patients experienced dose-limiting toxicities (DLT) in cycle 1. DLTs were defined as any drug-related grade ≥3 adverse event or any cardiac-
related adverse event. Documented fatigue events were based on CTC criteria and not a formal patient reported outcome; thus, mechanism of fatigue (central nervous system central vs. neuromuscular) requires additional study. Pharmacokinetic parameters were determined from plasma concentration–time data using standard noncompartmental methods.

Radiologic response was assessed according to modified RECIST v1.0, with nonconfirmation per RECIST v1.1. Bone scan progression was assessed per RECIST rather than per PCWG2 criteria, which came into practice after the initiation of this study. The endocrine and cortisol assays in phases I and II, respectively, were performed at different laboratories using assays with different lower limits of quantification. In phase II and in phase I patients ongoing after the start of phase II, liquid chromatography/mass spectrometry (LC/MS) was used for evaluation of testosterone, DHEA-S, and other steroid hormones, except cortisol. The validated LC/MS testosterone assay was performed by Esoterix Laboratories (LabCorp); between different laboratories, the lower limits of detection varied during the study between 50 and 200 pg/mL (0.05–0.2 ng/dL), and results below 0.2 ng/dL should be interpreted with caution.

CTCs were enumerated using validated Veridex CellSearch methodology (17). CTC counts were assessed as both dichotomous (<5 vs. \geq 5 per 7.5 mL of whole blood) and quantitative variables (18, 19).

Statistical methods

Planned enrolment was up to 123 patients: up to 35 in phase I and 88 (22 per dose group) in phase II to give 20 response-evaluable patients per group. The phase II portion had 80% power to detect a PSA50 response. Phase II patients treated at dose levels also evaluated in the phase II component of the trial were included in the phase II analysis.

Standard summary statistics were used for PSA and endocrine changes over time, as well as for observed values and change from baseline in CTCs. Time to disease progression (duration from the date of first dose until the date of the first documented evidence of progressive disease) was analyzed using Kaplan–Meier methodology.

Results

Patients

Twenty-six patients were enrolled in the phase I portion of the study and, because of slight overenrolment, 97 in the phase II portion. Enrollment commenced on April 2, 2008 and the last patient completed 6 months of treatment on March 15, 2011. Baseline demographics and patient characteristics are shown in Table 1.

Phase I patients received a median of 7 (range 0–36) 28-day treatment cycles. Twenty-two patients (85%) have discontinued therapy because of: adverse events in 8 patients, objective disease progression in 7, PSA progression in 3, voluntary withdrawal in 3, and other reasons in 1. Four patients remain on therapy (1 each at 200, 300, 600 mg twice a day, and 400 mg twice a day plus prednisone) with a maximum duration of 1,030 days’ treatment (>36 cycles).

Phase II patients completed a median of 9 (range 0–22) treatment cycles. At the time of analysis, 37 patients remained on treatment, with a maximum duration of

<table>
<thead>
<tr>
<th>Table 1. Patient demographics and disease characteristics</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>Median age, y (range)</td>
</tr>
<tr>
<td>Race, n (%)</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black/African American</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Native Hawaiian/other Pacific Islander</td>
</tr>
<tr>
<td>Unknown</td>
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<tr>
<td>Median PSA at baseline, ng/mL (range)</td>
</tr>
<tr>
<td>Disease stage at diagnosis, n (%)a</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Prior adrenal-directed therapyb, n (%)</td>
</tr>
</tbody>
</table>

aData missing for 2 patients in the phase II portion.

bAminoglutethimide, abiraterone, ketoconazole.
Table 2. Most common treatment-related adverse events [reported at any grade in \( \geq 20\% \) or at grade \( \geq 3 \) in \( \geq 5\% \) of phase I patients overall (\( n = 26 \)), or reported at any grade in \( \geq 15\% \) or at grade \( \geq 3 \) in \( \geq 5\% \) of phase II patients overall (\( n = 97 \))]

<table>
<thead>
<tr>
<th>Patients with adverse events, n (%)</th>
<th>Orteronel alone (steroid-free)</th>
<th>Orteronel plus prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase I 100–600 mg twice a day (( n = 20 ))</td>
<td>Phase II 300 mg twice a day (( n = 23 ))</td>
</tr>
<tr>
<td>Any drug-related adverse event</td>
<td>Any grade 19 (95)</td>
<td>Grade ( \geq 3 ) 11 (55)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (75)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (45)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (40)</td>
<td>–</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (30)</td>
<td>–</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (20)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>9 (45)</td>
<td>–</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (10)</td>
<td>–</td>
</tr>
<tr>
<td>Hot flush</td>
<td>2 (10)</td>
<td>–</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2 (10)</td>
<td>–</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (30)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>5 (25)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (5)</td>
<td>–</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (30)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>6 (30)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>2 (10)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Any drug-related SAE</td>
<td>4 (20)</td>
<td>–</td>
</tr>
</tbody>
</table>

NOTE: Discontinuations because of drug-related adverse events in phase II were fatigue (\( n = 3 \)), decreased performance status (\( n = 1 \)), diarrhea (\( n = 2 \)), nausea (\( n = 1 \)), [LV]EF dysfunction (\( n = 2 \)), somnolence (\( n = 1 \)), acute renal failure (\( n = 1 \)), dyspnea (\( n = 1 \)), maculopapular rash (\( n = 1 \)), and because of all-cause adverse events were edema (\( n = 1 \)), respiratory arrest (\( n = 1 \)), spinal cord compression (\( n = 1 \)), bacteremia (\( n = 1 \)), supraventricular extrasystoles (\( n = 1 \)), arthralgia (\( n = 1 \)), pain (\( n = 1 \)), meningioma (\( n = 1 \)).

Abbreviation: [LV]EF, left ventricular ejection fraction.
638 days’ treatment in a patient receiving 400 mg twice a day plus prednisone (>22 cycles), as of April 2013, 6 patients are ongoing. Sixty patients (62%) discontinued treatment because of: adverse event (n = 18, of which 11 were considered drug related), objective disease progression (n = 12), voluntary withdrawal (n = 11), and other (n = 1).

Phase I: dose escalation and DLTs
During dose escalation, there were no DLTs and an MTD was not established; however, at 600 mg twice a day, 3 of 5 patients experienced severe non-dose-limiting (grade 3) fatigue. All 3 patients were ages ≥80 years, and consequently, patients ≥80 years were excluded from the 600 mg twice a day plus prednisone cohort in the phase II portion. For phase II, prednisone 5 mg twice a day was added to the 400 or 600 mg twice a day dose regimens. The decision to not further test steroid-free dosing at those levels was based on ACTH and associated endocrine data which indicated increased risk for mineralocorticoid excess, as well as symptoms such as fatigue that may have been associated with (delayed) adrenal adaptation to 17α-hydroxylase inhibition. Other phase II cohorts were 300 mg twice a day (n = 23), 600 mg every day (n = 24), and 400 mg twice a day plus prednisone (n = 24).

Safety
In phase I, all patients experienced ≥1 treatment-emergent adverse event (TEAE) and 96% drug-related TEAEs (Table 2). In phase II, all but 1 patient had a TEAE; most common were fatigue (77%), nausea (47%), constipation (37%), and diarrhea (35%). Grade ≥3 adverse events were experienced by 51 patients (53%); most common were fatigue (12%), hypokalemia (8%), hyperglycemia (5%), and diarrhea (4%). Drug-related adverse events were reported in 97% of patients (Table 2). Two grade 3 hepatic transaminase “investigations” adverse events were reported (per NCI-CTCAE); however, there were no patient discontinuations related to hepatic abnormalities.

Serious adverse events (SAE) were experienced by 8 (31%) and 26 (27%) patients in phases I and 2, respectively, and were drug related in 5 and 7 patients. Drug-related SAEs in phase I were hypertension, nausea, vomiting, deep vein thrombosis (DVT), fatigue, increased amylase, increased lipase, diarrhea, skin infection, and dehydration (each n = 1); in patients receiving orteronel 400 mg twice a day plus prednisone, one drug-related SAE of vomiting was reported. SAEs related to single-agent orteronel in phase II were fatigue (n = 1) and hypertension (n = 1); in patients receiving orteronel plus prednisone, drug-related SAEs of acute renal failure, hypokalemia (each n = 2), pneumonia, decreased hemoglobin, hyperglycemia, hyperkalemia, pain in extremity, sensory neuropathy, and DVT (each n = 1) were reported.

As described above, although significant fatigue occurred in older patients receiving 600 mg twice a day without prednisone, overall there was no overt evidence of clinical ACTH-adrenal insufficiency in the phase I patients receiving steroid-free dose regimens. This is presumably due compensatory ACTH-driven increased levels of mineralocorticoids with intrinsic glucocorticoid activity, predominantly corticosterone.

There were 3 on-study deaths all in the phase II portion; all deaths were considered unrelated to study drug: cardiac-related events (n = 2, 600 mg every day) and infection (400 mg twice a day plus prednisone).
Pharmacokinetics

Mean orteronel plasma concentrations in cycle 1, day 8 (phase I) following the morning dose are shown in Fig. 1. Pharmacokinetic analysis indicates dose-related increases in single- and multiple-dose $C_{\text{max}}$ and $AUC_{0-8}$, over the 100 to 600 mg twice a day dose range. Fasting at the time of dosing was not required.

Endocrine pharmacodynamics

Pharmacodynamic analysis in phase I patients showed androgen suppression. DHEA-S levels decreased to below quantifiable levels (assays sensitive to 15 mg/dL) in all patients receiving orteronel $\geq 300$ mg twice a day. Testosterone levels decreased to $<10$ ng/dL in all patients receiving orteronel $\geq 300$ mg twice a day (local laboratory assays sensitive to 10 ng/dL).

In phase II, androgen suppression occurred by cycle 1, day 15, and responses were maximal by cycle 2, day 1. At 12 weeks, substantial mean reductions in testosterone [$-7.5$ ng/dL (SD = 3.14)] and DHEA-S [$-45.3$ µg/dL (SD: 40.26)] were observed from baseline (Fig. 2). At 12 weeks, 46% of patients (45 of 97) achieved testosterone $<1$ ng/dL and 54% and 32% of patients had DHEA-S levels $<10$ µg/dL or $<1$ µg/dL, respectively. The most profound reductions occurred in the 400 mg and 600 mg twice a day plus prednisone dose groups.

For phase II, the ACTH-adrenal axis was evaluated using measurements of ACTH, cortisol, and corticosterone. The normal range for ACTH is 9 to 52 pg/mL (20) and in patients receiving orteronel 400 mg and 600 mg twice a day plus prednisone, the ACTH-adrenal axis was effectively suppressed, with ACTH and cortisol levels reduced relative to baseline (Fig. 2). In the 300 mg twice a day dose group, mean ACTH levels increased post baseline combined with modest decreases in cortisol (baseline: 11–15 µg/dL; cycle 4: 3–10 µg/dL) and increased corticosterone.

Clinical response

In phase I, orteronel $\geq 300$ mg was associated with decreases in PSA levels. Overall, 13 of 20 evaluable patients (65%) had $\geq50\%$ decreases in PSA at 12 weeks.

At 12 weeks, PSA was evaluable in 84 phase II patients (Fig. 3A). Forty-five of 84 evaluable patients (54%) had $\geq50\%$ decline in PSA from baseline and 18 (21%) had $\geq90\%$ decline in PSA. At 24 weeks, a $\geq50\%$ decrease in PSA occurred in 37 of 59 evaluable patients (63%) and 17 (29%) of the 59 evaluable patients who remained on study treatment had $\geq90\%$ decline in PSA (Fig. 3B). Time to PSA progression is shown in Fig. 3C; the Kaplan–Meier estimated median was $>225$ days in all 4 dose groups.
Prior adrenal-directed therapy (predominantly ketoconazole; abiraterone acetate in 4 patients) seemed to be associated with a lower likelihood of obtaining a ≥50% decrease in PSA at 12 weeks, with only 12 of 33 patients (36%) with prior adrenal-directed therapy reaching this threshold, compared with 46 of 71 (65%) who had not received prior adrenal-directed therapy.

Fifty-one of 97 phase II patients (53%) had RECIST-evaluable radiographic lesions. Unconfirmed RECIST partial responses were observed in 10 of 51 evaluable patients (20%; Table 3), and 21 (41%) had stable disease.
Radiographic disease progression was reported in 16 patients.

CTC analyses

At baseline, the mean overall CTC count was 16.6/7.5 mL whole blood (SD = 33.2) among 88 evaluable patients. By 12 weeks, mean overall CTC counts had decreased to 3.9/7.5 mL (SD = 11.2) and the mean change in CTCs (baseline to week 12) was –76.5%.

Of 63 patients with evaluable CTC counts at both baseline and 12 weeks, 14 (22%) converted to a favorable CTC count and 36 (57%) retained a CTC count of <5 at 12 weeks.

Discussion

Findings of this clinical study demonstrate for the first time that selective inhibition of 17,20-lyase with orteronel with/without prednisone, and given without food requirement, results in PSA and radiographic responses with declines in CTCs in men with mCRPC. Pharmacokinetic data demonstrate a dose-dependent relationship that is stable over time. Although the study was not powered to compare doses, the 2 higher phase II doses with prednisone were most effective in lowering testosterone and DHEA-S levels. ACTH and corticosterone levels were modestly increased in the steroid-free regimens while relatively suppressed in the prednisone-supplemented groups. A more detailed analysis of the orteronel endocrine profile has been reported (21).

Orteronel was generally well tolerated with adverse events that were predictable based upon the proposed mechanism of action and co-administration with prednisone; the median orteronel treatment duration of 7 to 9 months is consistent with the overall pattern of maintained disease stability combined with adequate toleration. Grade ≥3 adverse events were experienced by 31 phase II patients (53%); most common were fatigue, hypokalemia, diarrhea, and hyperglycemia. No DLTs were observed during phase I. However, severe fatigue (grade 3) occurred in 3 older patients treated with 600 mg twice a day without prednisone. Isolated events of prolonged QT-interval were reported, but there was no relationship to orteronel dose or concentrations and overall across groups there were no directional changes in any ECG interval parameters. The absence of a dose response for the observed common adverse events in this study makes it difficult to judge their specific relationship to orteronel administration.

The phase I dose escalation data, combined with the phase II endocrine data, measured using more sensitive assays, together support that orteronel has selectivity for 17,20-lyase versus 17α-hydroxylase. At 300 mg twice a day, orteronel reduced testosterone concentrations by >90% in most patients, without clinically relevant inhibition of the ACTH-cortisol axis. At higher doses, some evidence of 17α-hydroxylase inhibition was apparent. In phase I, however, it is not clear whether the severe fatigue observed in patients >80 years receiving 600 mg twice a day was because of delayed adaptation to 17α-hydroxylase inhibition or rather the effects of acute more profound androgen withdrawal. Less fatigue was noted in subsequent patients receiving either 400 mg or 600 mg twice a day plus prednisone co-administration. However, there is no compelling evidence to support the exclusion of men ≥80 years from therapy with orteronel.

Based on the overall phase I and phase II results, 400 mg twice a day plus prednisone 5 mg twice a day was the dose regimen taken forward for phase III evaluation in both patients with chemotherapy-naïve (NCT01193244) and post-docetaxel (NCT01193257) mCRPC. Furthermore, as prednisone is known to have antitumor activity (22), it was thought that the addition of prednisone might further the benefit of orteronel for men with mCRPC.

Phase III patients who received total doses of 600 mg daily (300 mg twice a day or 600 mg every day) did not receive concomitant prednisone. Patients receiving this steroid-free regimen had similar PSA responses and radiographic stability versus those on the higher-dose regimens. The incidence of hypokalemia and hypertension was modestly increased in these 2 groups relative to 400 mg twice a day plus prednisone, but overall, the steroid-free regimens were well tolerated and did not have higher discontinuation rates. The favorable

### Table 3. Objective disease response by RECIST (phase IIa)

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Orteronel alone (steroid-free)</th>
<th>Orteronel plus prednisone</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>300 mg twice a day</td>
<td>600 mg every day</td>
</tr>
<tr>
<td>Best response by RECIST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluable patients</td>
<td>n = 12</td>
<td>n = 12</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>4 (33)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>SD</td>
<td>4 (33)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>PR or SD</td>
<td>8 (67)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4 (33)</td>
<td>4 (33)</td>
</tr>
</tbody>
</table>

Abbreviations: PR, partial response; SD, stable disease.

*Phase I patients treated at the same dose levels as phase II are included in this analysis.
results in patients receiving orteronel doses of 600 mg daily suggest that this agent may allow for effective androgen synthesis inhibition without glucocorticoid supplementation. This could be of particular benefit in patients receiving orteronel for prolonged periods or in those at increased risk from the effects of prednisone administration because of comorbidities such as diabetes or bone loss. The steroid-free regimen of orteronel 300 mg twice a day is undergoing further evaluation in patients with progressive (rising PSA) non-mCRPC (M0; ref. 23), as well as phase III studies in earlier stages of disease (NCT01546987, NCT01707966, and NCT01809691).

During the past decade, significant progress in understanding the biology of the androgen receptor has been translated into clinically relevant therapeutic developments. Two recently approved agents—the steroidal CYP17A1 inhibitor abiraterone acetate and the androgen receptor inhibitor enzalutamide—have both demonstrated survival benefits over placebo in patients with mCRPC post-docetaxel [14.8 months vs. 10.9 months (11) and 18.4 months vs. 13.6 months (24), respectively]. In this new, era of more intensive androgen synthesis inhibitors and androgen receptor–directed therapies, the optimal timing, sequencing, pharmacoeconomics, ease of administration, and therapy-related toxicity (e.g., effects or requirement for co-administered steroids and the timing of any subsequent chemotherapy) will likely drive decision making in this clinical setting.

**Disclosure of Potential Conflicts of Interest**

R. Dreicer is a consultant/advisory board member of Millennium, Endo Pharmaceuticals, Janssen, Dendreon, and Medivation. A. Suri is Director of Clinical Pharmacology in Takeda. W.M. Stadler has a commercial research grant from Takeda. G.R. MacVicar has Honoraria from Speakers Bureau of Janssen Pharmaceuticals and also is a consultant/advisory board member of Medivation. O. Hamid has other commercial research support from Takeda—To The Angeles Clinic and Research Institute funding. Y. Shi is Director of Takeda Boston. D.B. Agus is a consultant/advisory board member of Takeda Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

**References**


**Disclaimer**

Employees of Takeda Pharmaceuticals International Company 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: R. Dreicer, D. MacLean, A. Suri, D.B. Agus

Development of methodology: D. MacLean, A. Suri, D.B. Agus

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R. Dreicer, D. MacLean, W.M. Stadler, D. Shevrin, L. Hart, G.R. MacVicar, O. Hamid, M.E. Gross, D.B. Agus


Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Shi


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