Phase 1/2 Trial of Orteronel (TAK-700) – an Investigational 17,20-Lyase Inhibitor – in Patients with Metastatic Castration-Resistant Prostate Cancer

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**References:** 24 (limit 50)

**Supplemental materials:** 1 Table
Prior presentations of this study:


Role of the funding source

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.
Statement of Translational Relevance

This phase 1/2 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.
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, non-steroidal, selective, reversible inhibitor of 17,20-lyase, a key enzyme in the production of androgenic hormones.

Experimental Design: We conducted a phase 1/2 study in men with progressive, chemotherapy-naïve, metastatic castration-resistant prostate cancer (mCRPC) and serum testosterone <50 ng/dL. In the phase 1 part, patients received orteronel 100–600 mg twice-daily (BID) or 400 mg BID plus prednisone 5 mg BID. In phase 2, patients received orteronel 300 mg BID, 400 mg BID plus prednisone, 600 mg BID plus prednisone or 600 mg once-daily without prednisone.

Results: In phase 1 (n = 26), no dose-limiting toxicities were observed and 13/20 evaluable patients (65%) achieved ≥50% prostate-specific antigen (PSA) decline from baseline at 12 weeks. In phase 2 (n = 97), 45/84 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 (DHEA-S; –45.3 μg/dL) were observed. Unconfirmed partial responses were reported in 10/51 evaluable phase 2 patients (20%). Decreases in circulating tumor cells were documented. Fifty-three percent of phase 2 patients experienced grade ≥3 adverse events irrespective of causality; most common were fatigue, hypokalemia, hyperglycemia, and diarrhea.

Conclusions: 17,20-lyase inhibition by orteronel was tolerable and results in declines in PSA and testosterone, with evidence of radiographic responses.

Category: Clinical Trials

ClinicalTrials.gov identifier: NCT00569153
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 (AR) despite castrate serum levels with evidence for persistent expression of androgen-synthesising enzymes and ongoing androgen synthesis within prostate tumors collected from castrated patients (3, 4). The most common mechanism of early resistance is AR upregulation, which increases sensitivity to low remaining androgens (5). These findings have fostered an interest in CYP17A1 inhibition to deplete both intra-tumoral 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-3 trials with abiraterone acetate (Zytiga®) (11, 12) and AR antagonist enzalutamide (Xtandi®) (13). Both agents have demonstrated increased overall survival in patients with advanced mCRPC previously treated with docetaxel (11, 13).

Orteronel (TAK-700) is a non-steroidal, selective, reversible inhibitor of 17,20-lyase. Five-fold selectivity of orteronel for 17,20-lyase activity over 17α-hydroxylase activity of CYP17A1 has been demonstrated in preclinical studies (14). Orteronel may therefore result in near full inhibition of androgen synthesis with only partial inhibition of 17α-hydroxylase activity, allowing adrenal cortisol synthesis to continue – an important consideration as inhibition thereof can lead to mineralocorticoid excess. Preclinical data show that orteronel reduces and maintains low testosterone levels (14). This is the first clinical report to characterize the safety and efficacy of orteronel, based on findings from the phase 1/2 study.
in men with chemotherapy-naïve mCRPC.

Methods

Patients

Patients were recruited from 11 US 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 0–2, 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 aminoglutethimide, ketoconazole, or radiation therapy, but not within 30 days prior to first dose of study drug.

Study design

Phase 1 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-daily (BID). An additional cohort also received orteronel 400 mg BID plus prednisone 5 mg BID.

In phase 2, patients received open-label orteronel daily without food restrictions in 28-day cycles in four parallel dose cohorts: 300 mg BID, 400 mg BID plus prednisone 5 mg BID, 600 mg BID plus prednisone 5 mg BID, or 600 mg once-daily (QD) in the morning. These regimens were selected for further exploration based on 1) frequency of PSA responses at doses ≥300 mg BID; 2) the determination that any dose regimen ≥400 mg BID
would likely benefit from concomitant prednisone administration; and 3) to test whether administration of 600 mg QD was similarly efficacious to an equal but divided daily dose.

Patients continued to receive orteronel until PSA progression (prostate cancer working group 2 [PCWG2](15)), objective disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) (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 (CTCs).

Assessments

Sampling timepoints are shown in Supplemental Table 1. Adverse events (AEs) were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0. During phase 1, 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 (DLTs) in cycle 1. DLTs were defined as any drug-related grade ≥3 AE or any cardiac-related AE. Documented fatigue events were based on CTC criteria and not a formal patient reported outcome; thus, mechanism of fatigue (CNS 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 non-confirmation 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 1 and 2, respectively, were performed at different laboratories using assays with different lower limits of quantification. In phase 2 and in phase 1 patients ongoing after the start of phase 2, 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. ≥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 1 and 88 (22 per dose group) in phase 2 to give 20 response-evaluable patients per group. The phase 2 portion had 85% power and a one-sided significance of 0.05 for each BID dose group to detect a 50% PSA response (PSA50) rate at 12 weeks versus 20% for null hypothesis. The 600 mg QD group, added later to evaluate potential differences versus 300 mg BID, had 80% power to detect a PSA50 response. Phase-1 patients treated at dose levels also evaluated in the phase 2 component of the trial were included in the phase-2 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 1 portion of the study and, due to
slight over-enrolment, 97 in the phase 2 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 1 patients received a median of 7 (range 0–36) 28-day treatment cycles. 22
patients (85%) have discontinued therapy due to: AEs 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 BID, and 400 mg BID plus
prednisone) with a maximum duration of 1030 days’ treatment (>36 cycles). Phase-2
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 638 days’ treatment in a patient
receiving 400 mg BID plus prednisone (>22 cycles); as of April, 2013, 6 patients are
ongoing. Sixty patients (62%) discontinued treatment due to: AE (n = 18, of which 11 were
considered drug-related), objective disease progression (n = 18), PSA progression (n = 12),
voluntary withdrawal (n = 11), and other (n = 1).

Phase 1: Dose escalation and DLTs

During dose escalation, there were no DLTs and an MTD was not established;
however, at 600 mg BID, 3 of 5 patients experienced severe non-dose limiting (grade 3)
fatigue. All 3 patients were aged ≥80 years, and consequently, patients ≥80 years were
excluded from the 600 mg BID plus prednisone cohort in the phase 2 portion. For phase 2,
prednisone 5 mg BID was added to the 400 mg BID or 600 mg BID 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 2 cohorts were 300 mg BID (n = 23), 600 mg QD (n = 24), and 400 mg BID plus prednisone (n = 24).

Safety

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

Serious AEs (SAEs) were experienced by 8 (31%) and 26 (27%) patients in phases 1 and 2, respectively, and were drug-related in 5 and 7 patients. Drug-related SAEs in phase 1 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 BID plus prednisone, one drug-related SAE of vomiting was reported. SAEs related to single-agent orteronel in phase 2 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, while significant fatigue occurred in older patients receiving 600 mg BID without prednisone, overall there was no overt evidence of clinical ACTH-adrenal insufficiency in the phase 1 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 2 portion; all deaths were considered unrelated to study drug: cardiac-related events ($n = 2$, 600 mg QD) and infection (400 mg BID plus prednisone).

**Pharmacokinetics**

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

**Endocrine pharmacodynamics**

Pharmacodynamic analysis in phase-1 patients showed androgen suppression. DHEA-S levels decreased to below quantifiable levels (assays sensitive to 15 μg/dL) in all patients receiving orteronel ≥300 mg BID. Testosterone levels decreased to <10 ng/dL in all patients receiving orteronel ≥300 mg BID (local laboratory assays sensitive to 10 ng/dL).

In phase 2, 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 [standard deviation {SD}: 5.14]) 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 BID plus prednisone dose groups.

For phase 2, the ACTH-adrenal axis was evaluated using measurements of ACTH, cortisol, and corticosterone. The normal range for ACTH is 9–52 pg/mL (20) and in patients receiving orteronel 400 mg and 600 mg BID plus prednisone, the ACTH-adrenal axis was effectively suppressed, with ACTH and cortisol levels reduced relative to baseline (Fig. 2). In the 300 mg BID 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 1, orteronel ≥300 mg was associated with decreases in PSA levels. Overall, 13 of 20 evaluable patients (65%) had ≥50% decreases in PSA at 12 weeks.

At 12 weeks, PSA was evaluable in 84 phase-2 patients (Fig. 3A). Forty-five of 84 evaluable patients (54%) had ≥50% decline in PSA from baseline and 18 (21%) had ≥90% decline in PSA. At 24 weeks, a ≥50% 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 ≥90% 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) appeared to be associated with a lower likelihood of a 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-2 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 fallen 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 two higher phase 2 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 AEs that were predictable based upon the proposed mechanism of action and co-administration with prednisone; the median orteronel
Phase 1/2 trial of 17,20-lyase inhibitor orteronel in mCRPC

treatment duration of 7–9 months is consistent with the overall pattern of maintained disease stability combined with adequate toleration. Grade ≥3 AEs were experienced by 51 phase-2 patients (53%); most common were fatigue, hypokalemia, diarrhea, and hyperglycemia. No DLTs were observed during phase 1. However, severe fatigue (grade 3) occurred in 3 older patients treated with 600 mg BID 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 AEs in this study makes it difficult to judge their specific relationship to orteronel administration.

The phase 1 dose escalation data, combined with the phase 2 endocrine data, measured using more sensitive assays, together support that orteronel has selectivity for 17,20-lyase versus 17α-hydroxylase. At 300 mg BID, 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 1, however, it is not clear whether the severe fatigue observed in patients ≥80 years receiving 600 mg BID was due to 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 BID or 600 mg BID 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 1 and phase 2 results, 400 mg BID plus prednisone 5 mg BID was the dose regimen taken forward for phase 3 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 1/2 trial of 17,20-lyase inhibitor orteronel in mCRPC

Phase-2 patients who received total doses of 600 mg daily (300 mg BID or 600 mg QD) 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 two groups relative to 400 mg BID plus prednisone, but overall, the steroid-free regimens were well tolerated and did not have higher discontinuation rates. The favorable 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 due to comorbidities such as diabetes or bone loss. The steroid-free regimen of orteronel 300 mg BID is undergoing further evaluation in patients with progressive (rising PSA) non-mCRPC (M0) (23), as well as phase 3 studies in earlier stages of disease (NCT01546987, NCT01707966, NCT01809691).

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

RD, DBM, YS, IA, and DBA contributed to the conception and design of the study. RD, DS, OH, JH, MEG, and DBA contributed to the provision of study materials, patient recruitment, or acquisition of data. RD, AS, WMS, LH, GRM, OH, YS, and DBA participated in the collection and assembly of data. RD, DBM, AS, WMS, LH, GRM, OH, JH, MEG, YS, IA, and DBA participated in the data analysis and interpretation. All authors participated in the draft of the manuscript, revised it critically, and gave final approval to submit for publication.

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Phase 1/2 trial of 17,20-lyase inhibitor orteronel in mCRPC


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### Tables

**Table 1. Patient demographics and disease characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phase 1 (N = 26)</th>
<th>Phase 2 (N = 97)</th>
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<td>Median age, years (range)</td>
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<td>Disease stage at diagnosis, n (%)</td>
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<td>Prior adrenal-directed therapy†, n (%)</td>
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<td>29 (30)</td>
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Abbreviation: PSA, prostate-specific antigen.

†Data missing for 2 patients in the phase 2 portion.

†Aminoglutethimide, abiraterone, ketoconazole.
Table 2. Most common treatment-related AEs (Reported at any grade in $\geq 20\%$ or at grade $\geq 3$ in $\geq 5\%$ of phase 1 patients overall [$n = 26$], or reported at any grade in $\geq 15\%$ or at grade $\geq 3$ in $\geq 5\%$ of phase 2 patients overall [$n = 97$])

<table>
<thead>
<tr>
<th>Patients with AEs, $n$ (%)</th>
<th>Orteron alone (steroid-free)</th>
<th>Orteron plus prednisone</th>
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<tr>
<td></td>
<td>Phase 1 100–600 mg BID ($n = 20$)</td>
<td>Phase 2 300 mg BID ($n = 23$)</td>
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<tr>
<td></td>
<td>Any grade</td>
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<td>Any drug-related AE</td>
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<td>Fatigue</td>
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<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>

Abbreviations: AEs, adverse events; BID, twice-daily; [LV]EF, left ventricular ejection fraction; QD, once-daily; SAE, serious AEs.

Discontinuations due to drug-related AEs in phase 2 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 due to all-cause AEs were edema ($n = 1$), respiratory arrest ($n = 1$), spinal cord compression ($n = 1$), bacteraemia ($n = 1$), supraventricular extrasystoles ($n = 1$), arthralgia ($n = 1$), pain ($n = 1$), meningioma ($n = 1$).
Table 3. Objective disease response by RECIST (phase 2*)

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Orteronel alone (steroid-free)</th>
<th>Orteronel plus prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300 mg BID</td>
<td>600 mg BID</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: BID, twice-daily; PR, partial response; QD, once-daily; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.
*Phase 1 patients treated at the same dose levels as phase 2 are included in this analysis.
**Figure Legends**

**Figure 1.** Mean plasma orteronel concentrations (phase 1) following the morning dose of orteronel on day 8 of cycle 1

Abbreviation: BID, twice-daily.

**Figure 2.** Effect of orteronel on A, testosterone, B, DHEA-S, C, ACTH, and D, corticosterone levels (phase 2)

Abbreviations: ACTH, adrenocorticotropic hormone; BID, twice-daily; DHEA-S, dehydroepiandrosterone-sulfate; QD, once-daily.

**Figure 3.** Percent change in PSA at A, 12 weeks, and B, 24 weeks by dose group and prior ketoconazole therapy (phase 2), and C, phase 2 Kaplan-Meier plot for time to PSA progression

Abbreviations: BID, twice-daily; PSA, prostate-specific antigen; QD, once-daily
Figure 1

Graph showing the concentration of Orteronel (ng/mL) over time (hour) for different doses of BID (600 mg BID, 400 mg BID, 400 mg BID plus prednisone, 300 mg BID, 200 mg BID, 100 mg BID).
Clinical Cancer Research

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Robert Dreicer, David MacLean, Ajit Suri, et al.

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