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Phase 1/2 study of orteronel (TAK-700), an investigational 17,20-lyase inhibitor, with docetaxel–prednisone in metastatic castration-resistant prostate cancer

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Summary

Background—Docetaxel–prednisone (DP) is an approved therapy for metastatic castration-resistant prostate cancer (mCRPC). Orteronel (TAK-700) is an investigational, selective, non-steroidal inhibitor of 17,20-lyase, a key enzyme in androgenic hormone production. This phase 1/2 study evaluated orteronel plus DP in mCRPC patients.

Methods—Adult men with chemotherapy-naïve mCRPC, serum prostate-specific antigen (PSA) 5 ng/mL, and serum testosterone <50 ng/dL received oral orteronel 200 or 400 mg twice-daily (BID) in phase 1 to determine the recommended dose for phase 2, plus intravenous docetaxel 75 mg/m² every 3 weeks, and oral prednisone 5 mg BID. Phase 2 objectives included safety, pharmacokinetics, and efficacy.

Results—In phase 1 ($n=6$, orteronel 200 mg; $n=8$, orteronel 400 mg), there was one dose-limiting toxicity of grade 3 febrile neutropenia at 400 mg BID. This dose was evaluated further in phase 2 ($n=23$). After 4 cycles, 68, 59, and 23 % of patients achieved 30, 50, and 90 % PSA reductions, respectively; median best PSA response was –77 %. Seven of 10 (70 %) RECIST-evaluable patients achieved objective partial responses. Median time to PSA progression and radio-graphic disease progression was 6.7 and 12.9 months, respectively.

Dehydroepiandrosterone-sulfate (DHEA-S) and testosterone levels were rapidly and durably reduced. Common adverse events were fatigue (78 %), alopecia (61 %), diarrhea (48 %), nausea (43 %), dysgeusia (39 %), and neutropenia (39 %). Orteronel and docetaxel pharmacokinetics were similar alone and in combination.

Conclusions—Orteronel plus DP was tolerable, with substantial reductions in PSA, DHEA-S, and testosterone levels, and evidence for measurable disease responses.

Keywords

Genitourinary cancers; Prostate cancer; Phase 1/2 clinical trial; Orteronel; Docetaxel; Prednisone

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) remains a considerable therapeutic challenge [1, 2]. Since 2004, docetaxel-based therapy has been the cornerstone of treatment for mCRPC based on the survival benefit demonstrated in two landmark phase 3 studies (SWOG 9916 [3] and TAX327 [4]). Docetaxel plus prednisone (DP) is currently an approved therapy in this indication in the USA [5]; however, clinical benefit with this regimen remains modest [1]. The median survival of patients with mCRPC treated with docetaxel-based therapy is typically less than 2 years [1, 6], and more effective treatments are needed.

One of the most common mechanisms of early resistance in CRPC is an upregulation of the androgen receptor (AR), which confers sensitivity to low levels of circulating androgens that persist post-castration [7, 8]. Recent research efforts in prostate cancer treatment have focused on inhibiting this pathway, for example, by impairing signalling through AR blockade or inhibiting the activity of CYP17A1, an essential enzyme involved in the biosynthesis/production of steroidal hormones [9, 10], that has both 17,20-lyase and 17 α -hydroxylase activities [9–11]. Recently developed treatments for advanced prostate cancer include abiraterone acetate (Zytiga®) [12], an inhibitor of both the 17,20-lyase and 17 α -hydroxylase activities of CYP17A1, and enzalutamide (Xtandi®; MDV3100) [13], a novel AR inhibitor. Phase 3 trials with these agents have demonstrated improvements in overall survival (OS) in patients with progressive mCRPC with or without prior docetaxel-based therapy [14–17].

Orteronel (TAK-700) is an investigational, non-steroidal, selective inhibitor of 17,20-lyase that suppresses the conversion of gonadal, adrenal, and tumoral androgen precursors to androgens. It is possible that orteronel-mediated intracellular depletion of testosterone together with inhibition of AR translocation by another agent such as docetaxel [18] may provide synergistic or additive effects on impeding prostate cancer growth. The combination of orteronel plus DP may, therefore, offer a rational approach to treating patients with progressive CRPC, as each drug targets a different and potentially complementary mechanism [19].

During the conduct of the present study, a phase 1/2 trial (NCT00569153) in patients with chemotherapy-naïve mCRPC reported encouraging activity with orteronel±prednisone; 45 of 84 (54 %) evaluable patients had prostate-specific antigen (PSA)-50 responses (50 % PSA decrease from baseline), and 10 of 51 (20 %) patients evaluable per Response Evaluation Criteria in Solid Tumors (RECIST) had partial responses (PRs) [20]. Here we report results from an open-label, multicenter, phase 1/2 study that assessed the safety, efficacy, and pharmacokinetics (PK) of orteronel in combination with DP in men with chemotherapy-naïve mCRPC (NCT01084655).

Patients and methods

Study design

This US-based, open-label, multicenter, phase 1/2 study was designed to assess the safety and PK of, and allow estimation of the response to, oral orteronel in combination with DP in men with mCRPC. Using a modified 3+3 dose-escalation design in phase 1, the recommended phase 2 dose (RP2D) of orteronel in combination with DP was determined, and this orteronel dose was further evaluated in the phase 2 expansion of the study. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional review boards approved all aspects of the study and all participants provided written informed consent.

Patients

Patients were men aged ≥ 18 years. Key inclusion criteria were: histologically or cytologically confirmed diagnosis of mCRPC; no prior chemotherapy, with the exception of neoadjuvant/adjuvant therapy completed ≥ 2 years prior to screening; progressive disease (PD) defined by rising PSA values and/or radiographically documented progression of metastatic disease; serum PSA level ≥ 5 ng/mL; Eastern Co-operative Oncology Group (ECOG) performance status 0–2; surgical or ongoing medical castration, with serum testosterone levels <50 ng/dL; adequate bone marrow function (defined by an absolute neutrophil count [ANC] of ≥ 1500 cells/mm³ and platelet count of $\geq 100,000$ cells/mm³); adequate liver function (total bilirubin, alanine aminotransferase [ALT], and aspartate aminotransferase [AST] $\leq 1.5 \times$ the upper limit of normal); and adequate renal function (estimated creatinine clearance of >50 mL/min based on Cockcroft-Gault calculated clearance). Exclusion criteria included: prior therapy with orteronel, aminoglutethimide, ketoconazole, or abiraterone; receipt of anti-androgen therapy within the previous 4 weeks (flutamide) or previous 6 weeks (all others); or radiation therapy for prostate cancer within 30 days prior to enrollment.

Objectives

The primary objective of the phase 1 part of the study was to determine the maximum dose of orteronel between 200 and 400 mg twice-daily (BID) that could be safely administered in combination with standard doses of DP.

The primary objectives of phase 2 were: to further confirm the tolerability of the orteronel dose identified in phase 1 when administered in combination with DP; to estimate PSA response rates (PSA declines from baseline of ≥ 30 % [PSA-30], ≥ 50 % [PSA-50], and ≥ 90 % [PSA-90]) at 12 weeks (after 4 treatment cycles), and best PSA response at any time during treatment compared with baseline; and to characterize the PK of orteronel and docetaxel alone, and in combination. Secondary objectives were: to assess time to PSA progression and time to radiographic disease progression; to measure disease response according to RECIST v1.1 [21]; and to measure changes in the number of circulating tumor cells (CTC).

Treatment schedules

In cycle 1 (28 days in length) of phase 1, patients received orteronel 200 or 400 mg orally (PO) BID without regard to food intake on days 1–28, docetaxel 75 mg/m² intravenously (IV) on day 8, and prednisone 5 mg PO BID on days 8–28. From cycle 2 onwards, cycles were 21 days in length, and the first dose of each of the three study drugs (doses per the above) was administered on day 1. Dose escalation from orteronel 200 mg BID proceeded in a standard 3+3 design based on the occurrence of dose-limiting toxicities (DLTs) during cycle 1.

In the phase 2 part of the study, cycles were 21 days in length. Patients received docetaxel 75 mg/m² IV on day 1 of each cycle, prednisone 5 mg PO BID from day 1 of cycle 1 onwards, and orteronel PO BID at the RP2D defined in phase 1 from day 15 of cycle 1 onwards.

Patients continued treatment until radiographic disease progression, unacceptable treatment-related toxicity, or death. With the exception of patients who developed docetaxel intolerance, patients received a minimum of 6 cycles of docetaxel treatment. Patients achieving stable disease (SD) or better could continue with single-agent orteronel and prednisone. In both phase 1 and phase 2, post-docetaxel cycles were 28 days in length.

Assessments

Safety—Adverse events (AEs) were monitored throughout the study and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03 [22]. DLTs in phase 1 were defined as any of the following events that were possibly related to orteronel: grade 4 neutropenia (ANC <500 cells/mm³) lasting >7 consecutive days; grade 3 neutropenia with fever; grade 4 thrombocytopenia lasting >7 consecutive days; a platelet count of <10,000/mm³ at any time; grade 3 thrombocytopenia with clinically significant bleeding; grade 3 nausea and/or vomiting despite the use of anti-emetic prophylaxis; grade 3 diarrhea despite maximal supportive therapy; grade 3 fatigue lasting >7 consecutive days; other hematologic or non-hematologic toxicities that resulted in orteronel treatment hold, if the event persisted for ≥7 consecutive days during treatment hold or resulted in a delay of the next scheduled dose by >7 days. The RP2D was defined as the higher of the two orteronel doses tested (200 or 400 mg) at which ≥1 of the first 6 treated patients experienced DLTs during cycle 1.

PSA response and progression—In phase 2, blood samples for measurement of serum PSA levels were collected at the screening visit, within 3 days prior to the beginning (day 1) of each treatment cycle, at the end-of-treatment (EOT) and end-of-study visits, and at follow-up visits for patients who discontinued study treatment prior to progressive disease. All PSA measurements were performed at a central laboratory. For the primary phase 2 efficacy endpoints, PSA response was determined by measuring declines in serum PSA levels of ≥30, ≥50, and ≥90 %, (PSA-30, PSA-50, and PSA-90, respectively), and patients' best PSA response during treatment was also determined. For the secondary phase 2 efficacy endpoint of time to PSA progression, progression was defined as a ≥25 % increase over the baseline level and a ≥2 ng/mL increase in absolute PSA concentration for those patients

whose PSA concentration did not decline before the end of cycle 4, and a 25 % increase over the nadir and a 2 ng/mL increase in absolute PSA concentration for those patients with an initial PSA decline.

Tumor response and progression—Radiographic disease progression was defined as the presence of PD according to RECIST v1.1 criteria [21] and/or bone scan progression determined according to Prostate Cancer Clinical Trials Working Group 2 bone scan criteria [23]. If PD by RECIST v1.1 was observed at the time of the first on-treatment assessment, a confirmatory assessment was required 6 weeks later. Bone scan progression required the appearance of 2 new lesions. If two new lesions were observed at the time of the first on-treatment assessment, a confirmatory bone scan performed 6 weeks later must have demonstrated 2 additional new lesions to confirm PD. Measurable disease response by RECIST v1.1 was performed in the RECIST-evaluable population and classified as complete response (CR), PR, SD, or PD.

Endocrine response—Blood samples for central laboratory measurement of serum dehydroepiandrosterone-sulphate (DHEA-S) and testosterone were collected during the phase 2 part of the study at screening, on day 2 of cycle 1, on day 1 of cycles 2–5, within 3 days prior to the day 1 of every 4 cycles thereafter, and at the EOT visit. Ultra low level quantification of DHEA-S and ultra-sensitive detection of testosterone were achieved using liquid chromatography–mass spectrometry. The lower limits of detection for DHEA-S and testosterone were 0.1 and 0.2 ng/dL, respectively. Values for assays below the limit of detection were recorded at the lower limit of detection.

Enumeration of CTCs—During phase 2, blood samples for enumeration of CTCs were collected within 3 days of the beginning (day 1) of cycles 1, 2, and 5, and every 4 cycles thereafter, and at the EOT visit. CTCs were enumerated using validated Veridex CellSearch® methodology [24] and counts were assessed as both dichotomous (<5 versus 5 per 7.5 mL of whole blood) and quantitative variables.

Determination of orteronel and docetaxel PK—Orteronel and docetaxel PK were characterized alone and in combination during the phase 2 part of the study. In cycle 1, the PK of docetaxel alone was evaluated in the first 11 patients enrolled and the PK of orteronel alone was evaluated in the next 11 patients enrolled. Samples for docetaxel PK were collected on day 1 of cycle 1 within 1 h before initiation of, and at the end of, the docetaxel infusion, and then at 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h post-infusion. Blood samples for assessment of orteronel PK were collected on days 1 and 21 of cycle 1 within 1 h before the first morning dose of orteronel, and additionally on day 21 of cycle 1 at 0.5, 1, 2, 3, 5, and 8 h post-dosing. For assessment of the PK of orteronel and docetaxel in combination, blood samples were collected on day 1 of cycle 2 – for docetaxel, at the end of the docetaxel infusion, and then 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h post-infusion, and for orteronel, within 1 h before the first morning dose, and then at 0.5, 1, 2, 3, 5, and 8 h post-dosing.

Statistical methods

For phase 1, the sample size was based on traditional 3+3 dose-escalation rules. Phase 2 sample size was determined by the PSA-50 response rate after 4 treatment cycles. With the assumption that the true PSA-50 rate is 50 %, it was expected that assessing PSA response rate in 19 evaluable patients would ensure the 80 % confidence interval (CI) to be within 35–65 %. Standard summary statistics were used for PSA and endocrine changes over time, as well as for observed values and change from baseline in the number of CTCs. Time to disease progression, defined as the duration from the date of first dose until the date of the first documented evidence of PD, was analyzed using Kaplan-Meier methodology.

Results

Patients

Thirty-eight patients were enrolled at nine sites in the USA and received treatment either in phase 1 ($n=14$) or phase 2 ($n=24$) of the study. One phase 2 patient experienced an AE after receiving a 1-h infusion of docetaxel and was permanently removed from the study. This patient was not included in the safety population (or any of the other analysis populations) since at least one dose of orteronel had not been received, and results for the remaining 37 patients are presented herein. Demographics and baseline characteristics for these 37 patients are summarized in Table 1. Patients' median age was 66 years (range 53–85). The median baseline serum PSA concentration was 54.1 ng/mL (range 4.5–1052.0).

Phase 1 results – determination of RP2D of orteronel in combination with DP

Three patients were enrolled in cohort 1 (orteronel 200 mg BID) and no DLTs were reported during cycle 1; however, in cycle 2, 1 patient experienced grade 4 serious AEs (SAEs) of febrile neutropenia and pseudomonal sepsis, which were deemed by the investigator to be related to docetaxel. The patient subsequently died from a grade 5 SAE of cardiopulmonary arrest on study day 48 (relationship to study drug not indicated); the death was not deemed by the investigator to be related to treatment with study drug. Thus, an additional group of 3 patients were enrolled into cohort 1; none of these patients experienced a DLT, and the protocol criteria were met to allow escalation to the 400 mg BID dose level.

Three patients were enrolled in cohort 2 (orteronel 400 mg BID), and none experienced a DLT; however, 1 patient in this group received <75 % of the planned dose of orteronel in cycle 1 due to study drug-related AEs (grade 3 fatigue and asthenia on day 8, and then grade 3 decreased neutrophil count on day 15) and was replaced per protocol. The fourth patient enrolled to this cohort experienced a DLT of drug-related grade 3 febrile neutropenia during cycle 1, thus, 3 additional patients were enrolled into cohort 2. One of these patients received <75 % of the planned dose of orteronel in cycle 1 due to grade 3 hypophosphatemia and was replaced. No further DLTs were observed; therefore, 400 mg BID was deemed to be the RP2D, and this dose was evaluated further in the phase 2 part of the study.

At the data cut-off date of January 16, 2013, 5 patients who participated in the phase 1 part of the study were ongoing with treatment (1 patient in cohort 1 and 4 patients in cohort 2).

Phase 2 results

Exposure and treatment summary – orteronel 400 mg BID—Of the 24 patients enrolled in phase 2, all received at least one dose of orteronel, docetaxel, or prednisone. Twenty-three (96 %) patients received at least one dose of orteronel 400 mg BID in combination with DP, and 1 (4 %) patient was removed from the study prior to receiving orteronel. Patients received a median of 7.5 months (range 0.2–25.1) of orteronel, a median of 6 cycles (range 1–13) of docetaxel, and a median of 8.0 months (range 0.7–17.7) of prednisone. Fifteen (65 %) patients received orteronel treatment for more than 6 months and 8 (35 %) patients received orteronel treatment for more than 12 months. At the data cut-off date: 6 of 24 (25 %) patients had completed treatment per protocol, with 3 (13 %) being treated until radiographic disease progression and 3 (13 %) being treated until occurrence of unacceptable AEs; 5 (21 %) patients remained on treatment; and 13 (54 %) patients had discontinued treatment before completing treatment per protocol due to symptomatic deterioration, patient withdrawal (each $n=4$, 17 %), initiation of alternative therapy, other reasons (each $n=2$, 8 %), and PSA progression ($n=1$, 4 %).

Efficacy—PSA response was evaluable in 22 phase 2 patients. PSA response at the end of 4 cycles (12 weeks) and best PSA response at any time on study are summarized as waterfall plots in Fig. 1. PSA-30, PSA-50, and PSA-90 response rates are summarized in Table 2. After 4 cycles, 68, 59, and 23 % of patients had achieved a PSA-30, PSA-50, and PSA-90 response, respectively. The median best PSA response was -77 % (range -99 % to $+110$ %), including 3 patients who did not achieve PSA reduction.

Seventeen (74 %) phase 2 patients eventually experienced PSA progression. Kaplan-Meier estimates of freedom from PSA progression were 57 % at 6 months and 18 % at 12 months, and the median time to PSA progression was 6.7 months (95 % CI: 4.9, 10.3; Fig. 2a). Ten (43 %) patients experienced radiographic progression. Kaplan-Meier estimates of freedom from radiographic progression were 84 % at 6 months and 54 % at 12 months. The median time to radiographic progression was 12.9 months (95 % CI: 8.7, not estimable; Fig. 2b). Kaplan-Meier estimates of freedom from either PSA progression or radiographic disease progression were 48 % at 6 months and 15 % at 12 months; the median time to either PSA progression or radiographic disease progression was 6.0 months (95 % CI: 4.9, 9.7; Fig. 2c).

Ten of 23 (43 %) phase 2 patients were evaluable for response by RECIST. The objective response rate (ORR: CR+PR) was 70 % (7 of 10 evaluable patients) with all responding patients achieving PR. A further 3 (30 %) patients achieved SD.

Among the phase 2 patients, median DHEA-S and testosterone levels declined appreciably as early as cycle 1, day 2 (Supplementary Fig. 1). After 4 treatment cycles, the median DHEA-S level declined by 99.1 % from baseline (from 68.1 $\mu\text{g/dL}$ [range 5.9–224.7] at baseline to 0.6 $\mu\text{g/dL}$ [range 0.1–51.9] at cycle 5, day 1) and declined further, to a 99.8 % decrease from baseline after 8 cycles (0.1 $\mu\text{g/dL}$ [range 0.1–27.7] at cycle 9, day 1, which is the lower limit of detection for the DHEA-S assay). The median testosterone level was also reduced by 95.8 % from baseline after 4 and 8 cycles of treatment (from 7.1 ng/dL [range 2.6–13.8] at baseline to 0.3 ng/dL [range 0.3–7.2] at cycle 5, day 1, and to 0.3 ng/dL [range

0.3–1.7] at cycle 9, day 1, which is nearing the lower limit of detection for the testosterone assay).

Sixteen patients had CTC assessments taken at baseline and after 4 cycles of treatment; the remaining 7 patients had missing assessments either at baseline or cycle 4. Of 8 patients with a CTC count of ≥ 5 cells/7.5 mL at baseline, 4 (50 %) showed a reduction in CTC count to <5 cells/7.5 mL after 4 treatment cycles. CTC counts for the remaining 4 patients remained at ≥ 5 cells/7.5 mL. Of 8 patients with a CTC count of <5 cells/7.5 mL at baseline, none showed an increase in CTC count to ≥ 5 cells/7.5 mL after 4 cycles of treatment. Thus, CTC counts were decreased to, or maintained at, <5 cells/7.5 mL in 75 % of assessed patients.

Safety—Of the 23 patients who received orteronel in the phase 2 part of the study, all experienced at least one treatment-emergent any-grade AE and at least one treatment-emergent grade ≥ 3 AE. Common AEs reported during this study are summarized in Table 3. The most common any-grade AEs were fatigue (78 %), alopecia (61 %), diarrhea (48 %), nausea (43 %), dysgeusia, and neutropenia (each 39 %). The most common grade ≥ 3 AEs were neutropenia (39 %), total white blood cell count decrease (26 %), fatigue (22 %), leukopenia, and neutrophil count decrease (each 17 %). Treatment-emergent SAEs were reported in 16 (70 %) patients. SAEs occurring in ≥ 2 patients included dehydration, febrile neutropenia (each $n=3$ [13 %]), anemia, asthenia, pneumonitis, and urinary tract infection (each $n=2$ [9 %]). AEs leading to discontinuation of study drug occurred in 9 (39 %) patients, the most common of which was fatigue, reported in 2 (9 %) patients. There were 2 (9 %) on-study deaths during the phase 2 part of the study, both of which were deemed unrelated to treatment. In 1 patient with a history of chronic pulmonary obstructive disorder, death on study day 265 was due to respiratory arrest, after hospitalization for urinary tract infection, confusion, shortness of breath, and respiratory distress. Death in a second patient on study day 199 was due to disease progression.

In the phase 2 part of the study, 1 (4 %) patient experienced an SAE of pancreatitis, 1 patient (4 %) experienced SAEs of amylase increased and lipase increased, and 1 (4 %) patient experienced a non-serious treatment-emergent AE of lipase increased. All of these events were deemed to be related to treatment. Study drug was discontinued due to these AEs in 2 (9 %) patients; in 1 patient, study drug was discontinued prior to the event due to a different AE, and in the other patient, study drug was held and re-started at a reduced dose, after which the event resolved.

With the exception of a small isolated increase in ALT and expected decrease in leukocyte and neutrophil counts, no clinically meaningful trends were observed for the hematology and clinical chemistry laboratory evaluations, including hemoglobin, platelets, AST, bilirubin, and potassium. Further, orteronel appeared to have an acceptable cardiovascular profile based on assessment of cardiac enzymes, electrocardiograms, and left ventricular ejection fraction.

PK—The PK of orteronel and docetaxel alone, and in combination, were assessed in 16 patients during the phase 2 part of the study. PK parameters are summarized in

Supplementary Table 1. The plasma concentration of orteronel increased rapidly after dosing, with a median time to maximum concentration (T_{max}) of 2 h. A rapid increase in docetaxel concentration was also observed after dosing, with a median T_{max} of approximately 1 h (the end of infusion). The mean plasma concentration-time profile of orteronel was similar in the presence or absence of docetaxel, and the mean plasma concentration-time profile of docetaxel was similar in the presence or absence of orteronel (Supplementary Fig. 2). As shown in Fig. 3, orteronel $AUC_{0-\tau}$ (area under the concentration-time curve within the dosing interval) and C_{max} (maximum observed concentration) were similar in the presence or absence of docetaxel and vice versa. A statistical analysis of plasma PK parameters for orteronel and docetaxel, alone and in combination, is summarized in Supplementary Table 2. The ratio of geometric least square means for $AUC_{0-\tau}$ and $C_{max,ss}$ (maximum observed concentration at steady state) was similar for the two drugs when administered alone or in combination (Supplementary Table 2). Overall, co-administration with docetaxel did not impact the plasma PK parameters of orteronel, and vice versa.

Discussion

During the past decade, significant progress has been made in understanding the biology of the AR pathway, and this has translated into advances in the development of novel therapies for mCRPC [25, 26]. The United States Food and Drug Administration has approved two novel agents that target the AR signalling pathway and that have shown particular promise in the treatment of mCRPC [1, 27]. Abiraterone acetate, an inhibitor of CYP17A1, and the AR inhibitor enzalutamide have demonstrated improved OS compared with placebo in patients with mCRPC following docetaxel therapy (median 15.8 versus 11.2 months [15] and 18.4 versus 13.6 months [17], respectively), and more recently, in chemotherapy-naïve mCRPC patients (median not reached versus 27.2 months [16] and not reached versus 31.0 months [14], respectively). Both agents are now indicated for the treatment of patients with mCRPC [12, 13]. With the increasing availability of these and other novel therapies for mCRPC, additional studies are required to evaluate their efficacy and safety with the aim of informing the optimal treatment combination and/or treatment sequence in this indication.

Historically, patients with mCRPC have been treated with docetaxel-based therapy [28]. To date, attempts to combine docetaxel with bone-targeting agents (atrasentan, zibotentan), tyrosine kinase inhibitors (dasatinib), angiogenesis-targeting agents (bevacizumab, aflibercept, lenalidomide), vaccines (GVAX), or metabolic agents (calcitriol) have not resulted in improved survival in mCRPC [19, 29–34]. This may be due, in part, to a lack of independent activity demonstrated by these agents in mCRPC, as well as their respective mechanisms of action. To this end, targeting the AR as well as its ligand(s) may lead to improved or synergistic efficacy in mCRPC. Docetaxel is thought to exert its antitumor activity, in part, via effects on the AR [18, 35], but it is currently unclear whether sequencing or combining docetaxel treatment with other drugs that interact with the AR signalling pathway (such as enzalutamide [36, 37] or abiraterone acetate [38]) may be beneficial or detrimental. In a retrospective study evaluating docetaxel therapy in abiraterone-pretreated mCRPC patients, the activity of docetaxel was lower than anticipated [39] suggesting that there may be cross-resistance between the two agents. Orteronel is an

inhibitor of the 17,20-lyase activity of CYP17A1 and is not thought to interact with the AR; as such, orteronel was thought to potentially offer an alternative combination treatment approach for mCRPC. Results from the present phase 1/2 study suggest that the combination of orteronel 400 mg BID with standard doses of DP is tolerable and active in patients with chemotherapy-naïve mCRPC.

Orteronel 400 mg BID in combination with DP demonstrated efficacy in this patient population. A decline in serum PSA levels was the principle surrogate of tumor response in this study. Patients achieved a median best PSA response of -77 % from baseline; only 3 patients failed to show PSA reduction at any time on-study. The median time to either PSA or radiographic disease progression in this study (6.0 months) was comparable with the reported median time to progression of 6.3 months with docetaxel-based therapy in the pivotal SWOG 9916 trial [3]. These data imply that orteronel plus DP has similar, but not improved efficacy to docetaxel-based doublet therapy (docetaxel/estramustine). However, cross-study comparisons such as these should be interpreted with caution due to differences in study interventions, study designs, and patient populations. Despite the small number of RECIST-evaluable patients (10 of 23 patients with RECIST-evaluable radiographic disease at baseline), the ORR of 70 % observed with orteronel plus DP was encouraging.

Hormone concentrations were used to assess pharmacodynamic parameters and demonstrated that plasma DHEA-S and testosterone levels were rapidly and substantially decreased from baseline as early as the second day of therapy, and remained low for at least 1 year. The observation that CTC numbers were decreased to or maintained at <5 cells/7.5 mL in 75 % of assessed patients is additionally suggestive of the activity of the triplet combination in this patient population; however, the CTC results should be interpreted with caution due to the limited sample size ($n=16$).

Since this trial was conducted, results from two phase 3, placebo-controlled studies of orteronel 400 mg BID plus prednisone versus placebo plus prednisone in men with progressive, previously treated (post docetaxel) or chemotherapy-naïve mCRPC have been reported [40, 41]. Both studies found that while orteronel plus prednisone significantly extended radiographic progression-free survival compared with placebo plus prednisone (median 8.3 vs 5.7 months in post-docetaxel patients and median 13.8 vs 8.7 months in chemotherapy-naïve patients; both $p<0.001$), this combination did not significantly prolong OS in either patient population. These findings have resulted in the sponsor's termination of orteronel clinical development in mCRPC. Of note, the median time to radiographic progression in the present study was 12.9 months; in the context of the phase 3 data in chemotherapy-naïve patients, these data further suggest a similar benefit with triplet (orteronel plus DP) and doublet (orteronel plus prednisone) therapy in this setting.

Orteronel 400 mg BID plus DP appeared tolerable with manageable toxicity. AEs were consistent with the known safety profiles for each drug [4, 20]. The most common AEs experienced by patients receiving orteronel 400 mg in combination with DP (fatigue, alopecia, diarrhea, nausea, dysgeusia, and neutropenia – each reported in 39 % of patients) were not unexpected based on AEs reported in the phase 3 TAX 327 study of DP in men with mCRPC [4] and in recent studies of orteronel 400 mg BID plus prednisone in men with

progressive, chemotherapy-naïve mCRPC [20, 40]. Fatigue (the most common drug-related AE and most common AE leading to treatment discontinuation in this study), in particular, was not unexpected as this is a common toxicity associated with the use of taxanes [5] and 17,20-lyase inhibitors [12].

Analysis of the plasma concentration-time profiles for orteronel and docetaxel, alone and in combination, revealed little effect of co-administration on the PK parameters of the individual drugs, thus highlighting the feasibility of the triplet combination regimen. This finding expands on previously reported data suggesting that there is little risk of drug–drug interactions between orteronel and other drugs that are metabolized by related CYP family enzymes [42].

In conclusion, orteronel 400 mg BID administered together with standard doses of DP appears to be tolerable in men with mCRPC, with no unexpected safety effects, and with evidence for androgen-lowering activity and tumor responses in some patients. As the clinical development of orteronel in mCRPC has been terminated, further study of this triplet regimen is unlikely.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. PSA response following treatment with orteronel, docetaxel, and prednisone after (a) 4 cycles and (b) best PSA response at any time on study. *PSA*, prostate-specific antigen; PSA-30, -50, and -90 indicate PSA declines of 30, 50, and 90 % from baseline, respectively.

Fig. 2. Kaplan-Meier plots of time to (a) PSA progression, (b) radiographic progression, and (c) PSA or radiographic progression. *PSA*, prostate-specific antigen

Fig. 3. $AUC_{0-\tau}$ and C_{max} for orteronel and docetaxel alone, and in combination. $AUC_{0-\tau}$, area under the concentration–time curve within the dosing interval; C_{max} , maximum observed concentration; SD , standard deviation

Table 1

Patients' demographics and baseline characteristics

Characteristic	N=37
Median age, years (range)	66 (53–85)
Race, White / Black or African American, <i>n</i> (%)	32 (86) / 5 (14)
ECOG performance status 0 / 1, <i>n</i> (%)	30 (81) / 7 (19)
Median baseline serum PSA concentration, ng/mL (range)	54.1 (4.5–1052.0)
Gleason score at initial diagnosis, 6–7 / 8–10, <i>n</i> *	14 / 18
Median time since diagnosis, years (range)	5.1 (0.5–21.2)

ECOG, Eastern Cooperative Oncology Group; *PSA*, prostate-specific antigen

* Gleason score at initial diagnosis was unknown in 5 patients

Table 2

PSA response following treatment with orteronel, docetaxel, and prednisone in the PSA-evaluable population ($n=22$)

PSA response, n (%)	
Response after 4 cycles *	
[80 % CI]	
PSA-90	5 (23) [11.5, 38.1]
PSA-50	13 (59) [43.2, 73.6]
PSA-30	15 (68) [52.3, 81.3]

CI, confidence interval; PSA, prostate-specific antigen; PSA-90/-50/-30, PSA declines of 90 %, 50 %, and 30 % from baseline, respectively

* 4 of the 22 PSA-evaluable patients did not have response assessments taken at the end of 4 cycles

Table 3

Treatment-emergent AEs reported at any grade in 25 % of patients or reported at grade 3 in 10 % of patients, plus corresponding rates of drug-related any-grade and grade 3 AEs

AE, n (%)	Orteronel 400 mg BID+DP (n=23)			
	Treatment-emergent		Drug-related	
	Any grade	Grade 3	Any grade	Grade 3
Any AE	23 (100)	23 (100)	22 (96)	22 (96)
Fatigue	18 (78)	5 (22)	18 (78)	5 (22)
Alopecia	14 (61)	0	12 (52)	0
Diarrhea	11 (48)	0	10 (43)	0
Nausea	10 (43)	0	10 (43)	0
Dysgeusia	9 (39)	0	8 (35)	0
Neutropenia	9 (39)	9 (39)	9 (39)	9 (39)
Constipation	8 (35)	0	6 (26)	0
Decreased appetite	8 (35)	0	7 (30)	0
Cough	7 (30)	0	1 (4)	0
Anemia	6 (26)	3 (13)	4 (17)	2 (9)
Arthralgia	6 (26)	0	2 (9)	0
Peripheral sensory neuropathy	6 (26)	0	4 (17)	0
Total white blood cell count decreased	6 (26)	6 (26)	5 (22)	5 (22)
Gamma-glutamyltransferase increased	4 (17)	3 (13)	3 (13)	2 (9)
Leukopenia	4 (17)	4 (17)	4 (17)	4 (17)
Neutrophil count decreased	4 (17)	4 (17)	4 (17)	4 (17)
Blood alkaline phosphatase increased	3 (13)	3 (13)	3 (13)	3 (13)
Febrile neutropenia	3 (13)	3 (13)	2 (9)	2 (9)
Leukocytosis	3 (13)	3 (13)	2 (9)	2 (9)

AE, adverse event; BID, twice-daily; DP, docetaxel-prednisone