Original Study

Phase 2 Study of Seviteronel (INO-464) in Patients With Metastatic Castration-Resistant Prostate Cancer After Enzalutamide Treatment

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Abstract

We conducted an open-label phase 2 clinical study to evaluate the safety and efficacy of seviteronel (provided once or twice daily without oral steroids) in patients with metastatic castration-resistant prostate cancer previously treated with enzalutamide. The study was terminated early as a result of suboptimal dosing strategies and significant central nervous system toxicity. Further evaluation of seviteronel is not warranted in this patient population as a result of limited tolerability and insufficient clinical activity.

Background: Seviteronel was being developed by Innocrin Pharmaceuticals as a selective cytochrome P450c17a (CYP17) 17,20-lyase (lyase) inhibitor and androgen receptor antagonist with activity against prostate cancer cells in vitro and in vivo. This open-label phase 2 clinical study evaluated the tolerability and efficacy of seviteronel in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with enzalutamide. **Patients and Methods:** Patients with mCRPC whose disease previously progressed while receiving enzalutamide therapy were divided into 2 cohorts on the basis of prior exposure to docetaxel. Seviteronel was administered without routine oral steroids either twice daily with dose titration (450 mg) or once daily without dose titration (600 or 750 mg). The primary objective was to determine the rate of significant prostate-specific antigen response (ie, decline of $\geq$ 50%) after 12 weeks of seviteronel therapy. **Results:** Seventeen patients, with a median (range) age of 71 (60-92) years, were enrolled, with 8 patients having received prior docetaxel. Patients received a median of 2 cycles of treatment, with most patients discontinuing treatment because of toxicity related to the study drug. The most common adverse events included concentration impairment, fatigue, tremor, and nausea. Despite changes in dosing, the study was closed prematurely because of the high magnitude of toxicity. One (6%) of 17 patients experienced a significant decline in prostate-specific antigen. **Conclusion:** Seviteronel was not generally well tolerated nor associated with significant clinical responses in patients with mCRPC who had previously received enzalutamide. Further investigation of single-agent seviteronel in this patient population is not warranted; however, studies investigating seviteronel with low-dose dexamethasone are ongoing in patients with androgen receptor–positive tumors.

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Introduction

The recent introduction of highly potent and efficacious antihormonal therapies has improved the treatment landscape of patients with castration-resistant prostate cancer (CRPC). Since 2011, the US Food and Drug Administration (FDA) has approved several antihormonal agents for the treatment of CRPC, including

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abiraterone acetate (AA), enzalutamide (ENZ), and apalutamide (APA).[1-6] AA is an irreversible and potent inhibitor of the 17,20-lyase activity of cytochrome P450c17a (CYP17), blocking downstream production of androgens. However, AA also potently inhibits the 17-alpha-hydroxylase activity of CYP17, requiring the coadministration of oral steroids (eg, prednisone) to reduce upstream steroid accumulation, cortisol suppression, and mineralocorticoid excess.[7-9] AA has shown a significant overall survival (OS) advantage in patients with metastatic CRPC (mCRPC).[1,3] ENZ and APA are both second-generation androgen receptor (AR) antagonists that have also been shown to improve OS in patients with CRPC.[2,4-6,10]

Despite favorable responses in castration-resistant disease, disease progression is inevitable after treatment with current second-generation antihormonal agents, often as a result of acquired resistance mediated via the AR pathway.[11] Increased intratumoral androgen biosynthesis, AR overexpression, AR splice variation, and AR point mutations are implicated in treatment resistance to potent AR antagonists and CYP17 inhibitors.[12-17] *T878A* and *L702H* mutations in the AR have been associated with resistance to AA therapy, conferred via AR pathway activation by progesterone/pregnenolone[9] and prednisone,[18,19] respectively. Notably, the *F876L* mutation converts ENZ and APA from AR antagonists into AR agonists in vitro, with several cases documented clinically.[20,21] Numerous clinical trials have been initiated to investigate newer antihormonal agents (eg, orteronel, darolutamide, EPI-506) that aimed to overcome AR pathway–mediated acquired resistance associated with the currently approved agents.[22]

Seviteronel (INO-464) is an orally bioavailable dual inhibitor of CYP17 lyase activity and the AR, with approximately 10-fold selectivity toward the CYP17 lyase over hydroxylase,[23] and competitive inhibition of wild-type and mutated forms of the AR (eg, *T877A*, *F876L*).[24] The unique mechanism of action of seviteronel may offer a potential therapeutic option in the setting of prior AR-targeted treatment failure while sparing the use of concomitant steroids. Seviteronel was shown to be effective in several in vivo models using CRPC cell lines, including MR49F, MDA-PCA-133, and LNCaP (expressing the AR *F876L*, *H874Y*, and *T877A* mutations, respectively).[24-26] Additionally, seviteronel was shown to be more potent than AA in established ENZ-resistant cell lines (eg, C4-2, C4-2B, MR49C, MR49F).[24,25]

There is currently an unmet clinical need to improve treatments in the post-ENZ setting of mCRPC. Sequential use of AA after ENZ has shown minimal improvements in both progression-free survival and OS as a result of AR-mediated cross-resistance,[27] as evidenced by clinical biomarkers such as AR-V7 expression.[11,13,14] The safety, tolerability, pharmacokinetics (PK), and, notably, preliminary clinical activity of seviteronel have been evaluated for both twice-daily and once-daily dosing regimens in patients with treatment-naive and previously treated CRPC (NCT02012920, NCT02361086).[28,29] Patients with prostate-specific antigen (PSA) declines were observed on both studies, but limited seviteronel tolerability associated with twice-daily dosing (eg, frequent dose reductions, treatment discontinuations) ultimately led to 600 or 750 mg once-daily dosing regimens.[29]

The current phase 2 study (NCT02130700) investigated the use of seviteronel in patients with progressive mCRPC who experienced disease progression after at least 3 months of ENZ monotherapy with and without prior exposure to cytotoxic chemotherapy.

Patients and Methods

Study Population

Patients aged 18 years or older with progressive mCRPC previously treated with ENZ for longer than three 28-day cycles were eligible for this study. Progression was defined as either a minimum of 2 rising PSA levels at least 1 week apart, appearance of one or more new lesions on bone scan, or new or growing lesions on computed tomographic scan. Patients were required to have an Eastern Cooperative Oncology Group performance status of ≤ 1 (≤ 2 allowed for patients after chemotherapy) with adequate organ and marrow function, have castrate levels of testosterone (< 50 ng/dL, obtained via orchiectomy or continuous luteinizing hormone-releasing hormone agonist/antagonist therapy), and have discontinued previous treatment at least 28 days before study entry.

Patients with an uncontrolled intercurrent illness, HIV positivity while receiving combination antiretroviral therapy, active hepatitis B or C infections, or a history of another invasive malignancy within the preceding 3 years were excluded from this study. No more than one prior course of cytotoxic chemotherapy was permitted, and only patients with prior cytotoxic chemotherapy may have received prior therapy with agents targeting CYP17 (eg, abiraterone, galeterone, orteronel). Patients with adrenal insufficiency requiring daily hydrocortisone/prednisone or prior palliative radiation within 2 weeks of study entry were not eligible. Additionally, patients with known brain metastases or a history of seizures were excluded from this study.

Study Design

This was a phase 2 open-label study designed to explore the benefit of seviteronel in patients with mCRPC who were previously treated with ENZ. The primary objective of this study was to determine the rate of significant PSA response, as defined by a $\geq$ 50% decrease in baseline serum PSA after 12 weeks of seviteronel administered without routine oral steroids (per Prostate Cancer Clinical Trials Working Group [PCWG2] criteria).[30] Patients were stratified into 2 cohorts, before and after docetaxel-based chemotherapy. In each cohort, a Simon optimal 2-stage design was used, with alpha = 0.10 and beta = 0.10, to rule out a 5% response rate ($P_0 = .05$) in favor of a targeted 25% PSA response rate ($P_1 = .25$). The first stage of accrual would include 9 patients in each cohort (18 patients total initially). A significant PSA response in 1 or more of 9 patients in a study arm would increase enrollment to a total of 24 patients in that arm, with 3 or more responses in 24 patients warranting further study. The secondary objective for this study was to determine the radiographic response and time to progression as per the modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[31]

Treatment and Toxicity Evaluation

Patients initially received seviteronel 150 mg by mouth twice daily with titration in increments of 150 mg every 2 weeks to a final dose of 450 mg twice daily. After the results of a simultaneous trial became available,[29] the protocol was amended to modify the dose and administration schedule of seviteronel to 750 mg by mouth once daily in an effort to improve tolerability. Seven patients were treated with the original dosing regimen, followed by 6 patients who received seviteronel 750 mg by mouth once daily. Frequent dose

Table 1 Patient Demographics and Baseline Characteristics

Characteristic	Before Docetaxel (N = 9)	After Docetaxel (N = 8)	Total (N = 17)
Age (y)	71 (60-85)	72 (65-92)	71 (60-92)
Race			
White	7 (78)	8 (100)	15 (88)
Other	2 (22)	0	2 (12)
Weight (kg)	96.5 (76.6-129.4)	89.1 (74.3-112.7)	93.0 (74.3-129.4)
ECOG performance status			
0	2 (22)	0	2 (12)
1	7 (78)	7 (87.5)	14 (82)
2	0	1 (12.5)	1 (6)
Baseline PSA	36.13 (6.92-69.23)	75.97 (14.69-190)	54.88 (6.92-190)
Site of metastasis			
Bone	3 (33)	5 (62.5)	8 (48)
LN	1 (11)	0	1 (6)
Bone and LN	4 (45)	0	4 (24)
Bone and viscera	1 (11)	3 (37.5)	4 (24)
Gleason score at diagnosis			
6	1 (11)	1 (12.5)	2 (12)
7	1 (11)	2 (25)	3 (17)
8-10	7 (78)	5 (62.5)	12 (71)
Prior treatment[a]			
Bicalutamide	7 (78)	7 (87.5)	14 (82)
Nilutamide	2 (22)	3 (37.5)	5 (29)
Flutamide	3 (33)	4 (50)	7 (41)
Ketoconazole	2 (22)	2 (25)	4 (24)
Immunotherapy[b]	7 (77)	6 (75)	13 (76)
Antiangiogenic therapy[c]	0	5 (62.5)	5 (29)

Data are presented as n (%) or average (range).
Abbreviations: ECOG = Eastern Cooperative Oncology Group; LN = lymph node; PD-1 = programmed cell death 1; PD-L1 = programmed death ligand 1; PSA = prostate-specific antigen.
[a]Other than enzalutamide or docetaxel.
[b]Treatments included anti—PD-1/PD-L1 antibodies, sipuleucel-T, PANVAC, PROSTVAC, and ME-TARP.
[c]Treatment regimens containing the following agents: TRC-105, AMG386, thalidomide, lenalidomide, bevacizumab.

reductions and treatment discontinuations led to an additional amendment, reducing the dose of seviteronel to 600 mg by mouth once daily for the remaining 4 patients enrolled onto the study.

Adverse events (AEs) were classified and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0. Treatment was held for a grade 3 AE that was possibly, probably, or definitely related to seviteronel until resolution to grade 1 or baseline. Dose reductions were allowed for low-grade AEs at the discretion of the investigator. Reescalation of the dose was not permitted; patients requiring more than 2 dose reductions permanently discontinued seviteronel. Seviteronel was permanently discontinued for a grade 4 AE or a treatment delay of > 6 weeks.

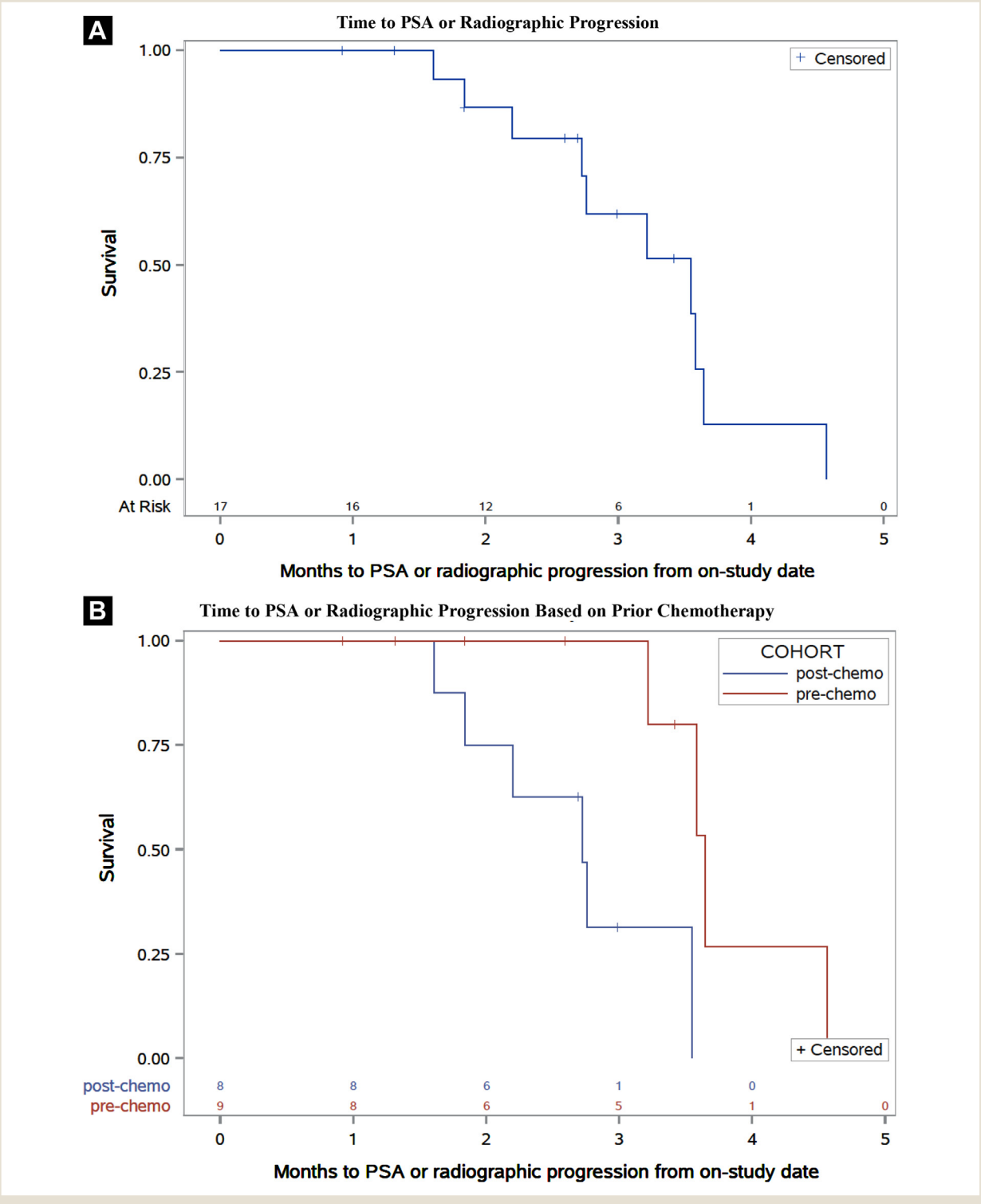
PK Analysis

To better understand the PK of seviteronel, a subset of men on this trial were provided with a single oral dose (600 or 750 mg) with food and had PK samples drawn to 48 hours after dose on the first day of cycles 1 and 2. For these patients, the day 2 dose was withheld, with daily dosing resuming on day 3 of cycles 1 and 2, and continued through each 28-day cycle. Blood for PK measurements was drawn into sodium heparin (green top; BD Biosciences, San Jose, CA) tubes, processed into plasma immediately, and stored frozen until bioanalytical analysis. Seviteronel plasma concentrations were measured using a validated liquid chromatography-tandem mass spectrometric assay with a lower limit of quantitation of 20 ng/mL. PK parameters were calculated using noncompartmental methods by Phoenix WinNonlin 7.0 (Certara, Cary, NC). Exposure-response analyses of ordered grades of AE were assessed by propotional odds models in R v3.5.

Statistical Analyses

The Kaplan-Meier method was used to evaluate time to progression and OS, separately by cohort as well as overall. Analyses of progression were done by evaluating time to PSA or radiographic progression (whichever came first); the analysis censored each patient's follow-up at their off-study date if they did not experience either PSA progression or radiographic progression noted while on the study. The log-rank test was used to determine the statistical significance of the difference between pairs of Kaplan-Meier curves. The data cutoff for this analysis was February 8, 2019.

Figure 1 Kaplan-Meier Plots of Time to PSA or Radiographic Progression in Patients With Metastatic Castration-Resistant Prostate Cancer. Shown is Time to PSA or Radiographic Progression of (A) Total Population and (B) Patients Who Received or did Not Receive Previous Docetaxel Therapy



Abbreviation: PSA = prostate-specific antigen.

Figure 2 Kaplan-Meier Plots of Median Overall Survival in Patients With Metastatic Castration-Resistant Prostate Cancer. Shown is Overall Survival of (A) Total Population (B) and Patients Who Received or did Not Receive Previous Docetaxel Therapy (B). Median Potential Follow-Up was 37.4 Months

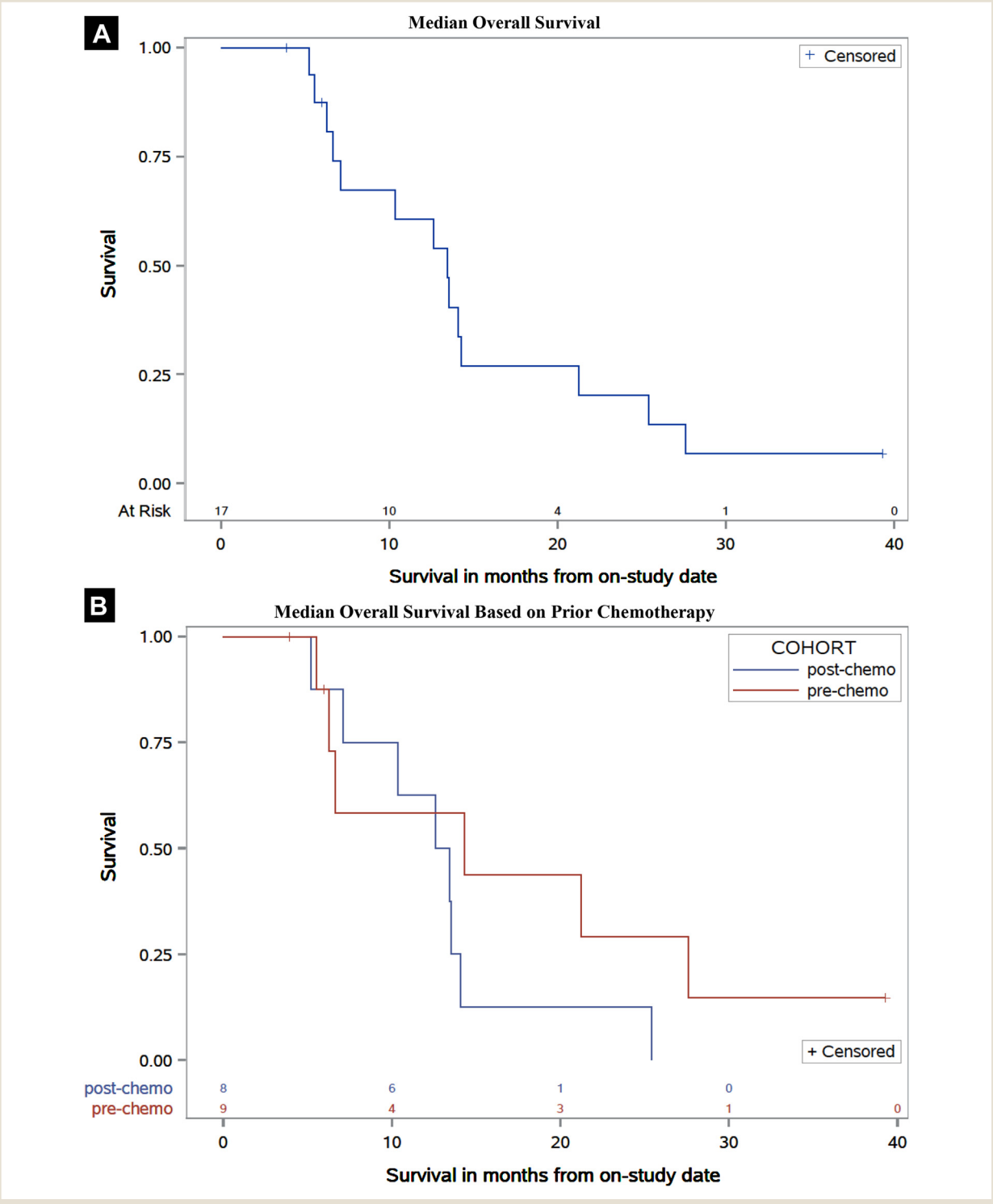


Table 2 AEs in > 15% of Study Population

AE	All Grades 1-3	Grade 1	Grade 2	Grade 3
Concentration impairment	14 (82)	9 (53)	4 (24)	1 (6)
Fatigue	11 (65)	3 (18)	8 (47)	0
Tremor	10 (59)	9 (53)	1 (6)	0
Nausea	9 (53)	7 (41)	0	2 (12)
Dizziness	6 (35)	3 (18)	1 (6)	2 (12)
Blurred vision	4 (24)	3 (18)	1 (6)	0
Hypotension	4 (24)	1 (6)	2 (12)	1 (6)
Vomiting	3 (18)	3 (18)	0	0
Edema (limbs)	3 (18)	2 (12)	1 (6)	0
Fall	3 (18)	1 (6)	1 (6)	1 (6)
Gait disturbance	3 (18)	3 (18)	0	0
Malaise	3 (18)	0	3 (18)	0
Presyncope	3 (18)	0	3 (18)	0

Data are presented as n (%). AEs are those with attribution of at least possibly occurring in > 15% of patients who received study treatment (n = 17). AEs are based on National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
Abbreviation: AE = adverse event.

Results

Patient Characteristics

A total of 17 patients with mCRPC were enrolled onto the study from April 2014 to August 2016. Baseline characteristics according to cohort are presented in Table 1. Approximately half of the patients had previous exposure to docetaxel (n = 9, 53%). Most patients had high-risk prostate cancer at time of initial diagnosis, as demonstrated by Gleason score (ie, Gleason score ≥ 8; n = 12, 71%), and metastatic disease with bone involvement at baseline (n = 16, 94%). Most patients had previously been treated with a first-generation AR antagonist (antiandrogens such as bicalutamide, flutamide, nilutamide; n = 16, 94%) in addition to prior treatment with ENZ as required by the study eligibility criteria. Thirteen patients (76%) had been previously treated with immunotherapy, with 12 patients (71%) receiving either investigational anticancer vaccines (eg, PROSTVAC, PANVAC, ME-TARP; n = 8, 47%) or FDA-approved sipuleucel-T (n = 4, 24%). Additionally, 5 patients (29%) had received prior treatment with antiangiogenic targeted agents, the most notable regimen being one comprising bevacizumab, docetaxel, and either thalidomide or lenalidomide (n = 3, 18%).

Clinical Response

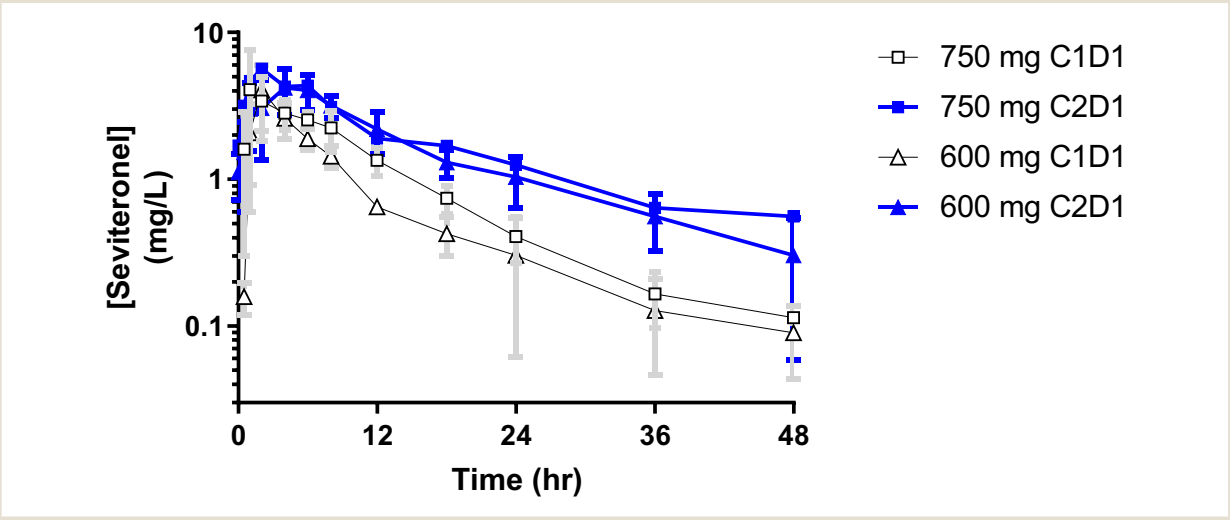
Patients received a median of 2 cycles (range, 1-8 cycles) of the study drugs, thereby limiting clinical evaluation of PSA response and radiographic progression as per PCWG2, which recommends waiting at least 12 weeks before documenting response or progression.[30] Of the 17 patients with evaluable data, 10 patients (59%) discontinued therapy because of AEs, 4 patients (24%) because of disease progression, 2 patients (12%) at physician discretion, and 1 patient (6%) because of intercurrent illness unrelated to study treatment. Of all patients, only one patient from the prechemotherapy cohort receiving 750 mg once daily met the primary objective (6%), with a maximal PSA decline of 88% occurring

Table 3 Pharmacokinetics of First Dose (Cycle 1) Versus SS (Cycle 2)

	600 mg[a]		750 mg[b]	
Variable	C1D1 (N = 4), Mean ± SD	C2D1 (N = 4), Mean ± SD	C1D1 (N = 3), Mean ± SD	C2D2 (N = 1), Mean ± SD
C_{MAX} (mg/L)[c]	4.07 ± 1.92	4.66 ± 1.16	5.11 ± 1.9	5.65
C_{MAX}/D (μg/L/mg)[c]	6.77 ± 3.20	7.76 ± 1.93	6.82 ± 2.54	7.53
T_{MAX} (hours)	2.0 ± 0.0	5.00 ± 2.58	2.0 ± 1.7	2.0
AUC (h × mg/L)	33.0 ± 4.33	55.4 ± 5.96	44.2 ± 2.15	63.5
AUC/D (hr × μg/L/mg)[c]	55.1 ± 7.21	92.3 ± 9.94	58.9 ± 2.87	84.6
$t_{1/2}$ (hours)	16.4 ± 4.78	14.8 ± 5.94	10.5 ± 4.35	18.3
CL/F (L/h)[d]	18.4 ± 2.50	10.9 ± 1.32	17.0 ± 0.84	11.8
Vz/F (L)	438 ± 146	229 ± 77.7	260 ± 121	312

Abbreviations: AUC = area under plasma concentration versus time curve (extrapolated to infinity for first dose, AUC_{TAU} for SS); AUC_{INF} = AUC extrapolated to time infinity; C1D1 = cycle 1 day 1; C2D1 = cycle 2 day 1; C2D2 = cycle 2, dose 2; CL/F = apparent oral clearance; C_{MAX} = maximum plasma concentration; D = dose; SS = steady state; $t_{1/2}$ = half-life; T_{MAX} = time to C_{MAX}; Vz/F = apparent oral volume of distribution in terminal phase (determined based on CL/F method used, ie, Vz/F = CL/F/k_{EL}).
[a]Three patients received 600 mg for both C1D1 and C2D1; one patient was reduced to 450 mg for C2D1 (data not included here).
[b]Only one patient with PK data received 750 mg for both C1D1 and C2D1; one patient was reduced to 600 mg for C2D1 and another did not have C2D1 data available.
[c]Dose-normalized parameters.
[d]CL/F for first dose calculated as Dose/AUC_{INF}; CL/F for SS calculated as Dose/AUC_{TAU}.

Figure 3 Mean Seviteronel Plasma Concentration Versus Time Curves by Dose and Cycle in Patients With Metastatic Castration-Resistant Prostate Cancer



after 3 cycles of treatment and disease progression occurring after 6 months on the study. An additional patient in the prechemotherapy cohort, who received 750 mg once daily with a dose reduction to 450 mg once daily during cycle 1, experienced a minimal decline in PSA (15%) after 11 weeks of treatment before discontinuing the study drug because of toxicity. All remaining patients had rising PSA values while on the study, with 8 of those patients having documented PSA progression per PCWG2. Four (24%) of 17 patients underwent restaging for the indication of radiographic progression of disease, with only one patient undergoing a secondary scan to confirm progression per PCWG2.[30]

Kaplan-Meier plots for time to PSA progression or radiographic progression, and OS are provided in Figures 1 and 2, respectively. Median time to disease progression (mTDP), measured as either PSA progression or radiographic progression (whichever came first), was 3.5 months (95% confidence interval [CI], 2.2-3.6). Patients without previous chemotherapy had a mTDP of 3.6 months (95% CI, 3.2-4.6), and patients previously treated with docetaxel had a mTDP of 2.7 months (95% CI, 1.6-3.5). Although the log-rank assessment demonstrated a statistically significant difference in mTDP between cohorts ($P = 0.0096$), this finding was not interpreted to be clinically meaningful. Median OS for all patients was 13.4 months (95% CI, 6.6-14.3 months). Patients who had received prior chemotherapy had a median OS of 13.0 months (95% CI, 5.2-14.1), whereas patients who had not received prior chemotherapy had a median OS of 14.3 months (95% CI, 5.6-27.6).

Toxicity

Grade 1, 2, and 3 AEs that were probably, possibly, or definitely related to study treatment that was reported in > 15% of patients are listed in Table 2. The most common AEs included concentration impairment, fatigue, tremor, and nausea, each of which each occurred in > 50% of the patients. Reported grade 3 AEs at least possibly related to study treatment included concentration impairment, dizziness, nausea, hypotension, fall, and dehydration (2 patients, 12%, experienced grade 3 dehydration; data not reported in Table 2). No grade 4 AEs related to the study treatment were reported. Only one patient experienced two grade 4 AEs while on the study, respiratory failure and pneumonitis; these AEs were likely due to association with existing comorbidities and were attributed as unrelated and unlikely, respectively. Supplemental Table 1 in the online version lists the incidence of the most common AEs by dosing group. Toxicities that occurred in > 50% of all patients were mostly consistent across all dosing strategies, with the exception of diarrhea, which was not reported in patients receiving the drug 750 mg once daily. Ultimately, 9 patients had central nervous system (CNS) toxicities (most commonly concentration impairment and fatigue) that contributed to their treatment discontinuation.

In addition to dose modifications, alternative toxicity management strategies were attempted in a small number of patients (n = 5). The precise mechanism of the CNS toxicities associated with seviteronel is unclear, but hormone or steroid alterations were proposed to be potential factors. As a result, some patients received estrogen supplementation (n = 3) or prednisone (n = 2), either prophylactically or after symptom development. No symptomatic improvement was noted with either approach.

Pharmacokinetics

Of the 8 patients with PK samples obtained, 7 had a full PK time course in cycle 1, and 6 patients had full time courses in both cycles 1 and 2 for calculation of PK parameters. Seviteronel demonstrated an apparent monophasic elimination that began approximately 2 to 4 hours after administration of the dose. Patients who received 750 mg demonstrated higher C_{MAX} ($P = .50$) and AUC_{INF} ($P = .01$) compared to those receiving 600 mg on cycle 1, day 1, yet with comparable T_{MAX}, clearance, and half-life (Table 3). Figure 3 depicts mean plasma concentration−time curves for each cycle on each dose level, where steady-state (cycle 2, day 1) levels are higher

than those at first dose as a result of extensive accumulation. Exposure–response analyses assessing the correlation of either C_{MAX} or area under the plasma concentration versus time curve (AUC) to AE grade for concentration impairment, tremor, confusion, and nausea found no significant associations. This was most likely due to the narrow dose (i.e. exposure) range found in this small study.

Discussion

Seviteronel, provided both as twice-daily and once-daily regimens in the absence of oral steroid supplementation, was generally not well tolerated in this phase 2 study that assessed patients with mCRPC whose disease had previously progressed on ENZ. While the toxicity profile largely reflects what has been previously published in both patients with breast cancer[32] and prostate cancer,[29] the high prevalence of concentration impairment per se seen in this study has not been previously reported and was not expected based on preclinical toxicology data with this agent. It is worth noting, however, that the phase 1 study of seviteronel with once-daily dosing was not devoid of CNS toxicity, with 71% of patients experiencing fatigue, 52% dizziness, and 33% blurry vision, all of which could be different manifestations of CNS toxicity.[29] In this study, fatigue was commonly associated with concentration impairment, and those AEs could present with overlapping symptomatology. Concentration impairment occurred in 14 (82%) of 17 patients, with grade 2 or higher occurring in 5 of those patients, and it contributed to treatment discontinuation in 9 patients. Additionally, concentration impairment frequently resulted in dose reductions or treatment cessation. Other toxicities occurring in $>$ 50% of this patient population included fatigue, tremor, and nausea, for which fatigue was previously reported at a similar frequency. This study did not find a correlation between drug exposure and AE severity; however, these analyses were limited by a small sample size. Although these patients had often previously received immunotherapy and angiogenesis inhibitors while on clinical trials, it is unlikely that those treatments contributed to the CNS toxicity seen.

The most common toxicities observed with seviteronel, which included those with apparent CNS origin, are also found in patients experiencing adrenal glucocorticoid insufficiency.[33-35] This suggests that minor CYP17 hydroxylase inhibition may be present with seviteronel administration, and to aid in ameliorating those toxicities, the coadministration of the glucocorticoid mimetic dexamethasone was investigated in other new and ongoing breast and prostate cancer studies.[29,32] Though no grade 4 AEs attributable to seviteronel were reported in this study, nine grade 3 AEs did occur, including concentration impairment and dizziness. Limited tolerability greatly affected the analysis of clinical endpoints, including radiographic response and time to disease progression. Only 1 (6%) of 17 study patients experienced the study's primary endpoint of a PSA decline $\geq$ 50%, although toxicity required multiple changes in dosing strategy, which limits our ability to evaluate the potential efficacy of seviteronel.

The PK analysis of seviteronel in the present study uncovered significant increases in AUC from first dose to steady state. This phenomenon was observed with unpublished sponsor data when PK sampling stopped at 24 hours at first dose and 8 hours at steady state; however, this was not reported in either of the previously published studies, which only reported first-dose PK.[29,32] The data collected in this trial was sampled to 48 hours in order to better estimate the elimination rate, which ultimately leads to a more accurate half-life estimate compared to previous analyses.[29,32] With a mean first dose half-life of 13.9 hours (range, 7.9-23.5 hours), seviteronel was expected to accumulate 43% above first dose with once-daily dosing until reaching steady state (69.5 hours, or 2.9 days, to reach 97% steady state). This half-life estimate was based on a 48-hour sampling window and was considered to be more accurate than prior PK studies that only sampled to 24 hours after the first dose or 8 hours at steady state ($t_{1/2}$ $\sim$ 6-9 hours).[29,32] Steady-state dose-normalized C_{MAX} was 20% higher than cycle 1 (means: 6.79 μg/L/mg vs. 8.16 μg/L/mg; $P = .44$). Dose-normalized steady-state AUC_{TAU} was on average 61% higher than first-dose AUC_{INF} (6 of 6 patients with available data had increases; 56.7 hours × μg/L/mg vs. 91.3 hours × μg/L/mg; $P = .001$). This significant accumulation (61% by AUC) to steady state supports the toxicity profile, especially with persistent CNS events that take several half-lives to resolve.

Efforts to improve the seviteronel toxicity profile were ongoing through the duration of this study, as evidenced by 2 adjustments to the on-study dosing strategy. Drug accumulation was originally postulated as a contributing factor to increased toxicity, with higher trough concentrations mediating CNS-related AEs, prompting reduction in dosing frequency from twice daily to once daily. The separate phase 1 dose escalation study evaluating once-daily dosing did not formally define a maximum tolerated dose, but instead suggested that seviteronel could be provided at 750 or 600 mg once daily.[29] The adoption of once-daily dosing of seviteronel 750 mg on the present study showed a minimal improvement in tolerability. Further investigation with 600 mg once daily provided a similar AE profile without a significant clinical response, suggesting that both doses were not truly viable for once-daily administration, especially without oral steroid coadministration. It is worth noting that interindividual variability in seviteronel disposition would not adequately explain these toxicities. Clinical characteristics such as body weight and prandial status, the latter of which significantly affects abiraterone bioavailability,[36] do not require clinically meaningful seviteronel dose modifications.[37] Like ENZ, seviteronel exhibits low interindividual variability in men with mCRPC, with only body weight having a minimal impact on seviteronel clearance.[37,38]

Currently available clinical data in patients with mCRPC previously treated with ENZ or AA may suggest a limited or absent therapeutic window for both twice-daily and once-daily dosing of single-agent seviteronel. Initial investigations of seviteronel 450 mg provided twice daily yielded several PSA declines of $\geq$ 50% in 2 of 7 patients who had previously received ENZ,[28] providing the initial rationale for the current study. Cumulative assessment of once-daily dosing regimens in 28 patients with mCRPC previously treated with AA or ENZ is associated with only 2 clinical responses (7%), both at the 750 mg dose: one patient previously treated with AA with a PSA decline of $>$ 30%,[29] and the clinical response reported in the current study. Total daily doses of $\geq$ 750 mg appear to be associated with PSA declines in patients with mCRPC previously treated with AA or ENZ; however, tolerability has greatly limited treatment duration and potentially clinical response. It is possible that a tolerable and efficacious dose of seviteronel is not achievable for a majority of patients with mCRPC after antihormonal therapy

or chemotherapy, at least by utilizing currently established dosing strategies in the absence of oral steroid coadministration, which was thought to be an important attribute of seviteronel in its clinical development.

Another potential contributing factor to the limited clinical response is exposure to prior lines of treatment. In patients receiving sequential lines of standard-of-care treatments (ie, docetaxel, AA, and ENZ and cabazitaxel), reported PSA response rates associated with second, third, and fourth lines of treatment are 38%, 24%, and 16%, respectively.[27] When specifically analyzing sequences of ENZ followed by AA, 2 studies reported PSA response rates of 3% and 8%,[39,40] which is similar to the currently evaluated treatment sequence of ENZ followed by seviteronel. PSA response rates in treatment-naive patients receiving seviteronel were 11% (n = 26) and 33% (n = 9) for twice-daily dosing and once-daily dosing, respectively (daily cumulative doses of $\geq$ 600 mg).[28,29] Importantly, an association with increased response rates in treatment-naive patients compared to pretreated patients (33% vs. 0) was shown in the phase 1 study evaluating once-daily dosing.[29] The only significant PSA decline in the present study occurred in a patient not previously treated with chemotherapy. Available clinical data do not support the utility of seviteronel's unique mechanism of action in the post-ENZ setting. Though characterization of tumor alterations was not performed in this study, it is possible that the role of AR point mutations with an affinity to seviteronel was negligible, either as a result of a minimal role driving ENZ-resistant disease (eg, *T877A*, *H874Y*)[41] or limited prevalence based on previous clinical reports in patients with mCRPC after ENZ monotherapy (eg, *F876L*).[12,15,16,20] Moreover, seviteronel's proposed specificity for the CYP17 lyase activity, proposed to mitigate mineralocorticoid excess associated with AA, was overshadowed by intolerable CNS toxicity. The inability of seviteronel to produce robust clinical responses may be indicative of the drug's ineffectiveness to target acquired resistance in a generalized post-ENZ mCRPC patient population in addition to the drug's suboptimal dose density resulting from limited tolerability.

This trial provides a cautionary tale as the field of prostate cancer looks to target an AR pathway that has mutated or is otherwise resistant to standard AR-directed therapies. In developing next-generation AR-targeted therapy, heretofore underappreciated neurocognitive toxicity may be a significant limitation despite promising preclinical rationale, as it was with seviteronel. Preclinical studies have previously demonstrated the capability of ENZ and APA to penetrate the blood–brain barrier.[42] Furthermore, this is not the first agent targeting the AR that has suggested neurotoxicity. There have been several studies suggesting that androgen deprivation therapy has been associated with some degree of cognitive decline.[43] ENZ has also been associated with severe fatigue in some patients, and even seizures.[44] Notably, an episode of seizure activity coupled with limited antitumor activity during phase 1 evaluation terminated the development of the novel antiandrogen BMS-641988.[45] As further AR-targeting strategies are investigated, great care needs to be taken to monitor for off-target neurologic toxicity.

Conclusion

None of the dosing strategies implemented for seviteronel administration in the present study was well tolerated by patients with mCRPC previously treated with ENZ. The limited tolerability coupled with a clinically insignificant response rate does not support further development of seviteronel, especially without oral steroid coadministration, in patients with mCRPC.

Clinical Practice Points

- Improving the efficacy of available treatments for patients with mCRPC after either antihormonal therapy or chemotherapy is an important objective currently under clinical investigation.
- Seviteronel is an orally bioavailable dual inhibitor of CYP17 lyase activity and the AR, proposed to limit toxicity associated with mineralocorticoid excess and target AR pathway–mediated resistance after treatment with ENZ or AA in patients with mCRPC.
- Seviteronel provided via twice-daily or once-daily dosing in patients with mCRPC previously treated with ENZ and/or docetaxel was associated with dose-limiting CNS toxicities and insignificant clinical response.
- This study highlights the importance of appropriate dose selection and well-designed PK analyses, as AUC assessments demonstrated significant increases in drug exposure after one cycle of treatment compared to the first dose.
- Clinical experience with seviteronel highlights the potential for dose-limiting neurocognitive toxicity often associated with the development of newer AR-targeted therapies, especially in the setting of acquired resistance.

CRediT authorship contribution statement

Ravi A. Madan: Funding acquisition, Project administration, Supervision, Methodology, Conceptualization, Investigation, Writing - original draft, Writing - review & editing. **Keith T. Schmidt:** Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Fatima Karzai:** Project administration, Investigation, Supervision. **Cody J. Peer:** Formal analysis, Software, Validation, Visualization, Writing - original draft. **Lisa M. Cordes:** Project administration, Investigation, Supervision. **Cindy H. Chau:** Methodology, Conceptualization, Investigation, Writing - original draft. **Seth M. Steinberg:** Formal analysis, Data curation, Software, Validation, Visualization. **Helen Owens:** Data curation. **Joel Eisner:** Methodology, Conceptualization, Resources. **William R. Moore:** Methodology, Conceptualization, Resources. **William L. Dahut:** Funding acquisition, Project administration, Methodology, Conceptualization, Investigation, Supervision. **James L. Gulley:** Funding acquisition, Project administration, Methodology, Conceptualization, Investigation, Supervision. **William D. Figg:** Funding acquisition, Project administration, Methodology, Conceptualization, Investigation, Writing - original draft, Writing - review & editing.

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Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental data and table accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2019.11.002.

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Supplemental Methods

Noncompartmental Pharmacokinetic Analysis

First-dose pharmacokinetic (PK) parameters were calculated by noncompartmental methods using Phoenix WinNonlin 7.0 (Certara Pharsight, Cary, NC). Any plasma concentration measured below the lower limit of quantitation (LLOQ) was excluded from analyses. The maximum Pplasma concentration (C_{MAX}) and time to C_{MAX} (T_{MAX}) were recorded as observed values. The area under the plasma concentration versus time curve to the last observed time point (AUC_{LAST}) was calculated by the Linear Up Log Down trapezoidal rule. The elimination rate (k_{EL}) was calculated as the slope of the log-transformed concentrations versus terminal time points. AUC extrapolated to time infinity (AUC_{INF}) was calculated as $AUC_{LAST} + C_{LAST}/k_{EL}$, where C_{LAST} is the concentration at the last observed time point. Half-life ($t_{1/2}$) was calculated as $\ln 2/k_{EL}$. Apparent oral clearance (CL/F) was calculated as dose/AUC_{INF}; apparent oral volume of distribution (Vz/F) was calculated as CL/F divided by k_{EL}. PK parameters at steady-state (cycle 2, day 1) Were calculated the same way, except AUC was calculated over the dosing interval tau = 24 hours (AUC_{TAU}), clearance (CLss/F) as dose/AUC_{TAU}, and Vz/F as CLss/F divided by k_{EL}. The number of subjects included in the PK analysis was insufficient for proper statistical testing.

Supplemental Table 1 AEs in > 15% of Study Population Sorted by Dosing Strategy

	450 mg Twice Daily (N = 7)		750 mg Once Daily (N = 6)		600 mg Once Daily (N = 4)	
AE	Grade 1/2	Grade 3	Grade 1/2	Grade 3	Grade 1/2	Grade 3
Concentration impairment	6 (86)	0	5 (83)	1 (17)	2 (50)	0
Fatigue	5 (71)	0	4 (67)	0	2 (50)	0
Tremor	3 (43)	0	5 (83)	0	2 (50)	0
Nausea	4 (57)	1 (14)	0	0	3 (75)	1 (25)
Dizziness	2 (29)	1 (14)	1 (17)	1 (17)	1 (25)	0
Blurred vision	1 (14)	0	1 (17)	0	2 (50)	0
Hypotension	3 (43)	0	0	0	0	1 (25)
Vomiting	1 (14)	0	0	0	2 (50)	0
Edema (limbs)	1 (14)	0	1 (17)	0	1 (25)	0
Fall	1 (14)	1 (14)	0	0	1 (25)	0
Gait disturbance	3 (43)	0	0	0	0	0
Malaise	1 (14)	0	2 (33)	0	0	0
Presyncope	3 (43)	0	0	0	0	0

Data are presented as n (%). AEs are those with attribution of at least possibly occurring in > 15% of patients who received study treatment (n = 17). AEs are based on National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).
Abbreviation: AE = adverse event.