Published OnlineFirst July 16, 2018; DOI: 10.1158/1078-0432.CCR-18-0564

Clinical Trials: Targeted Therapy

Clinical Cancer Research

Phase I Study of Seviteronel, a Selective CYP17 Lyase and Androgen Receptor Inhibitor, in Men with Castration-Resistant Prostate Cancer

Shilpa Gupta[1], Luke T. Nordquist[2], Mark T. Fleming[3], William R. Berry[4], Jingsong Zhang[5], Sharon L. Ervin[6], Joel R. Eisner[6], Edwina S. Baskin-Bey[6], and Neal D. Shore[7]

Abstract

Purpose: Seviteronel (INO-464) is a selective cytochrome P450c17a (CYP17) 17,20-lyase (lyase) and androgen receptor (AR) inhibitor with antitumor activity *in vitro* and *in vivo*. This open-label phase I clinical study evaluated the safety, tolerability, pharmacokinetics and activity of once-daily seviteronel in male chemotherapy-naïve subjects with castration-resistant prostate cancer (CRPC).

Patients and Methods: Seviteronel was administered at 600 mg once daily with dose titration (DT) and in modified 3 + 3 dose escalation once-daily cohorts at 600, 750, and 900 mg without DT. The primary objectives of this study were to establish safety, tolerability, and the MTD of seviteronel in chemotherapy-naïve subjects with or without prior treatment with FDA-approved CRPC treatments, abiraterone acetate (AA), and enzalutamide. Secondary objectives were to assess pharmacokinetics, PSA, tumor response, and endocrine results.

Results: Twenty-one subjects were enrolled. No dose-limiting toxicities (DLT) were observed through 750 mg once daily. Most treatment-emergent adverse events (AE) reported at grade 1–2. The most commonly reported AEs were fatigue (71%), dizziness (52%), blurred vision (38%), and dysgeusia (33%), with most AEs improving after dose reduction or dose interruption.

Conclusions: Once-daily seviteronel was generally well tolerated in this phase I study of men with CRPC, a majority of which had progressed on prior AA or enzalutamide, or both. Of the doses evaluated, 600 mg once daily was chosen as the recommended phase II dose for future studies in subjects with CRPC. *Clin Cancer Res; 24(21); 5225–32. ©2018 AACR.*

Introduction

Abiraterone acetate (AA) + prednisone and enzalutamide are FDA-approved antihormonal therapies for the treatment of castration-resistant prostate cancer (CRPC; refs. 1–4). AA is a nonselective, irreversible, and potent inhibitor of cytochrome P450c17a (CYP17; i.e., it inhibits both 17-α-hydroxylase [hydroxylase] and 17,20-lyase [lyase]). Because of AA's potent hydroxylase inhibition, prednisone is coadministered in an attempt to abate the increased steroids upstream of CYP17, cortisol suppression, and mineralocorticoid excess syndrome (1, 2, 5–7). Enzalutamide is a second-generation AR antagonist (8).

Although a majority (62%–78%) of chemotherapy-naïve patients initially responded to AA/prednisone and enzalutamide (1, 4), acquired resistance occurs over time in greater than 90% of patients due to multiple resistance mechanisms. Over 50% of metastatic CRPCs display changes to the AR, which include, but are not limited to, AR overexpression (9), AR splices variants (AR-Vs; refs. 10–12), and AR point mutations. The AR point mutations T878A and L702H cause AR agonism by progesterone/pregnenolone (associated with AA/prednisone use; ref. 5), and prednisone (used with AA), respectively (13, 14). Similarly, the AR F876L point mutation confers resistance to enzalutamide, where it becomes a strong agonist of the AR variant (14, 15).

Currently, there are very limited options for patients progressing on AA/prednisone and or/enzalutamide, representing an unmet clinical need for new AR-directed therapies that can improve responses in this patient population. We hypothesize that cotargeting the AR and CYP17 lyase with a single agent may be a more effective strategy to improve responses in CRPC than targeting either AR or CYP17 alone. Development of dual inhibitors of CYP17 lyase and AR represent an optimal strategy to achieve increased responses in CRPC while limiting the toxicities of two separate agents.

Seviteronel (INO-464) is an orally bioavailable, selective CYP17 lyase and AR inhibitor that blocks androgen biosynthesis and AR activation in multiple *in vitro* and/or *in vivo* models. Seviteronel has an approximately 10-fold selectivity toward CYP17 lyase over hydroxylase (16) and is a competitive antagonist of both wild-type and mutated forms of the AR (e.g., T877A and F876L; ref. 17). With regards to enzalutamide-resistant

[1]University of Minnesota, Minneapolis, Minnesota. [2]Urology Cancer Center & GU Research Network, Omaha, Nebraska. [3]Virginia Oncology Associates, Norfolk, Virginia. [4]Duke University Cancer Center, Durham, North Carolina. [5]Moffitt Cancer Center, Tampa, Florida. [6]Innocrin Pharmaceuticals Inc., Durham, North Carolina. [7]Carolina Urologic Research Center, Myrtle Beach, South Carolina.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Authors: Neal D. Shore, Carolina Urologic Research Center, 823 82nd Parkway, Myrtle Beach, SC 29572. Phone: 843-449-1010; Fax: 843-286-0119; E-mail: nshore@gsuro.com; and Shilpa Gupta, Division of Hematology, Oncology and Transplantation, University of Minnesota, 420 Delaware St. SE, MMC 480, 14-142C Phillips Wangansteen Building, Minneapolis, MN 55455. Phone: 612-626-3003; Fax: 612-625-6919; E-mail: guptash@umn.edu

doi: 10.1158/1078-0432.CCR-18-0564

Published OnlineFirst July 16, 2018; DOI: 10.1158/1078-0432.CCR-18-0564

Translational Relevance

Seviteronel is a selective inhibitor of both cytochrome P450c17a (CYP17) 17,20-lyase (lyase) and the androgen receptor (AR) that has shown antitumor activity in models of castration-resistant prostate cancer (CRPC) *in vivo* and *in vitro*. Abiraterone acetate (AA), a CYP17 17-α-hydroxylase (hydroxylase) inhibitor, and enzalutamide, an AR antagonist, are FDA-approved treatments for CRPC that show initial response in chemotherapy-naïve patients with CRPC; however, resistance to these therapies develops over time. With limited treatment options for patients progressing on AA and/or enzalutamide, and potential side effects for drugs targeting CYP17 hydroxylase, there is a need for novel therapies for this patient population. With its dual mechanism of action and CYP17 lyase selectivity, seviteronel may provide a new treatment option for men with CRPC who have progressed on other AR-targeted agents.

cell-line growth, C4-2, C4-2B, MR49C, and MR49F, seviteronel was a more potent inhibitor than AA (18, 19). *In vivo*, seviteronel inhibits the growth of multiple CRPC cell lines, including MR49F, MDA-PCA-133, and LNCaP (17, 19, 20).

The preliminary safety, tolerability, pharmacokinetics, and clinical activity of twice daily dosing in men with CRPC was described previously (NCT02012920; ref. 21). Potent androgen declines, accompanied by PSA reductions, were observed in subjects following twice-daily seviteronel administration. However, frequent dose reductions and treatment discontinuations, due to a lack of seviteronel tolerability, prevented adequate evaluation of its full clinical activity. It was postulated that twice-daily dosing lead to seviteronel accumulation. Therefore, once-daily dosing with seviteronel in men with CRPC was investigated in this study (NCT02361086), with the initial safety, tolerability, pharmacokinetics, and initial clinical activity reported here within.

Patients and Methods

Major eligibility criteria

Men with documented histologic or cytological evidence of adenocarcinoma of the prostate with rising PSA [Prostate Cancer Clinical Trials Working Group 2 (PCWG2); ref. 22], despite castration testosterone concentrations [1.74 nmol/L (<50 ng/dL)] were enrolled. Subjects must have undergone orchiectomy, or have initiated LHRH agonists/antagonists at least 3 months prior to study entry with the LHRH agonists/antagonists continued for the duration of the study. PSA-only progression was allowed as was previous use of AA and/or enzalutamide, provided both agents were discontinued prior to enrollment. Eligibility required an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, white blood cell count $\geq$3,000/μL, absolute neutrophil count $\geq$1,500/μL, platelet count $\geq$100,000/μL, hemoglobin $\geq$10 g/dL and not transfusion dependent, aspartate transaminase and alanine transaminase levels $\leq 3\times$ the upper limit of normal, bilirubin levels of $\leq$2.0 mg/dL, serum creatinine of $\leq$2.0 mg/dL, and potassium levels >3.5 mEq/L. Use of first-generation antiandrogens with a PSA reduction upon withdrawal, prior use of investigational products directed toward the AR or androgen biosynthesis, and 5-α-reductase inhibitor use <3 months from study drug initiation were exclusionary. Prior chemotherapy for prostate cancer was not allowed, or the use of sipuleucel-T treatment within 30 days of study drug initiation. Subjects who required pharmacologic or replacement doses of systemic corticosteroids or were administered systemic corticosteroids within 30 days of study drug administration were ineligible.

Study design and treatment

The primary objective of this phase I study was to determine the safety, tolerability, and MTD of once-daily oral seviteronel in chemotherapy-naïve subjects with CRPC. The pharmacokinetics of seviteronel and its effect on PSA, tumor response, and endocrine laboratory correlates were secondary objectives. The study was approved by the Institutional Review Board at each site and was conducted in accordance with The World Medical Association Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation. All subjects provided a written informed consent prior to study participation.

Seviteronel was administered orally as 150 mg tablets at 600 mg once daily with dose titration (DT; 150 mg once daily for 2 weeks and 300 mg once daily for 2 weeks) and in escalating dose cohorts of 600, 750, or 900 mg once daily without DT. Following DT or in cohorts without DT, study drug was administered in 28-day continuous dosing cycles. Study drug was discontinued if they were no longer clinically benefitting, had an adverse event (AE) that precluded further participation in the study, or withdrawal of consent.

The study followed a traditional modified "3 + 3" Fibonacci study design. Three subjects were enrolled in each dose cohort, and with a single dose-limiting toxicity (DLT), the cohort was expanded to 6 subjects. DLT was defined as any grade 3 or greater AE possibly/probably/definitely related to seviteronel that occurred from the first dose of study drug through the end of the first 28-day continuous dosing cycle (cycle 1). In the presence of 0 or 1 DLT, the dose was escalated in the next higher dose-level cohort. Two or more DLTs in a cohort resulted in expansion of the lower dose-level cohort to 6 subjects. Expansion of open cohorts up to 12 subjects was allowed to further investigate safety (non-DLT), endocrine, or efficacy observations at that dose. MTD was defined as the highest dose level in which the incidence of DLTs was less than 33%. Toxicity was graded using the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

Evaluations

Baseline evaluations were conducted within 28 days of study drug initiation and included medical history, physical examination, vital signs, ECOG performance status, electrocardiogram, complete blood counts and serum chemistries, urinalysis, PSA, and imaging assessments.

Repeat evaluations were conducted on day 1 and 2 of the DT stage (DT cohort only), biweekly for cycle 1 and then monthly thereafter through the end of treatment visit. Holter monitoring was only repeated the first day of dosing and at cycle 2 day 1. Efficacy assessments by imaging were repeated at the end of each even-numbered cycle and compared with baseline according to PCWG2 criteria (22) in the subjects shown to have metastatic disease at screening, or suspected of having developed metastatic

Published OnlineFirst July 16, 2018; DOI: 10.1158/1078-0432.CCR-18-0564

disease. The evaluation included all appropriate radiographic or scintigraphic procedures to document areas of metastatic disease, including bone scans, CT scans, and/or MRI, dependent upon what modality was utilized at baseline.

Endocrine analysis

A standard cortrosyn stimulation test was performed at baseline and at cycle 1 day 14 baseline to assess the impact of seviteronel on cortisol reserve. Blood samples were collected for an endocrine panel (DHEA, testosterone, cortisol) at baseline and at each study visit through the end of treatment visit. Endocrine samples were analyzed using a central lab (Quest Diagnostics). The lower limit of quantitation (LLOQ) for serum testosterone assessed using LC/MS-MS was 1.0 ng/dL (0.03 nmol/L).

Pharmacokinetic analysis

Blood samples for pharmacokinetic analysis were collected prior to first dose of seviteronel and 0.5, 1, 2, 4, 6, 8, and 24 hours after for dense pharmacokinetic analysis. Additional samples were collected at cycle 1 day 14, cycle 2 day 1, and then every even-numbered cycle for spot pharmacokinetics analysis. The LLOQ of seviteronel plasma concentrations analyzed using LC/MS-MS was 20 ng/mL (0.05 μmol/L; Tandem Laboratories). Dense pharmacokinetics parameters were analyzed by noncompartmental methods using WinNonlin (Certara).

Results

Subject characteristics

A total of 21 subjects with CRPC were enrolled from June 2014 to July 2015 with data presented as of November 18, 2016. Baseline characteristics, including disease status and prior exposure to AA or enzalutamide, are presented in Table 1. Over half (57%) of the subjects enrolled across cohorts had prior AA, enzalutamide or AA + enzalutamide, and most (73%) also had prior exposure to first-generation antiandrogens, such as bicalutamide and flutamide. All subjects enrolled had either bone or soft tissue involvement, with approximately one third (29%) with visceral disease.

Dose escalation

No DLTs (grade 3 or greater drug-related AE in the first 28-day dosing cycle) were reported through 750 mg once daily. The 600 and 750 mg once-daily cohorts were expanded to gain a better understanding of the tolerability and activity of seviteronel at those dose levels. In the 900 mg once-daily cohort, one DLT was reported in the first subject enrolled (grade 3 muscular weakness considered related to seviteronel); further subjects were not enrolled at that dose level. Although MTD was not achieved in the dose cohorts evaluated, 750 mg once daily was the highest dose that was fully explored.

Tolerability

Treatment with seviteronel was generally well tolerated with the majority of AEs grade 1 or 2 and the most common AEs were fatigue, dizziness, blurred vision, and dysgeusia, independent of relationship (Table 2). Fourteen grade 3 AEs were reported in 9 subjects, of which 5 were deemed per investigator possibly related to seviteronel [syncope (600 mg QD + DT), hyponatremia (600 mg QD + DT), fatigue (600 mg once daily), atrial fibrillation (750 mg once daily), and muscle weakness (900 mg once daily)]. One grade 4 AE was reported [sepsis (750 mg once daily)] and it was not deemed per the investigator related to seviteronel. No deaths were reported. Nine serious AEs (SAE) were reported in 8 subjects with 4 considered at least possibly related to seviteronel [syncope (600 mg QD + DT), deep vein thrombosis (750 mg once daily), atrial fibrillation (750 mg once daily), and muscular weakness (900 mg once daily)]. No cases of overt adrenal insufficiency were reported.

Overall median treatment duration was 65 days (11, 565) and with the longest median duration observed in the 750 mg once daily cohort [107 days (11, 262); Supplementary

Table 1. Demographics and baseline characteristics

Category	600 mg + DT *n* = 3	600 mg *n* = 8	750 mg *n* = 9	900 mg *n* = 1	Total *N* = 21[a]
Age (y)[b]	74 (72–77)	68 (44–83)	68 (57–79)	81 (81–81)	68 (44–83)
Race[c]					
White	3 (100)	7 (88)	7 (78)	1 (100)	18 (86)
Black	0 (0)	0 (0)	2 (22)	0 (0)	2 (10)
Other	0 (0)	1 (12)[d]	0 (0)	0 (0)	1 (5)
BMI (kg/m^2)[b]	28.1 (23.6–29.1)	30.5 (26.3–42.9)	29.7 (25.8–42.5)	25.2 (25.2–25.2)	29.1 (23.6–42.9)
Disease status					
PSA (ng/mL)[b]	18.5 (2.1–140.5)	27.8 (5.4–186.8)	22.4 (3.5–145.5)	20.3	22.5 (2.1–186.8)
Bone disease[c,e]	2 (67)	5 (63)	7 (78)	1 (100)	15 (71)
Lymph node[c,e]	2 (67)	5 (63)	5 (56)	0 (0)	12 (57)
Visceral disease[c,e]	1 (33)	4 (50)	1 (11)	0 (0)	6 (29)
Prior treatments					
AA- and ENZA-Naïve[c]	3 (100)	4 (50)	2 (22)	0 (0)	9 (43)
Prior ENZA[c]	0 (0)	2 (25)	1 (11)	1 (100)	4 (19)
Prior AA[c]	0 (0)	2 (25)	4 (44)	0 (0)	6 (29)
Prior ENZA + AA[c]	0 (0)	0 (0)	2 (22)[a]	0 (0)	2 (10)

Abbreviations: AA, abiraterone acetate; DT, dose titration; ENZA, enzalutamide.
[a]One subject discontinued before Cycle 1 Day 14 and is only included in the safety population.
[b]Median (range).
[c]*n* (%).
[d]Not reported.
[e]Subjects may be counted more than once.

Published OnlineFirst July 16, 2018; DOI: 10.1158/1078-0432.CCR-18-0564

Table 2. Incidence of most common (>20%) of treatment-emergent AEs independent of relationship

	All grades ($n = 21$)	600 mg QD + DT ($n = 3$)		600 mg QD ($n = 8$)		750 mg QD ($n = 9$)		900 mg QD ($n = 1$)	
Adverse event[a]	Gr 1–3	Gr 1–2	Gr 3	Gr 1–2	Gr 3	Gr 1–2	Gr 3	Gr 1–2	Gr 3
Fatigue	15 (71)	2 (67)	0 (0)	6 (75)	1 (13)	6 (67)	0 (0)	1 (100)	0 (0)
Dizziness	11 (52)	2 (67)	0 (0)	4 (50)	0 (0)	4 (44)	0 (0)	1 (100)	0 (0)
Blurred vision	8 (38)	1 (33)	0 (0)	2 (25)	0 (0)	4 (44)	0 (0)	1 (100)	0 (0)
Dysgeusia	7 (33)	2 (67)	0 (0)	1 (13)	0 (0)	4 (44)	0 (0)	0 (0)	0 (0)
Constipation	6 (29)	1 (33)	0 (0)	2 (25)	0 (0)	3 (33)	0 (0)	0 (0)	0 (0)
Disturbance in attention	6 (29)	2 (67)	0 (0)	2 (25)	0 (0)	1 (11)	0 (0)	1 (100)	0 (0)
Tremor	6 (29)	1 (33)	0 (0)	0 (0)	0 (0)	4 (44)	0 (0)	1 (100)	0 (0)
Memory impairment	5 (24)	2 (67)	0 (0)	0 (0)	0 (0)	3 (33)	0 (0)	0 (0)	0 (0)
Muscular weakness	5 (24)	1 (33)	0 (0)	1 (13)	0 (0)	2 (22)	0 (0)	0 (0)	1 (100)
Tachycardia	5 (24)	1 (33)	0 (0)	2 (25)	0 (0)	1 (11)	0 (0)	1 (100)	0 (0)
Nausea	5 (24)	2 (67)	0 (0)	2 (25)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)
Vomiting	5 (24)	0 (0)	0 (0)	3 (38)	0 (0)	2 (22)	0 (0)	0 (0)	0 (0)

Abbreviations: DT, dose titration; Gr, grade; QD, once daily.
[a]*n* (%).

Table S1]. A majority of subjects discontinued treatment for progressive disease or AEs. Approximately 33% of subjects underwent a dose reduction or dose interruption due to an AE, which typically resulted in an improvement in the AE (Fig. 1).

Pharmacodynamic effects

All subjects were chemically or surgically castrated prior to enrollment with serum testosterone concentrations <1.74 nmol/L (50 ng/dL); mean testosterone at entry was 0.22 ± 0.15 nmol/L (mean ± SD), almost 8-fold lower than the cutoff for castration. Across dose-level cohorts, there was an 18.8% and 12.5% decline, from baseline to cycle 2 day 1, in serum testosterone and DHEA concentrations. Progesterone concentrations were unchanged from baseline to cycle 2 day 1 and remained at or below the LLOQ (0.30 nmol/L). Peak cortisol response to synthetic ACTH (cortrosyn stimulation test) was 785.9 (491, 1,143) at baseline and 861.3 (635, 1,217) at cycle 1 day 14 (>500 nmol/L considered clinically normal). Baseline cortisol was 375.5 ± 178.0 nmol/L, with a 2% increase at cycle 1 day 14 and 6.4% decline at cycle 2 day 1. Baseline corticosterone was 13.6 ± 26.7 nmol/L and did not change significantly by cycle 2 day 1, and remained within the normal range.

Pharmacokinetics

A noncompartmental pharmacokinetics summary is presented in Table 3. Plasma concentrations from each cohort after a single dose of seviteronel are presented in Supplementary Fig. S1. Half-life ranged from 8.1 to 9.2 hours at the 750 and 600 mg once-daily dose levels, which supports once-daily dosing in men.

Efficacy

Twenty of 21 subjects had postdosing PSA results available. Although the main focus of this study was safety and tolerability, 11 of 20 subjects had a PSA decline of any magnitude from baseline while on study, including all subjects naïve to

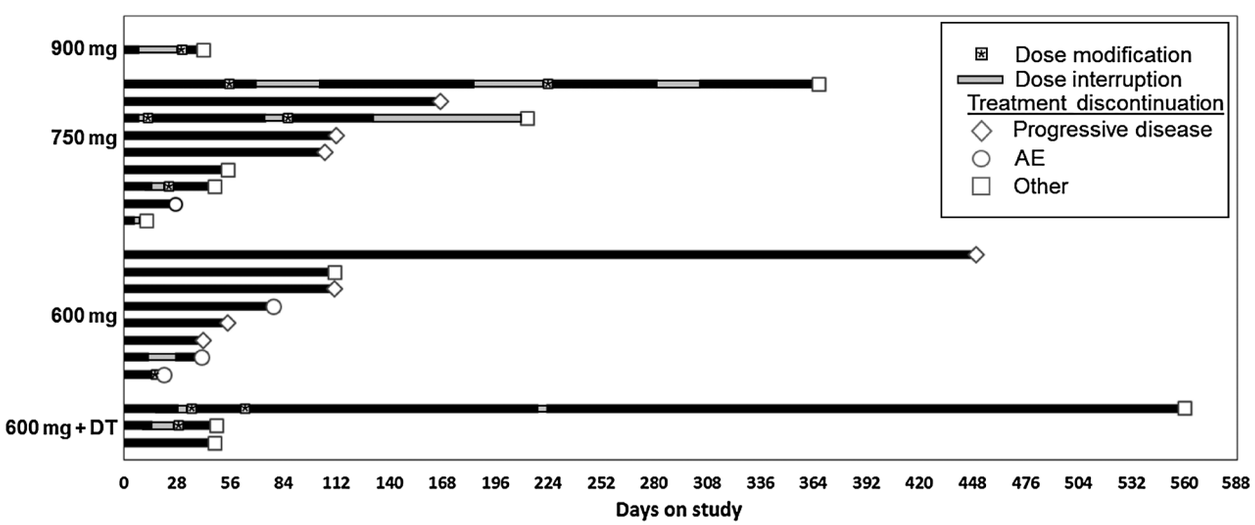

Figure 1.
Duration of seviteronel therapy. DT, dose titration.

Published OnlineFirst July 16, 2018; DOI: 10.1158/1078-0432.CCR-18-0564

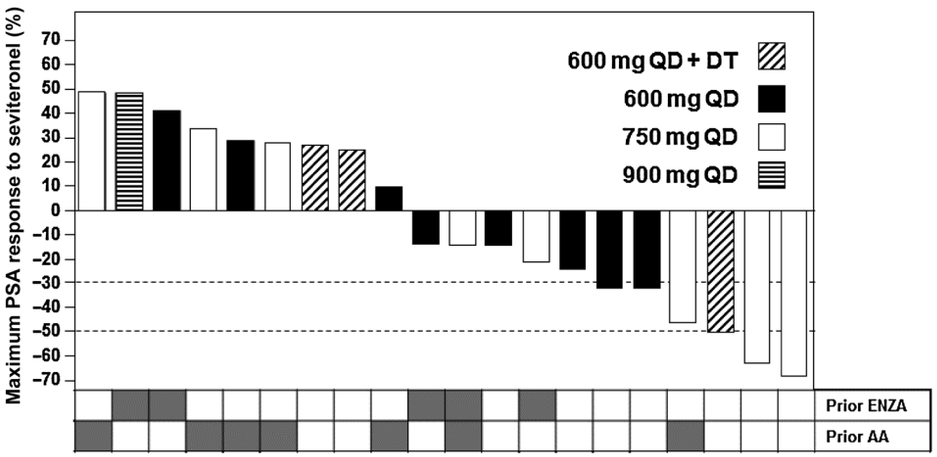

Figure 2.
Maximum PSA response to seviteronel. DT, dose titration; QD, once daily.

AA and enzalutamide in the 600 or 750 mg once-daily cohorts (Fig. 2). Six of 20 subjects had a significant PSA decline [3 $\geq$ 30% (PSA30) and 3 $\geq$ 50% (PSA50)], which included a PSA30 in 2 subjects at 600 mg once daily and PSA30 and PSA50 in 1 and 2 subjects, respectively, at 700 mg once daily. Across all dose levels examined, 4 of 11 subjects (36%) with prior exposure to AA, enzalutamide, or AA + enzalutamide demonstrated a PSA decline of any magnitude while on study. This included one subject at 750 mg once daily with prior exposure to AA + enzalutamide that had postdosing PSA results available. Nine subjects across all cohorts had 12-week PSA values available, three of which were PSA30 or PSA50.

Seventeen of 21 subjects had at least one postdose scan. Time to radiographic progression across all cohorts was a median of 106 days with a range of 55 to 449 days. This included subjects both naïve to or having had prior exposure to AA and/or enzalutamide. A majority of subjects had stable disease as their best overall response [10 of 17 (58%)]; 6 had progressive disease (35%), and 1 subject had a partial response (6%; Fig. 3). No complete responses were reported.

Subject 05-016 (Fig. 3) enrolled in the 750 mg once-daily cohort. His prior therapies included leuprolide and sipuleucel-T. He had a maximum PSA decline from baseline of 64%, which continued to cycle 8 day 1. Baseline scans included soft-tissue disease, including four target lesions: renal vasculature left peri-aortic node, left external iliac adenopathy, left peri-aortic adenopathy above bifurcation of aorta and renal vasculature aortocaval node. On repeat scan at the end of cycle 6,

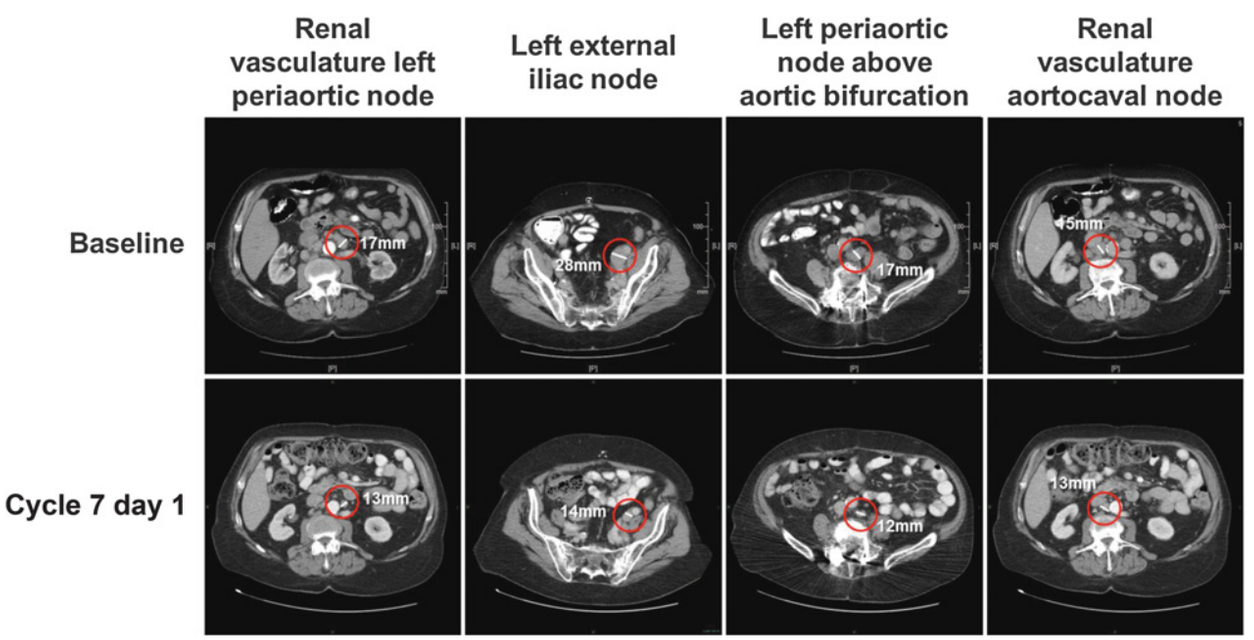

Figure 3.
Baseline and cycle 6 scans for 05-016.

Published OnlineFirst July 16, 2018; DOI: 10.1158/1078-0432.CCR-18-0564

Table 3. Pharmacokinetic parameters after a single dose of seviteronel

Treatment	AUC_{0-24} (h/ng/mL)	AUC_{INF} (h/ng/mL)	CL/F (L/h)	C_{max} (ng/mL)	T_{max} (h)	C_{min} (ng/mL)	$T_{1/2}$ (h)
600 mg + DT ($n = 2$)	31,702 ± 12,978[a]	44,049 ± 0	13.6[b]	4,515 ± 1,704	1.0 ± 0.02	370 ± 43.41	6.8[b]
600 mg QD ($n = 7$)	30,410 ± 7,126	37,668 ± 6,267	16.3 ± 3.0	4,403 ± 1,817	2.8 ± 2.5	376 ± 148	9.2 ± 2.1
750 mg QD ($n = 8$)	34,445 ± 13,432	44,422 ± 8,369	17.4 ± 3.0	3,809 ± 2,238	5.1 ± 7.8	562 ± 364	8.1 ± 2.4
900 mg QD ($n = 1$)	79,824[b]	NC	NC	5,600[b]	4.0[b]	2070[b]	NC

Abbreviations: AUC_{0-24}, AUC from the time of dosing 0–24 hours; AUC_{INF}, AUC from the time of dosing extrapolated to infinity; CL/F, apparent clearance; C_{max}, maximum concentration; C_{min}, minimum concentration; DT, dose titration; NC, not calculated; QD, once daily; T_{max}, time of maximum observed concentration; $T_{1/2}$, terminal half-life.
[a]Mean ± SD.
[b]$n = 1$

there was a 32% (25 mm) decline in the sum of target lesion diameter (77–52 mm), which was accompanied by the 64% PSA decline from baseline. The subject completed thirteen 28-day treatment cycles prior to withdrawing consent.

Discussion

Once-daily seviteronel was generally well tolerated in this phase I study of men with CRPC, a majority of which had progressed on prior AA or enzalutamide, or both. The most frequent AEs seen with seviteronel (Table 2) are similar to the approved AR-directed agents AA and enzalutamide (1, 3, 4, 23). No seizures were reported in this study, even though subjects with a prior history of seizures were not excluded from study participation. Similarly, signs and symptoms of mineralocorticoid excess syndrome, abnormal liver function tests, hypertension, headache, musculoskeletal pain, and urinary tract infections were not frequently reported.

Syncope has been observed with early studies of both AA and galeterone (24, 25). One subject in the 600 mg QD + DT cohort experienced an episode of syncope in the second dosing cycle, but remained on study at a reduced dose for over 20 cycles. Overall, the presence of syncope with seviteronel administration was reduced with the once daily dosing regimen compared with the prior BID + DT dosing regimen (21). Preclinical syncope models showed that seviteronel did not have any effect on ion channels, and the modest MT-1 and GABA-1 activity was not predictive of *in vivo* and clinical effects (26).

Although AEs such as dizziness, blurring of vision, memory impairment/disturbance in attention, and tremors were reported with seviteronel, they resolved or improved with dose interruptions or dose reductions. The frequency of tremors was reduced by almost one half with once-daily dosing compared with twice-daily dosing (21). Typically, drug-related AEs resolved to baseline within 2 to 3 weeks of dosing discontinuation.

One subject at 750 mg once daily experienced an SAE of atrial fibrillation. However, a detailed Holter monitor analysis of subjects treated with seviteronel did not show any proarrhythmogenic potential of seviteronel or general cardiotoxicity (26).

Across the full range of doses examined in this study, there was a dose-proportional relationship for peak and trough plasma concentrations, and overall exposure (AUC), after a single dose of seviteronel. With respect to the 600 and 750 mg dose levels, the dose-proportional relationship is less evident, which may help explain the relatively similar safety, tolerability, and initial activity profiles between the two doses.

Although the initial dosing regimen in this study included DT, it was not further explored, as it appeared to have an unfavorable impact on tolerability. All subjects in the 600 mg QD + DT cohort had a dose reduction and CNS/neuromuscular AEs that were similar to subjects treated with BID + DT dosing (21). In contrast, in the 600 mg once daily cohort, only 13% experienced a dose interruption or dose reduction. Although the subject numbers are small, more subjects in the 750 mg once-daily cohort experienced dose reductions or dose interruptions compared with 600 mg once daily. However, AEs were similar between the two dosing regimens. Overall median treatment duration was the longest in the 750 mg once-daily cohort compared with 600 mg QD + DT and 600 mg once daily.

More than half of subjects had prior exposure to both AA plus prednisone and enzalutamide and there did not appear to be differences in endocrine responses between the 600 and 750 mg once-daily cohorts. Given the relatively small sample size, all subjects were combined for endocrine analysis. With the prevalence of prior antiandrogen use and continuous castration, plasma testosterone concentrations at baseline were relatively low. Thus, the modest but consistent decline in testosterone seen with seviteronel treatment was not unexpected. Although not evaluated in this study, CRPC men naïve to AA and enzalutamide, who received seviteronel at either 450 or 600 mg twice daily, had nadir testosterone concentrations at or near 0.03 nmol/L (the assay LLOQ) during the first 28-day treatment cycle, which represented an >80% decline from baseline (21).

CYP17 lyase selectivity was evident in subjects administered seviteronel. Plasma progesterone concentrations remained at or near the LLOQ, and corticosterone concentrations were predominantly below the upper limit of normal in this study. These findings are consistent with what was previously demonstrated with twice-daily seviteronel administration (21). However, this is in contrast to nonselective CYP17 inhibition with single-agent AA, which results in increased upstream steroids, including progesterone and corticosterone, along with cortisol suppression, all of which is only partially ameliorated with steroid supplementation (5). The changes in steroid concentrations are due to the potent activity of AA on CYP17 hydroxylase, instead of CYP17 lyase. Preclinically, this was demonstrated in castrated male nonhuman primate model. Administration of a single dose of either seviteronel or AA resulted in similar testosterone reductions, but AA caused significant increases in progesterone and corticosterone. In contrast, changes to these upstream steroids with seviteronel were no different than vehicle control (27). A potential resistance mechanism of AA is progesterone-dependent stimulation of AR with T878A point mutation (14). Given seviteronel's lack of effect on progesterone levels, this resistance mechanism may be avoided with seviteronel treatment.

Human genetic mutations that lead to isolated CYP17 lyase deficiency, or combined CYP17 hydroxylase/lyase deficiency, result in potent androgen decreases. However, only the latter results in significant progesterone increases and significant cortisol decreases (28, 29). Although, seviteronel is a potent and

selective CYP17 lyase inhibitor, its lyase activity is not completely isolated from hydroxylase, and it still harbors some activity against CYP17 hydroxylase. Significant CYP17 hydroxylase inhibition results in cortisol suppression and an increase in ACTH, which can drive upstream steroid accumulation, including corticosterone and the associated mineralocorticoid excess syndrome (MES; ref. 5). Baseline and cycle 1 day 14 cortisol response to cortrosyn stimulation were similar in this study, and in the prior investigation of twice-daily dosing of seviteronel (21). Increases in corticosterone concentrations were also not observed. Also, significant CYP17 hydroxylase inhibition does not appear to be occurring in men or women treated with seviteronel as the common signs and symptoms of MES, which include hypertension, hypokalemia, and fluid overload, were not observed in this study or in women with breast cancer treated with seviteronel (Bardia and colleagues, submitted). However, the most common AEs observed with seviteronel, including those that appear to have a CNS origin, are also found in patients experiencing adrenal glucocorticoid insufficiency (30–32), suggesting a minor CYP17 hydroxylase inhibition. Accordingly, to ameliorate associated AEs, the addition of the glucocorticoid mimetic dexamethasone to seviteronel is currently being investigated in ongoing prostate and breast cancer studies.

Even though this was primarily a safety and tolerability study, preliminary activity of oral, once-daily, seviteronel was demonstrated in this study with most subjects experiencing a PSA decline and demonstrating radiographic stable disease. Although a formal MTD was not reached in this phase I study, it did appear that the maximum effect of seviteronel on PSA decline was at 750 mg once daily, but significant PSA declines (PSA decline $\geq$ 30%) were also observed in subjects enrolled at 600 mg once daily.

Combined time to radiographic progression across all cohorts was 106 days, with over half of the subjects enrolled having prior exposure to AA and/or enzalutamide. Overall duration of treatment, as a surrogate of PFS, was 107 days in the 750 mg once-daily cohort where approximately 80% enrolled had prior exposure to AA, enzalutamide, or both. This is favorable to the treatment duration observed with sequential AA/enzalutamide or enzalutamide/AA where the second intervention is typically shorter than seen with seviteronel (33–36). A limitation of this study is that duration of use and best response to prior AA and/or enzalutamide were not collected. These data should be collected in future studies to better understand impact on response to seviteronel.

In conclusion, once-daily seviteronel is generally well tolerated and has activity in men with CRPC, regardless of prior exposure to AA and/or enzalutamide. Although both 600 mg and 750 mg once daily were considered acceptable as phase II doses for men, ultimately, 600 mg once daily was chosen as the recommended phase II dose for future studies in subjects with CRPC based upon fewer AE-related dose modifications compared with 750 mg once daily. Given that doses below 600 mg once daily were not explored in this study, future examination of lower doses may be warranted. With its dual mechanism of action and CYP17 lyase selectivity, seviteronel may provide a new treatment option for men with CRPC who have progressed on other AR-targeted agents. Seviteronel is currently being explored in several phase II clinical studies of men with CRPC who are resistant to current antihormonal therapies (NCT02130700, NCT02445976, and NCT02012920), as well as for women and men with breast cancer (NCT02580448).

Disclosure of Potential Conflicts of Interest

S. Gupta reports receiving speakers bureau honoraria from Bristol-Myers Squibb and Exelixis, and is a consultant/advisory board member for AstraZeneca, Genentech, Merck, and Pfizer. N.D. Shore is a consultant/advisory board member for Innocrin. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: M.T. Fleming, J.R. Eisner, E.S. Baskin-Bey, N.D. Shore
Development of methodology: S. Gupta, J.R. Eisner, E.S. Baskin-Bey, N.D. Shore
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Gupta, L.T. Nordquist, M.T. Fleming, W.R. Berry, J. Zhang, E.S. Baskin-Bey, N.D. Shore
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.L. Ervin, E.S. Baskin-Bey, N.D. Shore
Writing, review, and/or revision of the manuscript: S. Gupta, L.T. Nordquist, M.T. Fleming, W.R. Berry, J. Zhang, S.L. Ervin, S.L. Ervin, J.R. Eisner, E.S. Baskin-Bey, N.D. Shore
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): W.R. Berry, J.R. Eisner
Study supervision: S. Gupta, J.R. Eisner, E.S. Baskin-Bey, N.D. Shore

Acknowledgments

The clinical study was supported by Innocrin Pharmaceuticals.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received February 16, 2018; revised April 24, 2018; accepted July 11, 2018; published first July 16, 2018.

References

1. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138–48.
2. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13:983–92.
3. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
4. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33.
5. Attard G, Reid AH, Auchus RJ, Hughes BA, Cassidy AM, Thompson E, et al. Clinical and biochemical consequences of CYP17A1 inhibition with abiraterone given with and without exogenous glucocorticoids in castrate men with advanced prostate cancer. J Clin Endocrinol Metab 2012;97:507–16.
6. Attard G, Reid AH, Yap TA, Raynaud F, Dowsett M, Settatree S, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. J Clin Oncol 2008;26:4563–71.
7. Attard G, Reid AH, A'Hern R, Parker C, Oommen NB, Folkerd E, et al. Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. J Clin Oncol 2009;27:3742–8.

8. Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009;324:787–90.
9. Chandrasekar T, Yang JC, Gao AC, Evans CP. Mechanisms of resistance in castration-resistant prostate cancer (CRPC). Transl Androl Urol 2015;4: 365–80.
10. Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roeser JC, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014;371:1028–38.
11. Efstathiou E, Titus M, Wen S, Hoang A, Karlou M, Ashe R, et al. Molecular characterization of enzalutamide-treated bone metastatic castration-resistant prostate cancer. Eur Urol 2015;67:53–60.
12. Dehm SM, Schmidt LJ, Heemers HV, Vessella RL, Tindall DJ. Splicing of a novel androgen receptor exon generates a constitutively active androgen receptor that mediates prostate cancer therapy resistance. Cancer Res 2008;68:5469–77.
13. Cai C, Balk SP. Intratumoral androgen biosynthesis in prostate cancer pathogenesis and response to therapy. Endocr Relat Cancer 2011;18: R175–82.
14. Boudadi K, Antonarakis ES. Resistance to novel antiandrogen therapies in metastatic castration-resistant prostate cancer. Clin Med Insights Oncol 2016;10:1–9.
15. Balbas MD, Evans MJ, Hosfield DJ, Wongvipat J, Arora VK, Watson PA, et al. Overcoming mutation-based resistance to antiandrogens with rational drug design. Elife 2013;2:e00499.
16. Rafferty SW, Eisner JR, Moore WR, Schotzinger RJ, Hoekstra WJ. Highly-selective 4-(1,2,3-triazole)-based P450c17a 17,20-lyase inhibitors. Bioorg Med Chem Lett 2014;24:2444–7.
17. Norris JD, Ellison SJ, Baker JG, Stagg DB, Wardell SE, Park S, et al. Androgen receptor antagonism drives cytochrome P450 17A1 inhibitor efficacy in prostate cancer. J Clin Invest 2017;127:2326–38.
18. Kuruma H, Matsumoto H, Shiota M, Bishop J, Lamoureux F, Thomas C, et al. A novel antiandrogen, Compound 30, suppresses castration-resistant and MDV3100-resistant prostate cancer growth *in vitro* and *in vivo*. Mol Cancer Ther 2013;12:567–76.
19. Toren PJ, Kim S, Pham S, Mangalji A, Adomat H, Guns ES, et al. Anticancer activity of a novel selective CYP17A1 inhibitor in preclinical models of castrate-resistant prostate cancer. Mol Cancer Ther 2015;14:59–69.
20. Maity SN, Titus MA, Gyftaki R, Wu G, Lu JF, Ramachandran S, et al. Targeting of CYP17A1 Lyase by VT-464 inhibits adrenal and intratumoral androgen biosynthesis and tumor growth of castration resistant prostate cancer. Sci Rep 2016;6:35354.
21. de Bono J, Pezaro CJ, Gillessen S, Shore ND, Nordquist LT, Efstathiou E, et al. . The oral CYP17-Lyase (L) inhibitor VT-464 in patients with CRPC. J Clin Oncol 2015;33:abstr 187.
22. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008; 26:1148–59.
23. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995–2005.
24. Ryan CJ, Smith MR, Fong L, Rosenberg JE, Kantoff P, Raynaud F, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. J Clin Oncol 2010;28:1481–8.
25. Taplin M, Chi KN, Chu F, Cochran J, Edenfield WJ, Eisenberger MA, et al. Galeterone in 4 patient populations of men with CRPC: Results from ARMOR2. Ann Oncol 2014;25:iv255–iv79.
26. Kurman M, Sager P, Rudoltz MS, Eisner JR, Goodman D, Heyman E, et al. Cardiovascular safety profile of VT-464 in patients (pts) with castrate-resistant prostate cancer (CRPC). J Clin Oncol 2016;34:abstr 198.
27. Eisner J, Abbott DH, Bird IM, Rafferty SW, Moore WR, Schotzinger RJ. Assessment of steroid hormones upstream of P450c17 (CYP17) in chemically castrate male rhesus monkeys following treatment with the CYP17 inhibitors VT-464 and abiraterone acetate (AA). In: Proceedings of The Endocrine Society's 94th Annual Meeting and Expo; 2012 Jun 23–26; Houston, TX. Endocrinal Society; 2012. Abstr SAT-266.
28. Martin RM, Lin CJ, Costa EM, de Oliveira ML, Carrilho A, Villar H, et al. P450c17 deficiency in Brazilian patients: biochemical diagnosis through progesterone levels confirmed by CYP17 genotyping. J Clin Endocrinol Metab 2003;88:5739–46.
29. Kok RC, Timmerman MA, Wolffenbuttel KP, Drop SL, de Jong FH. Isolated 17,20-lyase deficiency due to the cytochrome b5 mutation W27X. J Clin Endocrinol Metab 2010;95:994–9.
30. Michels A, Michels N. Addison disease: early detection and treatment principles. Am Fam Physician 2014;89:563–8.
31. Longo DL FA, Kasper DL, Hauser SL, Jameson J, Loscalzo J. eds. Harrison's principles of internal medicine. McGraw-Hill; 2012.
32. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet 2014;383:2152–67.
33. Yamada Y, Matsubara N, Tabata KI, Satoh T, Kamiya N, Suzuki H, et al. Abiraterone acetate after progression with enzalutamide in chemotherapy-naive patients with metastatic castration-resistant prostate cancer: a multi-center retrospective analysis. BMC Res Notes 2016;9:471.
34. Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol 2013;24:1807–12.
35. Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol 2013;24: 1802–7.
36. Feibus A, Guccione JR, Vasudevamurthy A, Ledet EM, Cotogno P, Manogue C, et al. Early assessment of PSA response in patients with mCRPC treated with enzalutamide and abiraterone. J Clin Oncol 2017;35:abstract e574.

Published OnlineFirst July 16, 2018; DOI: 10.1158/1078-0432.CCR-18-0564

Clinical Cancer Research

Phase I Study of Seviteronel, a Selective CYP17 Lyase and Androgen Receptor Inhibitor, in Men with Castration-Resistant Prostate Cancer

Shilpa Gupta, Luke T. Nordquist, Mark T. Fleming, et al.

Clin Cancer Res 2018;24:5225-5232. Published OnlineFirst July 16, 2018.