Original Study

A Phase I Study of Capivasertib in Combination With Abiraterone Acetate in Patients With Metastatic Castration-Resistant Prostate Cancer

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Abstract

Patients with metastatic prostate cancer can develop PI3K/AKT/PTEN pathway-associated resistance to androgen receptor-targeted therapy. In an open-label phase Ib study, 27 systemically treated patients received abiraterone acetate plus capivasertib, a potent, selective pan-AKT inhibitor. The combination demonstrated acceptable tolerability with no dose-limiting toxicity and pharmacokinetics consistent with monotherapy dosing. These data support further clinical evaluation in this patient population.

Background: Although androgen receptor-targeted agents prolong the lives of patients with metastatic prostate cancer, patients develop therapy resistance and most ultimately succumb to the disease. The PI3K/AKT/PTEN pathway has been associated with the development of resistance, raising the possibility that pathway inhibitors may produce a clinical benefit. This open-label phase Ib study examined the safety, tolerability, pharmacokinetics (PK) and preliminary clinical activity of adding capivasertib – a potent, selective inhibitor of AKT1/2/3 – to approved abiraterone acetate therapy. **Methods:** Twenty-seven patients with metastatic castration-resistant prostate cancer who had undergone at least 1 prior line of systemic therapy received abiraterone acetate 1000 mg (orally administered once daily), plus oral prednisone 5 mg (twice daily) with capivasertib 400 mg (orally, twice daily, with an intermittent schedule of 4 days on, 3 days off). **Results:** No dose-limiting toxicity was observed. The most frequent adverse events (all grade) were diarrhea (30%), anemia (26%), asthenia (22%), and nausea (22%). The most frequent grade 3 or higher adverse events were acute kidney injury (19%), hyperglycemia (7%), rash (7%), abdominal pain (7%), and asthenia (7%). Capivasertib and abiraterone PK were consistent with previously reported results from monotherapy dosing. Nine participants (33%) showed a 20% or greater decrease in prostate-specific antigen during study treatment. **Conclusion:** The combination of capivasertib and abiraterone acetate had an acceptable tolerability profile consistent with the known profile of each agent. These data support further evaluation of capivasertib and abiraterone acetate in patients with advanced prostate cancer.

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Introduction

Prostate adenocarcinoma is a common malignancy, with an estimated 1.4 million cases worldwide each year.[1] Around 80% of patients with metastatic prostate cancer will die from the disease.[2] While androgen deprivation therapy is foundational for advanced prostate cancer, nearly all patients with metastatic prostate cancer experience progression to metastatic castration-resistant prostate cancer (mCRPC), which is still incurable. Ongoing therapies focus on slowing progression and minimizing disease burden, while prolonging survival.

Next-generation androgen receptor-targeting agents (ARTAs), including abiraterone acetate (an inhibitor of the CYP17A1 androgen synthesis enzyme) and enzalutamide (an androgen receptor [AR] antagonist) have demonstrated improvements in progression-

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free survival (PFS) and overall survival for mCRPC.[3-5] Abiraterone acetate and enzalutamide are frequently preferred as first-line therapy over docetaxel, given their safety profile and oral route of administration. However, mCRPC invariably develops resistance to ARTAs,[6] and there is an unmet need for new treatments that slow or prevent resistance.

The PI3K/AKT/PTEN pathway that promotes cell proliferation and resistance to apoptosis has been associated with ARTA resistance. It is estimated that 40% to 60% of mCRPC tumors have lost expression of the negative pathway regulator, PTEN.[7] Preclinical studies have demonstrated reciprocal cross-talk between the AR and PI3K/AKT/PTEN pathway, whereby AR inhibition upregulates PI3K/AKT/PTEN pathway signaling, and PI3K/AKT/PTEN pathway inhibition activates AR signaling. Consistent with this, simultaneous inhibition of both pathways has demonstrated preclinical antitumor activity, particularly in PTEN-deficient models.[8,9] This has focused interest on the use of PI3K/AKT/PTEN pathway inhibitors to counter ARTA resistance.

Capivasertib is a potent, selective inhibitor of all 3 AKT isoforms (AKT1/2/3)[10] that has been investigated in numerous cancers, including prostate cancer.[11] The phase I/II ProCAID study showed that addition of capivasertib to docetaxel significantly extended the secondary endpoint of overall survival in patients with mCRPC, and a follow-on phase III trial (CAPItello-280; NCT05348577) has begun.[12] The ongoing phase III CAPItello-281 (NCT04493853) study is examining adding capivasertib to abiraterone acetate in patients with PTEN-deficient, de novo, metastatic, hormone-sensitive prostate cancer.[13] Additionally, the phase III IPATential150 trial demonstrated that the AKT inhibitor ipatasertib improved radiological PFS when added to abiraterone acetate in patients with PTEN-deficient mCRPC, albeit at the expense of additional toxicity.[14]

Here we report findings from a phase Ib, open-label, multicohort, multicenter study (NCT04087174) that examined the safety, tolerability, pharmacokinetics (PK) and preliminary signs of clinical activity from adding capivasertib to abiraterone acetate therapy in patients with mCRPC.

Materials and Methods

Patient Population

Eligible patients had documented evidence of mCRPC, a World Health Organisation performance status of 0 to2, life expectancy of at least 12 weeks or longer, and had received at least one line of systemic therapy for mCRPC (either chemotherapy or an ARTA, which could include abiraterone), unless no alternative approved therapy was available. Patients had to be eligible to receive abiraterone acetate treatment.

Patients were ineligible if they had received enzalutamide in the 8 weeks before the first dose of study treatment, or had received nitrosourea or mitomycin C within 6 weeks, major surgery or radiotherapy with a wide field of radiation within 4 weeks, any other anticancer agent (with the exception of luteinizing hormone-releasing hormone analogues) within 3 weeks, potent inhibitors, inducers or substrates of CYP3A4 within 2 weeks, and/or any investigational agent within 30 days before the first dose. Prior abiraterone was allowed. Other exclusion criteria included clinically significant abnormalities of glucose metabolism (defined as type 1 or type 2 diabetes mellitus that required insulin treatment or HbA1c $\geq$ 8.0% [63.9 mmol/mol]), previously identified brain metastases or spinal cord compression unless treated and considered stable over the 3 weeks leading up to the study, clinically significant cardiac disease, or any evidence of severe or uncontrolled systemic disease as judged by the investigator.

Study Design

The study had 2-parts. Part A examined whether the selected dosing regimen had acceptable safety and tolerability. Part B allowed for dose expansion and additional recruitment based on Safety Review Committee (SRC) examination of Part A data. The study was conducted according to Good Clinical Practice guidelines, the Declaration of Helsinki, and followed national ethics and regulatory approvals. Informed consent was obtained from all participants.

Study Objective

The primary objective was to investigate the safety and tolerability of capivasertib when given in combination with abiraterone acetate to patients with mCRPC. Other objectives were to characterize the PK of capivasertib and abiraterone under combination dosing, and to examine preliminary signs of clinical activity of combined capivasertib plus abiraterone acetate therapy. Adverse event (AE) and PK data were recorded for all patients who received capivasertib and abiraterone acetate. Clinical efficacy data were collected from 14 patients: 2 in Part A and 12 in Part B.

Treatment

Eight participants were recruited in Part A to receive capivasertib (400 mg, oral twice daily [BD]) by an intermittent schedule (4 days on, 3 days off) in combination with abiraterone acetate (1000 mg oral, once daily), together with prednisone or prednisolone 10 mg. Intermittent capivasertib administration was previously shown to maximize therapeutic benefit and reduce toxicities by allowing nontarget tissues to recover during dosing breaks and, based on accumulated efficacy and safety data, is being used in phase III trials.

The SRC examined Part A data to confirm the dosing level before expanding the study to additional participants (Part B). 10 participants received a 1-week pretreatment with abiraterone acetate before study treatment to allow within-subject comparison of abiraterone PK parameters in the presence and absence of capivasertib. Study treatment was continued until unacceptable toxicity, disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, confirmed progression in bone according to Prostate Cancer Working Group 3 (PCWG-3) criteria,[15] any skeletal-related event, or the decision of the participant to discontinue for any reason.

Assessments

Blood samples were collected for clinical laboratory testing on day 1 of study treatment, at a second visit that occurred before day 14, and weekly thereafter until withdrawal from the study. AEs were characterized by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.

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Radiological PFS (according to RECIST 1.1 and PCWG-3 criteria) was defined as the time from the first dose of study therapy until objective disease progression (soft tissue or bone) or death (by any cause), regardless of whether the participant withdrew from study therapy or received another anti-cancer therapy before progression. Circulating prostate-specific antigen (PSA) levels were measured before study initiation, on day 1 of study treatment, and at the end of each 28-day cycle thereafter. Tumor assessments by bone scans and computed tomography or magnetic resonance imaging were performed on day 1 and then every 8 weeks for the first 24 weeks, and every 12 weeks thereafter until disease progression. The baseline for efficacy measurements was defined as the value recorded on the day that treatment commenced or, if not available, the most recent value recorded before the start of study treatment.

PK

A predose blood sample was collected on day 1, 11, 18, and 29 of the study. Serial blood samples were collected on day 25 or day 29 (predose, 0.5, 1, 2, 4, 6, 8, and 12-hours postdose), with day 25 values used to calculate PK parameters. Plasma samples (25 µL) were analyzed for capivasertib, after the addition of ^{13}C-labelled internal standard, by solid phase extraction followed by reversed phase HPLC-MS/MS. For abiraterone, plasma samples (50 µL) were analyzed, after the addition of abiraterone-d4 internal standard, by liquid-liquid extraction followed by HPLC-MS/MS. A series of calibration standards containing known amounts of each compound (1.00-1000 ng/mL and 1.00–500 ng/mL for capivasertib and abiraterone, respectively) added to control human plasma were processed in parallel with trial samples. Both pre- and peri-study validation for all methods was successfully conducted according to the United States Food and Drug Administration Guidance for Industry Bioanalytical Method Validation.[16] PK parameters were derived using non-compartmental analysis. Capivasertib plasma concentrations were compared to those from previous studies in patients with solid tumors receiving capivasertib 480 mg BD (4 days on, 3 days off) as monotherapy, after dose-normalization that assumed dose-proportionality.[17, 18] Abiraterone plasma concentrations were compared to model-predicted concentrations using a previously published population PK model.[19]

Results

Participants

Thirty-four patients with mCRPC were enrolled. Seven did not pass screening procedures (Supplemental Table 1). The characteristics of participants who received study treatment (N = 27; the safety analysis set) are summarized in Table 1. Median age was 68 years (range 49-82 years). Eleven participants (41%) had received abiraterone acetate before entering the study, 18 participants (67%) had received enzalutamide, 22 (81%) had received docetaxel, 9 (33%) had received cabazitaxel, and 13 (48%) had previously received an immunotherapy, most commonly sipuleucel-T (7 participants) and/or pembrolizumab (5 participants).

Safety

No dose-limiting toxicities were observed during Part A (8 participants) and the study was expanded to Part B (19 participants)

Table 1 Patient Demographics, Disease Characteristics, and Previous Cancer Therapies

	Total Patients (N = 27)
Age (years); median (range)	68 (49-82)
Country; n (%)	
Spain	11 (41)
USA	16 (59)
Time from diagnosis to enrolment (years); median (range)	6.4 (0.1-17.1)
ECOG performance status, n (%)	
0	12 (44)
1	15 (56)
PSA at screening (µg/L); median (range)	83.4 (0.40-593)
Prior therapies; n (%)	
Abiraterone	11 (41)
Enzalutamide	18 (67)
Bicalutamide	9 (33)
Docetaxel	22 (81)
Cabazitaxel	9 (33)
Carboplatin	5 (19)
Immunotherapy	13 (48)
PARP inhibitor	7 (26)
Radiotherapy	4 (15)
Prior chemotherapy regimens; n (%)	
0	4 (15)
1	13 (48)
2	6 (22)
3	2 (7.4)
≥ 4	1 (3.7)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PARP = poly (ADP-ribose) polymerase; PSA = prostate-specific antigen.

without altering the treatment regimen. All participants in Part A (100%) and 17 participants (90%) in Part B discontinued treatment, most commonly owing to disease progression (14 participants total [52%]). AEs leading to permanent discontinuation of capivasertib (irrespective of relationship) were reported for 11 participants (41%), and AEs leading to permanent discontinuation of abiraterone acetate (irrespective of relationship) were reported for 9 participants (33%) (Supplemental Table 1). Two participants in Part B (11%) continued treatment at the time of data cut-off (Supplemental Table 1).

Participants received a median number of three 28-day treatment cycles. Five participants (63%) in Part A and 8 participants (42%) in Part B experienced an interruption and/or reduction to the planned capivasertib dosing. There were no abiraterone acetate treatment interruptions or dose reductions in Part A, although 6 participants in Part B (32%) experienced an interruption and/or reduction (Supplemental Table 2).

All participants experienced at least 1 AE. The most common AEs were diarrhea, anemia, nausea, asthenia, and fatigue (Table 2).

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Table 2 Adverse Events That Occurred in ≥ 10% of Patients

	Patients Who Experienced Any Adverse Event (N = 27), n (%)	Patients Who Experienced CTCAE Grade ≥ 3 (N = 27), n (%)
Any adverse event	**27 (100)**	**16 (59.3)**
Diarrhea	16 (59)	1 (3.7)
Anemia	8 (30)	0
Nausea	7 (26)	0
Asthenia	6 (22)	2 (7.4)
Fatigue	6 (22)	1 (3.7)
Acute kidney injury	5 (19)	5 (19)
Decreased appetite	5 (19)	0
Hyperglycemia	5 (19)	2 (7.4)
Rash maculopapular	5 (19)	2 (7.4)
Abdominal pain	4 (15)	2 (7.4)
Constipation	4 (15)	0
Dehydration	4 (15)	1 (3.7)
Headache	4 (15)	0
Hypokalemia	4 (15)	1 (3.7)
Hypomagnesemia	4 (15)	0
Hypophosphatemia	4 (15)	0
Pyrexia	4 (15)	0
Back pain	3 (11)	0
Dysphagia	3 (11)	0
Dyspnea	3 (11)	0
Hematuria	3 (11)	0
Hyperkalemia	3 (11)	1 (3.7)
Edema peripheral	3 (11)	0
Urinary tract infection	3 (11)	1 (3.7)
Vomiting	3 (11)	0

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

AEs of CTCAE grade 3 or higher were reported for 16 participants (59%; Table 2 and Supplemental Table 3). Serious AEs were reported for 10 participants (37%; Supplemental Table 4). Two participants (7.4%) died during the study. In both cases the investigator identified the cause of death as disease-related and not treatment-related.

PK

At least 1 capivasertib and 1 abiraterone plasma concentration was determined for all 27 participants. Some serial PK samples were collected on day 29 (after 3 days without capivasertib dosing) instead of on day 25 (day 4 of 4 days receiving capivasertib). Plasma capivasertib concentrations over time are shown in Figure 1A. Table 3 presents a summary of PK parameters calculated from day 25 plasma concentrations in participants who received capivasertib 400 mg BD without dose interruptions or reductions that might affect capivasertib PK. The geometric mean (gMean) area under the time-concentration curve over the dosing interval (AUC_τ) and maximum plasma concentration (C_{max}) for capivasertib were 10 300 ng·h/mL and 1934 ng/mL, respectively, and the median time to reach the maximum observed concentration (T_{max}) was 2 hours. The between-subject variability in capivasertib exposure was moderate, with geometric coefficient of variation percentages of 39% for AUC_τ and 36% for C_{max}. Figure 1B shows participant abiraterone plasma concentrations over time, and Table 4 shows PK parameters. The variability in abiraterone exposure was in line with previous abiraterone PK analyses that showed high between- and within-subject variability.[19] A predose gMean abiraterone concentration (C_{min}) was calculated at 13 ng/mL for the 10 participants who received abiraterone acetate for a 1-week run-in before commencing study treatment. This value was similar to the gMean abiraterone C_{min} values calculated for these participants under combination dosing (gMean C_{min} values on days 12, 18, 25, and 29 of study treatment were 7, 11, 16, and 18 ng/mL, respectively).

Treatment Efficacy

Tumor response was evaluated with RECIST 1.1 criteria in soft tissue and PCWG-3 criteria in bone, which required measurable disease at baseline; however not all participants had measurable

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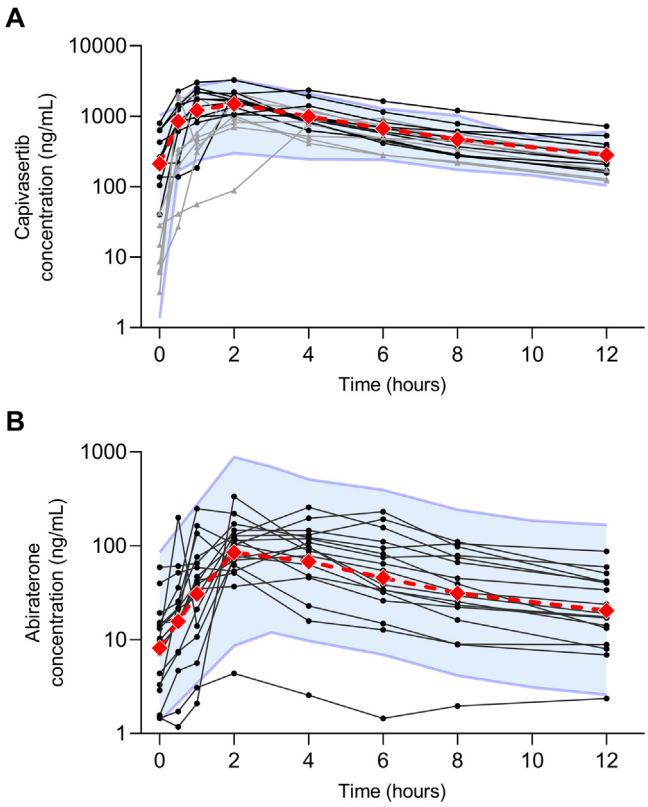
Figure 1 Capivasertib and abiraterone plasma concentrations versus time on day 25 or day 29. Black plots show plasma concentrations of (A) capivasertib (n = 18) and (B) abiraterone (n = 18) in individual participants following drug administration on day 25 (or day 29 for abiraterone). Grey plots (with triangles) in (A) show capivasertib plasma concentrations after dosing on day 29. These were not directly comparable to day 25 values as they followed a 3-day off-dose period. Note that abiraterone was dosed continuously. Red plots show the geometric mean for the study population. Capivasertib and abiraterone acetate were administered at 0 hours. Predose concentrations are plotted for 0 hours. Data from patients with dose interruptions or reductions were not included. Blue shading indicates the 95% prediction interval derived from (A) capivasertib dosed as monotherapy in previous studies[17,18] and (B) a published population PK model of abiraterone acetate monotherapy.[19]
PK = pharmacokinetics.



and evaluable soft tissue lesions at baseline. None of the 14 evaluable participants showed an objective response to study treatment. Median radiological PFS (according to RECIST 1.1 and PCWG-3 criteria) was 9.7 months (95% confidence interval [CI]: 2.1-15.6 months) in Part A and 2.3 months (1.7–3.8 months) in Part B. In an exploratory analysis, the change from baseline PSA levels was examined in all participants (Figure 2). Of the 27 evaluable patients, 1 patient (3.7%; 80% CI 0.39–13.66) had a 50% or greater reduction in PSA from baseline after 12 weeks of treatment. Nine showed a 20% or greater decrease in PSA concentration compared to day 1 of study treatment, including 1 participant where PSA remained low for the 306 days that they were in the study. The subset of participants whose PSA levels decreased on study treatment had a higher proportion of individuals without previous ARTA treatment (4 of 9 [44%]), compared with those whose PSA levels remained stable or increased (2 of 19 [11%] had no previous ARTA treatment).

Discussion

This phase Ib, multicenter, open-label study assessed the safety, tolerability and PK of capivasertib given in combination with abiraterone acetate in patients with mCRPC. The AEs that are most commonly associated with capivasertib (diarrhea, fatigue, hyperglycemia, and rash) occurred with a similar frequency and severity as previously reported for capivasertib monotherapy.[17, 18, 20] Abiraterone acetate therapy has been most commonly associated with mineralocorticoid-related AEs, including fluid retention, hypertension and hypokalemia;[4] these were also detected at a similar frequency as for abiraterone acetate monotherapy.[4] Unusually, the relatively high prevalence of acute kidney injuries seen in participants has not been previously associated with capivasertib or abiraterone acetate[4,17,18,20]; it is an AE that should be monitored and evaluated in ongoing and future clinical trials. This includes the phase III CAPItello-281 study that examines capivasertib addition

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Figure 2 Prostate-specific antigen levels. Plot shows the fold change in PSA levels for each participant relative to PSA levels on day 1 of the study. Black plots show values from participants who had received prior abiraterone, enzalutamide and/or apalutamide (ARTA) therapy. Red plots show values from participants with no prior ARTA therapy (at least 1 month of prior therapy). Dashed blue line indicates the threshold of a 20% decrease in PSA levels.
ARTA = androgen receptor-targeted agent; PSA = prostate-specific antigen.

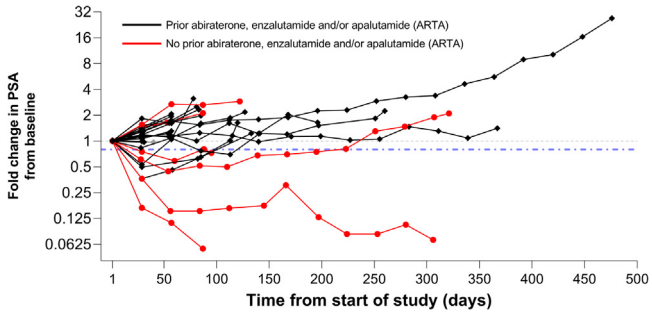

Table 3 Capivasertib Pharmacokinetic Parameters on day 25

Parameter (units); n	Statistic	Values
AUC_{τ} (ng·h/mL); n = 10	gMean	10 300
	CV%	39
	Min–Max	6400–18 400
$C_{predose}$ (ng/mL); n = 11	gMean	304
	CV%	73
	Min–Max	104–795
C_{max} (ng/mL); n = 11	gMean	1934
	CV%	36
	Min–Max	1050–3250
C_{min} (ng/mL); n = 11	gMean	275
	CV%	59
	Min–Max	104–629
C_{12} (ng/mL); n = 10	gMean	316
	CV%	57
	Min–Max	156–717
T_{max} (h); n = 11	Median	2.0
	Min–Max	1.0–4.1
CL/F (L/h); n = 10	Mean	41.3
	SD	14.3
	Min–Max	21.8–62.5

Abbreviations: AUC_{τ} = area under the time-concentration curve over the dosing interval; C_{12} = plasma concentration at 12 hours after dosing; CL/F = apparent total body clearance of drug from plasma; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; $C_{predose}$ = plasma concentration obtained before administering a dose; CV = coefficient of variation; gMean = geometric mean; Max = maximum; Min, minimum; SD = standard deviation; T_{max} = time to reach peak observed concentration following drug administration.

Table 4 Abiraterone Pharmacokinetic Parameters on day 25 or day 29

Parameter (units); n	Statistic	Values
AUC_{0-24} (ng·h/mL); n = 15	gMean	780
	CV%	65
	Min–Max	281–2130
AUC_{last} (ng·h/mL); n = 18	gMean	566
	CV%	116
	Min–Max	28.4–1280
C_{max} (ng/mL); n = 19	gMean	117
	CV%	124
	Min–Max	4.37–334
T_{last} (h); n = 18	Median	12.0
	Min–Max	11.0–12.2
T_{max} (h); n = 19	Median	2.1
	Min–Max	0.5–5.8

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve over 24 hours; AUC_{last} = area under the concentration-time curve from the time of administration to final quantifiable concentration; C_{max} = maximum plasma concentration; CV, coefficient of variation; gMean = geometric mean; Max, maximum; Min, minimum; T_{last} = time to the last quantifiable capivasertib measurement; T_{max}, time to reach the maximum observed concentration following administration.

to abiraterone acetate in patients with de novo metastatic, hormone-sensitive prostate cancer that features PTEN deficiency.[14]

The PK parameters calculated for capivasertib and abiraterone given in combination are similar to those reported for capivasertib and abiraterone acetate administered alone.[17,18,21,22] Additionally, the C_{min} of abiraterone in this study was similar when administered alone versus when administered with capivasertib. These data suggest that there is no drug–drug interaction between capivasertib and abiraterone, which further supports testing this combination in prostate cancer.

The efficacy analysis was limited by the small number of participants with evaluable tumor responses, limited information on the genetic status of tumors, as well as heterogeneity in the type and number of treatments received before the study. Thus, although no participant showed an objective response to study treatment, this does not necessarily reflect that patients with mCRPC will not benefit from adding capivasertib to abiraterone acetate therapy.

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Notably, capivasertib plus abiraterone acetate appeared to lower PSA levels in approximately one-third of participants, including 4 of the 6 with no prior ARTA exposure. Future studies should examine capivasertib in combination with abiraterone acetate for mCRPC, especially in patients who have not received an ARTA. It will also be important to examine if efficacy varies by whether tumors carry alterations in the PI3K/AKT/PTEN pathway.

Conclusions

The administration of capivasertib in combination with abiraterone acetate had an acceptable tolerability profile, with no dose-limiting toxicities observed, and AEs consistent with the known safety profile of each agent. These data support further studies to evaluate the safety and efficacy of capivasertib and abiraterone acetate in patients with metastatic prostate cancer.

Clinical Practice Points

- Next-generation androgen receptor-targeting agents, including abiraterone acetate and enzalutamide, have demonstrated improvements in PFS and overall survival for patients with metastatic prostate cancer. However, these patients can develop resistance to androgen receptor-targeted therapy due to mutations within the PI3K/AKT/PTEN pathway.
- Capivasertib is a potent, selective inhibitor of all 3 AKT isoforms (AKT1/2/3) that has been investigated in numerous cancers and has demonstrated the potential to prolong overall survival in patients with metastatic prostate cancer.
- The present phase Ib, open-label, multi-cohort and multicenter study examined the safety, tolerability, PK, and preliminary clinical activity of capivasertib administered in combination with abiraterone acetate.
- The combination with abiraterone acetate had an acceptable tolerability profile, with no dose-limiting toxicities observed.
- For AEs, the most frequent, including diarrhea, anemia, asthenia and nausea, were consistent with the known safety profile of each agent, and the PK of the agents in combination were similar to previously reported results for monotherapy dosing, suggesting no drug–drug interaction.
- Building on previous data, the new findings support the clinical evaluation of capivasertib and abiraterone acetate as an alternative therapy for patients with advanced prostate cancer.

Data Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy, described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

CRediT authorship contribution statement

Neal Shore: Investigation, Project administration, Writing – original draft, Writing – review & editing. **Begoña Mellado:** Investigation, Project administration, Writing – original draft, Writing – review & editing. **Satish Shah:** Investigation, Project administration, Writing – original draft, Writing – review & editing. **Ralph Hauke:** Investigation, Project administration, Writing – original draft, Writing – review & editing. **Dan Costin:** Investigation, Project administration, Writing – original draft, Writing – review & editing. **Nabil Adra:** Investigation, Project administration, Writing – original draft, Writing – review & editing. **Marie Cullberg:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Carlos Fernandez Teruel:** Formal analysis, Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Thomas Morris:** Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Disclosure

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2022.11.017.

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