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A phase 1 study of capivasertib in combination with abiraterone acetate in patients with metastatic castration-resistant prostate cancer

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Objective

Primary objective

- Investigate the safety and tolerability of capivasertib, a potent, selective inhibitor of AKT1, -2 and -3, when given in combination with the androgen synthesis inhibitor abiraterone acetate (AA) in patients with metastatic castration-resistant prostate cancer (mCRPC).

Key secondary objective

- Characterize the pharmacokinetics (PK) of capivasertib when given in combination with AA.

Exploratory objective

- Characterize the PK of AA when given in combination with capivasertib.
- Determine changes in circulating prostate-specific antigen (PSA) in patients with mCRPC treated with capivasertib and AA.

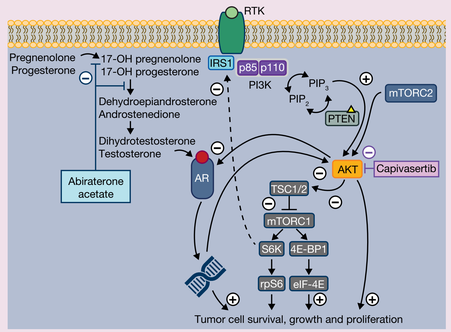
Conclusions

- No dose-limiting toxicities were observed with combined capivasertib and AA.
- Adverse events (AEs) related to capivasertib were consistent with those previously described in early clinical studies of capivasertib given as a monotherapy or in combination with paclitaxel or fulvestrant.
- PK data from patients given capivasertib and AA in combination are consistent with population PK models indicating no evidence of a PK interaction between the drugs.
- Moderate sustained decreases in PSA levels were observed in 3 of 15 patients.
- In this phase 1 study, combined capivasertib and AA exhibits an acceptable safety and tolerability profile.
- Further data on the clinical efficacy, safety and tolerability of the combination are now being collected in this study and in patients with metastatic hormone-sensitive prostate cancer in the phase 3 CAPItello-281 trial (NCT04493853).

Introduction

- Prostate adenocarcinoma is one of the most common malignancies, with an estimated 1.28 million cases worldwide in 2018.[1] In patients with advanced disease, androgen deprivation therapy is highly effective in shrinking tumors, decreasing PSA levels and enhancing quality of life. However, nearly all patients experience disease progression and develop mCRPC.
- Novel hormonal agents that target the androgen receptor (AR), including AA and enzalutamide, have demonstrated robust improvements in progression-free survival (PFS) and overall survival (OS) in patients with mCRPC.[2,3]
- Nonetheless, nearly all patients with mCRPC eventually progress under currently available treatments, and there is an unmet need for new first-line treatment options that improve patient quality of life and delay resistance.
- The PI3K/AKT/mTOR pathway plays a key role in tumor cell growth, proliferation and survival. Activation of the PI3K/AKT/mTOR pathway is common in mCRPC and contributes to tumor growth and treatment resistance, predominantly due to loss of the negative regulator of AKT, PTEN, that occurs in 40–60% of patients (**Figure 1**).[4]
- Preclinical studies have demonstrated reciprocal regulation between the AR and PI3K/AKT/mTOR pathways, whereby inhibition of one pathway leads to upregulation of the other.[5,6] Conversely, significant antitumor activity has been observed when both pathways are inhibited, particularly in models with PTEN loss. Thus, a rationale exists to inhibit both pathways in patients with mCRPC.
- In the clinical setting, a phase 2 trial (NCT01485861) has demonstrated that the AKT inhibitor ipatasertib combined with AA produces an improvement in PFS and OS in patients with mCRPC versus AA alone, providing evidence for the efficacy of combined AKT and AR inhibition.[7]
- Here we report interim results of a phase 1 multicohort study (NCT04087174) to confirm the acceptable dose of capivasertib to be used in combination with abiraterone in patients with prostate cancer.

Figure 1. PI3K/AKT/PTEN and AR signaling pathways

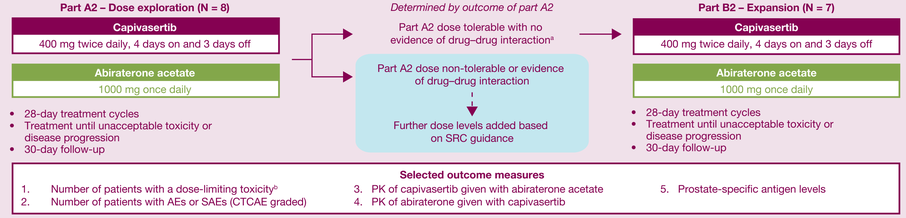


The yellow triangle marks known mutation in prostate cancer
4E-BP1, eukaryotic translation initiation factor 4E binding protein 1; AKT, protein kinase B; AR, androgen receptor; eIF-4E, eukaryotic translation initiation factor 4E; IRS, insulin receptor substrate; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase; PIP_2, phosphatidylinositol (4,5)-biphosphate; PIP_3, phosphatidylinositol (3,4,5)-triphosphate; PTEN, phosphatase and tensin homolog; rpS6, ribosomal protein S6; RTK, receptor tyrosine kinase; S6K, S6 kinase; TSC, tuberous sclerosis complex

Methods

- A multipart study design was used to allow exploration of different doses with intensive safety monitoring to ensure the safety of the patients. Parts A1 and B1 studied the combination of enzalutamide with capivasertib. Here we report interim results from parts A2 and B2 (**Figure 2**).
  - Part A2: dose exploration to determine if the recommended dose regimen of capivasertib administered in combination with AA has acceptable safety and tolerability.
  - Part B2: optional expansion group of part A.
- Patients with mCRPC were recruited at centers in the USA and Spain beginning August 5, 2019. Data cut-off was July 15, 2020.
- Patients in groups A2 and B2 were treated with the same capivasertib and AA regimen shown in **Figure 2**. Dose-limiting toxicity in the first 28 days of treatment (part A2) and AEs were recorded (parts A2 and B2).
- Samples for PSA measurements were planned to be collected prior to commencing study treatment (screening day –28 to –1) and on day 1 of each 28-day treatment cycle until study treatment was discontinued.
- Full PK samples (0–12 hours after drug dose) for capivasertib and abiraterone were collected on day 24–29 and analyzed by liquid chromatography-mass spectrometry.

Figure 2. Trial design and outcome measures



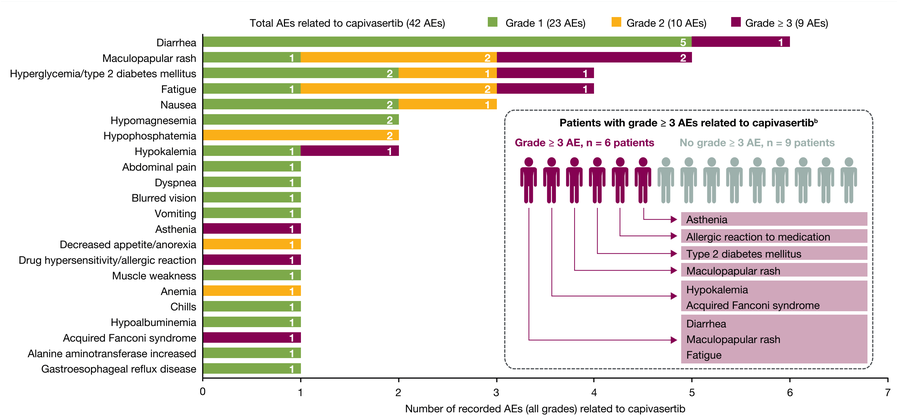
[a]The dose used in study part A was tolerable with no evidence of drug–drug interactions, therefore no further dose levels were added
[c]A dose-limiting toxicity is defined as an AE that occurs from the first capivasertib dose up to and including day 28 that is assessed as unrelated to the disease, intercurrent illness, or concomitant medications and that, despite optimal therapeutic interventions, meets any of the criteria defined in the protocol
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; PK, pharmacokinetics; SAE, serious adverse event; SRC, safety review committee

Results

- Fifteen male patients, median 67 years of age (range 49–82), were recruited (USA, n = 11; Spain, n = 4).
- Twelve patients had received prior chemotherapy; six patients had received two or more prior lines. Ten patients had received prior enzalutamide and seven had received prior AA; six patients had received both enzalutamide and AA (**Figure 3**).
- No dose-limiting toxicities were observed in part A2 (n = 8 patients). In all patients (parts A2 and B2, n = 15), capivasertib treatment was discontinued in four patients owing to AEs, one patient owing to patient choice, two patients owing to disease progression and one patient for unspecified reasons.
- One hundred AEs of any grade were recorded in 15 patients (grade 1, 55 AEs; grade 2, 28 AEs; grade ≥ 3, 17 AEs). AEs considered related to capivasertib are shown in **Figure 4** (42 AEs).
- AEs at grade ≥ 3 that were considered not related to capivasertib were acute kidney injury (4 AEs), urinary tract infection (1 AE), dehydration (1 AE), bladder neck obstruction (1 AE) and fungemia (1 AE).
- Median (range) baseline PSA levels were 47.3 (0.4–487.3) ng/mL (n = 15). Between baseline and day 29 of treatment, five patients had reduced (> 20%) PSA levels, with three patients showing sustained falls in PSA over 12 weeks (**Figure 5**).
- PK data for capivasertib and abiraterone given in combination are consistent with population PK models (**Figure 6**).

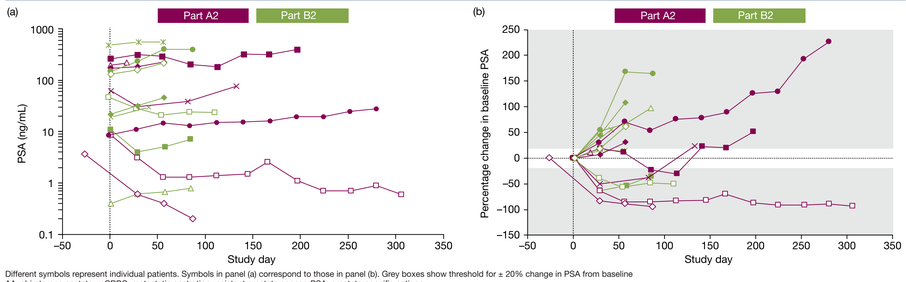
Figure 3. Previous prostate cancer therapies received by patients enrolled in the trial

Figure 4. AEs of all grades related to capivasertib treatment[a]



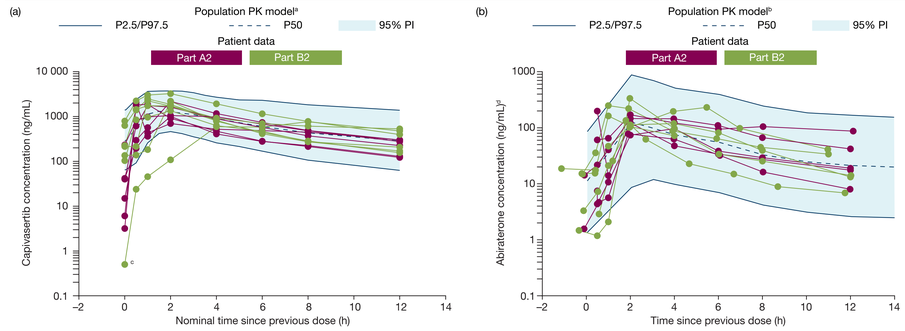
[a]AEs were reported by the patients and the causal relationship between capivasertib and each AE was assessed by the investigator
[b]Six patients had a total of nine CTCAE grade ≥ 3 AEs. Seven patients had AEs recorded as grade 1 or 2, and 2 patients had no recorded AEs
AE, adverse event

Figure 5. PSA levels (a) and percentage change in PSA levels from baseline (b) in patients with mCRPC treated with capivasertib and AA



Different symbols represent individual patients. Symbols in panel (a) correspond to those in panel (b). Grey boxes show threshold for ± 20% change in PSA from baseline
AA, abiraterone acetate; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen

Figure 6. PK profiles for (a) capivasertib and (b) AA given in combination



[a]Capivasertib PK data from 13 patients compared to 95% PI from capivasertib population PK model (based on previous phase 1/2 studies in 363 patients)
[b]AA PK data from 14 patients compared to 95% PI from published AA population PK model[8]
[c]LOQ for capivasertib is 1 ng/mL. For samples below LOQ, values were set at 0.5 ng/mL (LOQ/2)
[d]The concentration of abiraterone, not the prodrug AA, was measured
AA, abiraterone acetate; LOQ, limit of quantification; PI, prediction interval; PK, pharmacokinetic

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