Clinical Study Report	
Drug Substance	Capivasertib/AZD5363
Study Code	D3618C00002
Edition Number	Final
Date	28 January 2022
EudraCT Number	2019-000071-17
NCT Number	NCT04087174

A Phase I, Open-label, Multi-centre Study to Assess the Safety, Tolerability, and Pharmacokinetics of Capivasertib (AZD5363) in Combination with Novel Agents in Patients with Metastatic Castration Resistant Prostate Cancer

Study Dates: First patient enrolled: 05 August 2019
Last patient last visit: 05 May 2021
The analyses presented in this report are based on a clinical data lock date of 23 September 2021

Phase Of Development: Clinical pharmacology (I)

International Co-ordinating Investigator: PPD
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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study centres

This study was conducted at 6 clinical sites in 2 countries (5 centres in the United States and 1 centre in Spain).

Publications

Neal D. Shore, Begona Mellado, Satish Shah, Ralph J. Hauke, Dan Costin, Thomas Morris, et al. A phase I study of capivasertib in combination with abiraterone acetate in patients with metastatic castration-resistant prostate cancer. J Clin Oncol. 2021;39:6_suppl, 85-85.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of capivasertib when given in combination with a novel agent (abiraterone) to patients with metastatic CRPC.	• DLTs. • AEs and SAEs as characterised and graded by NCI CTCAE version 5, collection of clinical chemistry/haematology parameters, liver function tests, ECHO and ECGs, vital signs including BP and heart rate.
Secondary	
• To characterise the PK of capivasertib when given in combination with novel agents.	• Plasma concentration data for capivasertib and derived PK parameters.
• To determine the preliminary signs of activity of capivasertib in combination with novel agents in this patient population.	• Soft tissue ORR and radiological ORR by investigator assessment. • rPFS according to RECIST 1.1 and PCWG-3 criteria. • DoR and best percentage change in tumour size using RECIST 1.1 criteria.

Abbreviations: AE(s): adverse event(s); BP: blood pressure; CRPC: castration resistant prostate cancer; CTCAE: Common Terminology Criteria for Adverse Event; DLT(s): dose limiting toxicity(ies); DoR: duration of response; ECHO: echocardiogram; ECG(s): electrocardiogram(s); NCI: National Cancer Institute; ORR: objective response rate; PCWG: Prostate Cancer Clinical Trial Working Group; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumours; rPFS: radiographic progression free survival; SAE(s): serious adverse event(s).

Study design

This was a 2-part Phase Ib, multi-centre, open-label, study in metastatic castration resistant prostate cancer (CRPC) patients (Part A1, Part A2) with optional dose expansion parts (Part B1, Part B2). The study was conducted to determine the safety, tolerability and pharmacokinetics (PK) of capivasertib when given in combination with novel agents (enzalutamide or abiraterone) to inform the selection of capivasertib dose regimens for each combination for further clinical evaluation when given to patients with metastatic CRPC. The

study design allowed an exploration of different doses with intensive safety monitoring to ensure the safety of the patients.

The capivasertib plus enzalutamide combination part was not pursued due to change in development strategy; therefore, Part A1 and Part B1 were never conducted. For information related to Part A1 or Part B1 study design, refer to Section 4.1.1.1 and 4.1.2.1 of the clinical study protocol, respectively.

Part A:

The 2 planned combination treatments during Part A of this study were:

- Part A1: Capivasertib + enzalutamide.
- Part A2: Capivasertib + abiraterone.

Please note that the capivasertib plus enzalutamide combination part was not pursued due to change in development strategy.

Part A2: Capivasertib and abiraterone

This part of the Phase I study aimed to confirm that capivasertib 400 mg twice daily (BID), 4 days on/3 days off, administered in combination with abiraterone 1000 mg once daily (QD) had acceptable safety and tolerability. If this dose was considered tolerable and no evidence of DDI was observed, no further dose levels would be explored for this combination (ie, only 1 dose level would be examined for capivasertib and abiraterone combination). However, if a DDI or non-tolerable dose was determined for this combination further dose levels were to be added based on Safety Review Committee (SRC) guidance.

Part B:

Part B included any optional dose expansion cohorts based on SRC review of data from Part A of this study.

Part B2: Capivasertib and abiraterone

This optional expansion treated 19 patients at the recommended dose regimen of capivasertib and abiraterone to further characterise the safety and PK profile.

Target population and sample size

This study included patients with metastatic CRPC.

The study planned to include up to approximately 87 evaluable patients (per protocol), divided among 4 study parts. However, since Part A1 and Part B1 were not conducted, 27 patients were finally included:

- Part A2: 8 patients.
- Part B2: 19 patients.

Investigational product and comparators: dosage, mode of administration and batch numbers

The study treatments administered to patients included oral doses of capivasertib and abiraterone.

- Capivasertib (AZD5363), 160 mg or 200 mg/tablets for oral intake (number of tablets taken equivalent to selected dose), supplied by AstraZeneca: 4 days on/3 days off, BID under fasting conditions (only water to drink) from at least 2 hours prior to a dose of capivasertib to at least 1 hour post-dose.
  Batch/Lot numbers: CCI [redacted] (200 mg); CCI [redacted] (160 mg).
- Abiraterone (500 mg) tablets for oral intake (2 [500 mg] tablets), supplied by AstraZeneca: QD under fasting conditions (only water to drink) from at least 2 hours prior to dosing to at least 1 hour post-dose. Tablets had to be swallowed whole with water (not crushed or chewed). Abiraterone was dosed in combination with 10 mg prednisone or prednisolone daily.
  Batch/Lot numbers (500 mg): CCI [redacted]

Duration of treatment

The patients continued to receive study treatment until unacceptable toxicity, disease progression or withdrawal from study, whichever occurred first.

Statistical methods

Analysis sets:

- Enrolled Set: all patients who signed the informed consent form.
- Safety Analysis Set: all patients who took at least 1 dose of study treatment (capivasertib and/or abiraterone).
- Evaluable for Response Set: all patients who took at least 1 dose of any study treatment (capivasertib and/or abiraterone) and had measurable disease at baseline.
- PK Analysis Set: all patients who received at least 1 dose of study treatment with at least 1 reportable PK concentration.

Statistical analyses:

Safety analyses: Safety and tolerability were assessed in terms of dose limiting toxicities (DLTs), adverse events (AEs)/serious adverse events, vital signs, clinical chemistry/haematology parameters, electrocardiogram and echocardiogram data. These variables were collected for all patients. All safety analyses were performed on the Safety Analysis Set.

Pharmacokinetic analyses*:* Plasma concentrations and PK parameters (AUC, Cmax) of capivasertib, the capivasertib metabolite (AZ14102143) and abiraterone were summarised descriptively by study day.

Efficacy analyses: The efficacy endpoints for soft tissue objective response rate (ORR), overall radiological ORR, duration of response (DoR), and percentage change in tumour size were summarised on the Evaluable for Response Set. The efficacy endpoints of radiographic progression free survival (rPFS) were summarised on the Safety Analysis Set.

The Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 and Prostate Cancer Clinical Trial Working Group (PCWG)-3 tumour response data were used to programmatically determine each patient's visit response and derive the endpoints soft tissue ORR, overall radiological ORR, DoR, percentage change in tumour size and rPFS.

The rPFS was summarised descriptively and presented in Kaplan-Meier plots where there were sufficient number of patients at any given dose regimen.

Duration of response was presented in swimmer plots. The best percentage change in target lesions tumour size from baseline was summarised using descriptive statistics and presented in waterfall plots. Change in target lesions tumour size from baseline was also presented in spider plots.

Study population

Disposition: In total, 34 patients were enrolled in the study, 7 of which were screen failures. A total of 27 patients were assigned to receive treatment, 8 for Part A2 and 19 for Part B2. All patients in Part A2 and 17 (89.5%) patients in Part B2 discontinued treatment, most commonly due to disease progression (14 [51.9%] patients). Two (10.5%) patients in Part B2 continued treatment at the time of data cut-off. In total, 27 patients terminated the study, most commonly due to disease progression (13 [48.1%] patients) and following the occurrence of AEs (5 [18.5%] patients).

Protocol deviations: In total, 9 (Part A2: 2 [25.0%] patients; Part B2: 7 [36.8%] patients) patients had at least 1 important protocol deviation. There were no important protocol deviations due to coronavirus disease 2019 (COVID-19).

Study participants analysed: In total, 27 (Part A2: 8 patients; Part B2: 19 patients) patients were assigned to treatment and included in the safety and in the PK Analysis Set. A total of 14 (Part A2: 2 patients; Part B2: 12 patients) patients were included in the Evaluable for Response Set.

Demographic and other participant characteristics: The median (range) age was 68.0 (49 to 82) years, and approximately two thirds of the patients were over the age of 65, of which 7 (87.5%) in Part A2 and 10 (52.6%) in Part B2. All patients were White. The body mass index was balanced between Part A2 and Part B2.

Disease history: At screening, all patients had Eastern Cooperative Oncology Group performance status score of 0 or 1 (ie, normal activity or restricted activity). For the majority (25 [92.6%]) of patients, prostate gland was confirmed to be the primary tumour location. All patients had metastatic disease and 4 (14.8%) patients were also recorded as having locally advanced tumour.

Overall, 13 (48.1%) patients had 1 regimen of previous chemotherapy at baseline, 6 (22.2%) patients had 2 regimens, 2 (7.4%) patients had 3 regimens, and 1 patient (3.7%) had more than 3 regimens.

Medical and surgical history: The medical and surgical history reported was generally typical of the comorbidities seen in this patient population.

Concomitant medication after study entry: Overall, 3 (11.1%) patients took disallowed medication concomitantly with study participation. A wide range of allowed concomitant medications were taken and the most frequent (> 6 patients) were prednisone (17 [63.0%] patients), paracetamol (10 [37.0%]), leuprorelin acetate (8 [29.6%]), denosumab (7 [25.9%] patients), ibuprofen (7 [25.9%]), metformin (7 [25.9%]), omeprazole (7 [25.9%]), and triptorelin (7 [25.9%]).

Summary of efficacy results

Primary endpoints: There were no primary efficacy endpoints.

Secondary endpoints:

- Soft tissue ORR and radiological ORR by investigator assessment: There were no responders (complete response or partial response) in Part A2 or Part B2 patients included in the Evaluable for Response Set (N = 14). For the non-responders (N = 27), 7 (87.5%) patients in Part A2 and 9 (47.4%) patients in Part B2 were not evaluable. One (12.5%) patient in Part A2 and 3 (15.8%) patients in Part B2 had stable disease after at least 8 weeks, and in Part B2, 7 (36.8%) patients had progressed, and there was 1 (5.3%) death.
- Radiographic PFS according to RECIST 1.1 and PCWG-3 criteria: In Part A2 and Part B2, there were a total of 3 (37.5%) and 10 (52.6%) progression events, respectively.

In Part A2 patients, all the events were due to progression. In Part B2, 9 (47.4%) events were due to progression and there was 1 (5.3%) death in the absence of progression. Median rPFS (95%CI) was 9.66 months (2.07, 15.61) in Part A2 and 2.33 months (1.74, 3.81) in Part B2. For patients in Part A2 and Part B2, median (range) follow-up time was 1.87 (0.03 to 8.25) months and 1.71 (0.03 to 13.60) months, respectively.

- DoR and best percentage change in tumour size using RECIST 1.1 criteria: No data met the criteria for DoR. In Part B2, there were 4 patients with at least 1 post baseline RECIST target lesion assessment scan. The median (range) percentage change from baseline was -8.3% (-42.6 to 4.6). No change from baseline was reported for patients in Part A2.

Summary of pharmacokinetic results

Plasma PK parameters of capivasertib and metabolite AZ14102143 for Part A2 and Part B2: Following intermittent dosing of capivasertib 400 mg BID, 4 days on, 3 days off, the Day 25 capivasertib geometric mean AUCτ and Cmax were 10300 ng*h/mL and 1934 ng/mL, respectively, and the median tmax was 2 hours.

The variability in capivasertib exposure between patients was moderate with geometric coefficient of variation (CV)% values of 39% for AUCτ and 36% for Cmax.

The AUCτ and Cmax of the capivasertib metabolite AZ14102143 were approximately 7- and 5-fold higher, respectively, than the corresponding exposure of capivasertib. The concentration versus time profiles had a similar shape with a median tmax of 2 hours and a parallel decline.

Plasma PK parameters of abiraterone for Part A2 and Part B2: Following dosing of abiraterone 1000 mg QD, the Day 25 capivasertib geometric mean AUC(0-24) and Cmax values were 780 ng*h/mL and 116 ng/mL, respectively. The median tmax was 2 hours. The variability in abiraterone exposure between patients was high with geometric CV% values of 64.6% for AUC(0-24) and 123.9% for Cmax. The variability was particularly pronounced due to the low exposure to abiraterone observed in patient PPD

In patients who had a 1-week run-in of abiraterone prior to starting the capivasertib dose regimen, the geometric mean pre-dose concentrations were similar before (13 ng/mL) and after (7, 11, 16, and 18 ng/mL) the addition of capivasertib, although the variability was high (92 to 144% geometric CV). However, the individual line plots for the patients with 1-week run-in of abiraterone dosing do not indicate any increasing or decreasing trend in the pre-dose concentrations.

Summary of safety results

Extent of exposure:

The median total treatment exposure and median actual/dosed treatment exposure of capivasertib in Part A2 patients were 2.33 and 1.23 months, respectively; and 2.63 and 1.28 months in Part B2, respectively. For abiraterone, both the median total treatment exposure and the median actual/dosed treatment exposure in Part A2 patients were 2.51 months, and for Part B2 patients, 2.86 and 2.10 months, respectively.

For Part A2 patients, the number (percentage) of patients with capivasertib interruptions and/or dose reductions was 3 (37.5%) and 2 (25.0%) patients, respectively. For Part B2 patients, the number (percentage) of patients with interruptions and/or dose reductions was 5 (26.3%) and 3 (15.8%) patients, respectively.

There were no abiraterone treatment interruptions or dose reductions in Part A2 patients. For Part B2 patients, the number (percentage) of patients with abiraterone interruptions and/or dose reductions was 4 (21.1%) and 2 (10.5%) patients, respectively.

The median number of treatment cycles received for capivasertib and abiraterone were 3, both for Part A2 and Part B2 patients.

Dose intensity of capivasertib is summarised in Table 14.3.1.1.5. Mean (standard deviation) relative dose intensity was 93.9 (10.86) for Part A2 patients and 84.1 (27.54) for Part B2 patients.

Adverse events:

Overall, all patients experienced at least 1 AE: the majority of patients (25 [92.6%] patients) experienced at least 1 AE considered related to capivasertib (Part A2: 7 [87.5%] patients; Part B2: 18 [94.7%] patients) and approximately two thirds of patients (20 [74.1%] patients) experienced at least 1 AE related to abiraterone (Part A2: 8 [100%] patients; Part B2: 12 [63.2%] patients).

Adverse events with the outcome death were reported for 1 (5.3%) patient in Part B2, and no patients in Part A2. A total of 2 (10.5%) patients in Part B2 died during the study. All deaths were related to the disease under investigation and one of them was reported as having an AE with outcome of death (preferred term [PT]: acute kidney injury). No patients in Part A2 died during the study. There were no COVID-19 related deaths during this study.

Serious AEs (irrespective of relationship) were reported for 10 (37.0%) patients (Part A2: 5 [62.5%] patients; Part B2: 5 [26.3%] patients).

Serious AEs (including events with outcome of death) causally related to either treatment were reported for 5 (18.5%) patients (Part A2: 3 [37.5%] patients; Part B2: 2 [10.5%] patients).

Adverse events leading to permanent discontinuation of capivasertib (irrespective of relationship) were reported for 11 (40.7%) patients (Part A2: 3 [37.5%] patients; Part B2: 8 [42.1%] patients). Adverse events leading to permanent discontinuation of abiraterone (irrespective of relationship) were reported for 9 (33.3%) patients (Part A2: 3 [37.5%] patients; Part B2: 6 [31.6%] patients).

There was 1 confirmed COVID-19 non-serious AE of Common Terminology Criteria for Adverse Event grade 1 reported by a patient in Part B2.

For capivasertib, the following PTs were classed as adverse events of special interest (AESI): rash, hyperglycaemia, non-infectious diarrhoea, QT prolongation, hyperlipidaemia, infective pneumonia, stomatitis, and urinary tract infection (UTI).

The AESI most frequently reported were: non-infectious diarrhoea (16 [59.3%] patients), followed by hyperglycaemia (13 [48.1%] patients), rash (6 [22.2%] patients), UTI (3 [11.1%] patients) and infective pneumonia (2 [7.4%] patients).

The majority of patients experienced grade 1 and grade 2 AESI.

Adverse events of special interest of grade 3 were reported for 9 patients: hyperglycaemia (4 [14.8%] patients), rash (2 [7.4%] patients), infective pneumonia, non-infectious diarrhoea, and UTI (1 [3.7%] patient, each).

Conclusions

- The administration of capivasertib (400 mg) in combination with abiraterone was generally well tolerated, with no DLT reported. Overall, the safety and tolerability profile of the combination treatment was consistent with the know safety profile of capivasertib.
- No patients showed confirmed objective response following study treatment. The median rPFS was 9.66 months (2.07, 15.61) in Part A2 and 2.33 months (1.74, 3.81) in Part B2. The median reduction in target lesion size for the 4 patients analysed in terms of best percentage change in target lesion size in Part B2 was 8.3% reduction.
- The plasma PK parameters of capivasertib, metabolite AZ14102143 and abiraterone were characterised and were consistent with previously reported studies.
- Overall, the PK data do not suggest an interaction between capivasertib and abiraterone.