Protocol number: D8731C00002
Document title: A Phase II, Open-label Study to Assess the Efficacy, Safety, and Tolerability of AZD4635 in Combination with Durvalumab and in Combination with Cabazitaxel and Durvalumab in Patients Who Have Progressive Metastatic Castrate-Resistant Prostate Cancer (AARDVARC)
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2. SYNOPSIS

Study centre(s)

The study was conducted at 16 centres in 5 countries viz., Belgium, France, South Korea, Spain, and Unites States.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the efficacy (as assessed by radiographic progression free survival [rPFS]) of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel in participants with mCRPC.	• rPFS, defined as the time from first dose to radiographic progression as assessed by the Investigator per RECIST v1.1 (soft tissue) and Prostate Cancer Working Group 3 criteria (PCWG3) (bone) or death from any cause, whichever occurs first.
Secondary	
• To determine the efficacy of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel by assessment of overall survival (OS) in participants with mCRPC.	• OS, defined as the time from first dose until death due to any cause regardless of whether the participant withdraws from study treatment or receives another anti-cancer therapy.
• To determine the efficacy of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel, by assessment of ORR in participants with mCRPC.	• Confirmed ORR, defined as the proportion of participants with a confirmed CR or PR using overall radiographic response assessed by RECIST v1.1 and PCWG-3 criteria (bone), and will be based on a subset of all treated participants with measurable disease at baseline per the site Investigator.
• To determine the efficacy of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel by assessment of duration of response (DoR) in participants with mCRPC.	• DoR, defined as the date of first documented response (which is subsequently confirmed) until the date of documented progression or death in the absence of disease progression.
• To determine the efficacy of AZD4635 plus durvalumab and separately ofAZD4635 plus durvalumab plus cabazitaxel by assessment of prostate-specific antigen (PSA) response in participants with mCRPC.	• Confirmed PSA50 response, defined as the proportion of participants achieving a ≥ 50% decrease in PSA from baseline to the lowest post-baseline PSA, confirmed by a consecutive PSA at least 3 weeks later and will be based on PSA evaluable participants (dosed participants with an abnormal baseline PSA [≥ 1 ng/mL]).

Objectives	Endpoints
• Investigate the pharmacokinetics (PK) of AZD4635 when given in combination with durvalumab, and when given in combination with durvalumab plus cabazitaxel.	• AZD4635, durvalumab and cabazitaxel plasma concentration and derived PK parameters, where deemed appropriate.
• To determine the efficacy of AZD4635 plus durvalumab plus cabazitaxel in participants with mCRPC, by adenosine (ADO) signalling gene expression in high and low subgroups.	• rPFS, defined as the time from first dose to radiographic progression, assessed by the Investigator per RECIST 1.1 (soft tissue) and PCWG3 criteria (bone) or death from any cause, whichever occurs first by gene expression subgroup.
• To determine the effects of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel on pain and other prostate cancer-related symptoms.	• Change from baseline in worst pain, average pain and pain interference in the daily activities scales of the BPI-SF. • Time to pain progression based on BPI-SF Item 3 "pain at its worst in the last 24-hours". • Change from baseline in the FAPSI-6 as derived from 6 items and the FAPSI-8 as derived from 8 items within the FACT-P, and the PCS, as derived from the 12 items in the prostrate-specific module of the FACT-P.
Safety	
• To evaluate the safety and tolerability of each treatment regimen in participants with mCRPC.	• Physical examination, laboratory values (haematology, clinical chemistry, urinalysis, and tests for coagulation), vital signs, and electrocardiograms (ECGs). • Adverse events/serious adverse events (AEs/SAEs) collected throughout the study, from the time of the informed consent form signature through to the last safety follow-up visit.

ADO, adenosine; AE, adverse event; BPI-SF, Brief pain inventory – Short Form; CR, complete response; DoR, duration of response; ECG, electrocardiogram; FACT-P, Functional assessment of cancer therapy – prostate cancer; FAPSI, FACT advanced prostate symptom index; mCRPC, metastatic castrate-resistant prostate cancer; ORR, objective response rate; OS, overall survival; PCGW-3, Prostate Cancer Working Group 3 criteria; PCS, Prostate cancer symptoms; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; PSA, prostate-specific antigen; rPFS, radiographic progression free survival; RECIST, response evaluation criteria for solid tumours; RP2D, recommended Phase II dose; SAE, serious adverse event

Exploratory objectives and outcome measures are detailed in Section 3 of the CSP (Appendix 16.1.1). Exploratory objectives will be reported separately and will not form part of the CSR.

Study design

This was a Phase II, international, open-label, two-arm, non-randomised study of AZD4635 in participants with mCRPC. The primary objective was to determine the rPFS of AZD4635 plus durvalumab (Arm A) and separately of AZD4635 plus durvalumab plus cabazitaxel (Arm B).

Participants were allocated to one of the following treatment arms:

Arm A: AZD4635 (CCI mg *per os* [orally] daily) plus durvalumab (1500 mg intravenous every 4 weeks) OR

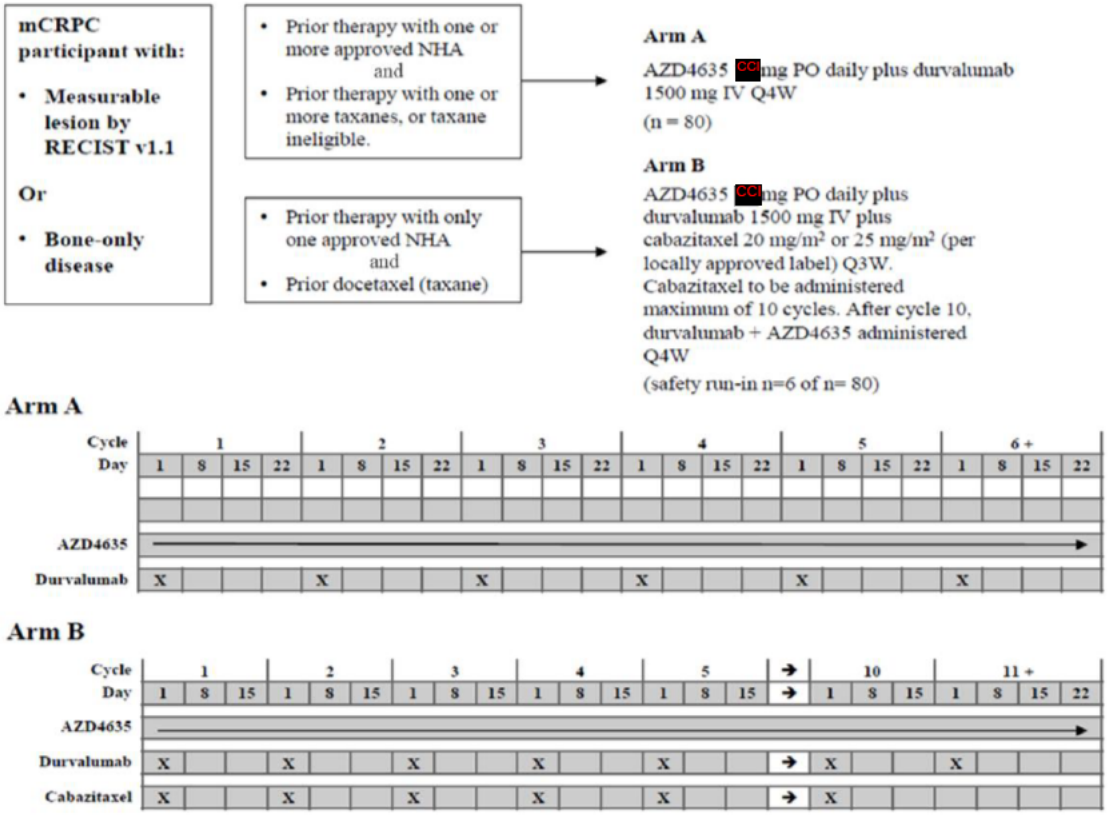
Arm B: AZD4635 (CCI mg *per os* [orally] daily) plus durvalumab (1500 mg intravenous every 3 weeks) plus cabazitaxel (20 or 25 mg/m2 intravenous every 3 weeks as per local prescribing guidelines).

AZD4635 plus durvalumab (Arm A) consisted of 2 participants with mCRPC previously treated with one or more approved new hormonal agent(s) (NHAs) (e.g., abiraterone acetate, enzalutamide, apalutamide and/or darolutamide) and one or more taxanes or participants who were taxane ineligible. Subjects in Arm A received AZD4635 (CCImg PO daily) plus durvalumab (1500 mg IV Q4W). As of November 2020, the Sponsor stopped enrolment in Arm A following decisions at the program level, not related to any safety issues.

AZD4635 plus durvalumab plus cabazitaxel (Arm B) consisted of 28 participants with metastatic castrate-resistant prostate cancer (mCRPC) who were previously treated with docetaxel and one prior new hormonal agent (NHA) (either abiraterone acetate or enzalutamide but not both; prior apalutamide was not permitted in Arm B). Eligible participants must have had histologically diagnosed mCRPC with no evidence of small cell histology, have had progression of disease $\leq$ 6 months prior to study entry either by response evaluation criteria for solid tumours (RECIST) v1.1 or bone lesions per Prostate Cancer Working Group 3 criteria (PCWG3), and have had ongoing androgen deprivation with serum testosterone < 50 ng/mL. As of 15 October 2021, it was communicated that based on review of the data from the interim analysis (data cut-off [DCO] 21 August 2021), further enrolment into Arm B of the study was futile based on efficacy data. The safety profile of the combination was consistent with the expected safety profile of the agents when used in combination; no new safety signals were identified.

Since Arm B was the only arm still open, the closure of this arm closed enrolment for the entire study. The DCO for this report was defined as 01 November 2021.

Figure S 1 Study Design for Arm A and Arm B



Target population and sample size

Participants with progressive mCRPC were included in the study. Arm A consisted of participants with mCRPC previously treated with one or more approved NHAs and one or more taxanes or participants who were taxane ineligible. Arm B consisted of participants with mCRPC previously treated with docetaxel and one prior NHA (either abiraterone acetate or enzalutamide but not both; prior apalutamide was not permitted in Arm B). The target sample size for Arm A and Arm B was 80 participants. However, only 2 participants were enrolled in Arm A, as the Sponsor stopped enrolment in Arm A following decisions at the program level. A total of 28 participants were enrolled in Arm B, enrolment was stopped at the interim analysis (data cut off 10 August 2021). The futility ("no go") criterion was met (PSA50 response rate < 35%), with less than 10 out of 27 (< 10/27) participants achieving a PSA50 response.

Table S 2 Investigational product and comparator(s): dosage, mode of administration and batch numbers

ARM Name	A and B	A and B	B only
Intervention Name	**AZD4635**	**Durvalumab**	**Cabazitaxel**
Dosage Level(s)	CCImg PO daily (Arm A and Arm B)	1500 mg IV Q4W (Arm A) 1500 mg IV Q3W (Arm B)	20 or 25 mg/m^2 IV Q3W as per the local label (Arm B only)
Route of Administration	Oral	Intravenous	Intravenous
Batch Numbers	**Manufacturing Batch**: CCI **Packaging Batch**: CCI CCI	**Manufacturing Batch**: CCI **Packaging Batch**: CCI	Not available [a]

[a] Batch numbers for Cabazitaxel are not available, because this study intervention was provided locally by the sites.

Duration of treatment

Participants in Arm A and Arm B continued treatment as planned (ie, as long as they received clinical benefit and did not meet any discontinuation criteria).

Statistical methods

The two arms (Arm A and Arm B) were analysed separately. Following the decision to stop enrolment in Arm A, data from Arm A was listed only because the number of enrolled participants was too small for a meaningful analysis. The analysis for Arm B was descriptive, including summaries from the Kaplan-Meier curve.

Disposition, demography, baseline characteristics (including disease characteristics), protocol deviations, concomitant medications, medical history and surgical history were listed and summarised for safety analysis set for Arm B. Data from Arm A were listed only. Tumour response data were listed using the following response categories: complete response (CR), partial response (PR), stable disease (SD), Non-CR/Non- progression of disease (PD), PD, and not evaluable (NE). Summaries (number of events, medians, proportion and 95% confidence interval for PFS at fixed time points using the Kaplan-Meier estimate) and Kaplan-Meier plots were provided for Arm B. Overall survival was analysed in the same manner as radiographic progression-free survival (rPFS) if the number of participants with events allowed, but without the subgroup analysis. The primary efficacy endpoint was rPFS defined as the time from first dose until radiographic progression as assessed by the Investigator per RECIST v1.1 (soft tissue) and PCWG3 (bone) or death from any cause, whichever came first. For the secondary

endpoint objective response rate (ORR) assessed by RECIST 1.1 and PCWG3, only dosed participants with measurable disease (target lesions) at baseline were included in the analysis.

Adverse events (Aes), serious adverse events (SAEs), deaths, and discontinuations due to AEs were summarized. Treatment-emergent AEs were summarized by Medical Dictionary for Regulatory Activities (MedDRA) (version 24.1), system organ class (SOC) and preferred term, with further splits by maximum Common Terminology Criteria for Adverse Events (CTCAE) grade (Version 5.0), causal relationship to any study medication, dose interruption or modification, and AEs classed as CTCAE Grade 3 or higher. Adverse events of special interest (AESIs) for durvalumab were summarized. Haematology, blood chemistry, lipid, cardiac enzyme, and coagulation parameters were summarized.

Study population

A total of 33 participants were enrolled in this study, of which a total of 30 participants received AZD4635 study treatment (2 participants in Arm A and 28 participants in Arm B). A total of 17 (60.7%) participants discontinued AZD4635 study treatment in Arm B, most of them due to disease progression (10 [35.7%] participants). The 2 participants enrolled in Arm A, discontinued AZD4635 study treatment due to AE and disease progression. At the time of data cut-off, a total of 29 participants had terminated the study and there was one participant ongoing in the study.

Arm A: There were 2 (100%) participants who received CCI mg AZD4635 plus 1500 mg durvalumab and discontinued study treatment due to adverse reaction and disease progression respectively.

Arm B: There were 28 (100%) participants who received CCI mg AZD4635 plus 1500 mg durvalumab plus 20 or 25 mg/m^2 cabazitaxel. Of these, 17 (60.7%) participants discontinued AZD4635 study treatment, the reasons for discontinuation were disease progression, adverse events, consent withdrawal, and other. The remaining 11 participants were on AZD4635 treatment when the study was terminated.

Summary of efficacy results

The futility ("no go") criterion was met with less than 10 out of 27 ($\leq$ 10/27) participants achieving a PSA50 response ie, the true PSA50 response rate was < 35% at data-cut off (10 August 2021). AZD4635 + durvalumab + cabazitaxel in mCRPC participants showed a confirmed PSA50 response of 14.8% (4/27). Therefore, it was concluded that further enrolment into Arm B of the study was futile, and enrolment was stopped.

Summary of safety results for Arm B

- The mean total treatment duration for AZD4635 was 157.8 days (SD=89.5), durvalumab was 166.9.8 days (SD=83.3), and cabazitaxel was 144.0 days (SD=64.1).

- Treatment interruptions were minimal and did not meaningfully affect the actual treatment duration.
- AZD4635 was well tolerated in combination with durvalumab and cabazitaxel.
- Of the total 28 (100%) participants who presented with one or more adverse events related to any study treatment, 23 (82.1%) participants had one or more adverse events related to AZD4635 as assessed by the Investigator. Nausea (11 participants [39.3%]), diarrhoea (10 participants [35.7%]) and vomiting (7 participants [25.0%]) were the most frequently reported AEs assessed by investigator as possibly related to AZD4635.
- The most frequently reported AEs were nausea reported in 17 (60.7%) participants, anaemia reported in 14 (50%) participants, and diarrhoea reported in 14 (50%) participants.
- There were 19 (67.9%) participants with at least one SAE. Of these 12 (42.9%) participants had at least one SAE which was possibly related to any study treatment as assessed by Investigator.
- The 3 AEs which led to discontinuation of AZD4635 and considered to be possibly related to AZD4635 treatment were nausea and vomiting in one participant, and myositis in one participant
- There were 24 (85.7%) participants with at least one AE of grade 3 or higher.
- There were no dose-limiting toxicities.
- There were no significant safety concerns that preclude further development of AZD4635 in combination with durvalumab and cabazitaxel.
- There were no clinically important trends or changes over time from baseline in haematology, clinical chemistry, and urinalysis parameters.
- There were no clinically significant changes in vital signs and electrocardiograms (ECGs) in this study.
- Overall, the safety and tolerability profile of AZD4635 in combination with durvalumab and cabazitaxel was consistent with the known safety profile.

Conclusion

AZD4635 in combination with durvalumab and in combination with cabazitaxel and durvalumab in participants who have progressive metastatic castrate-resistant prostate cancer, showed limited efficacy particularly considering the expected single-agent activity of cabazitaxel. The safety and tolerability profile were consistent with the known safety profile and there were no significant safety concerns that preclude further development.