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).

Published: 21-10-2020
Last updated: 08-04-2024

ObjectivesPrimary* 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.Secondary* To evaluate the...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON51202

Source
ToetsingOnline

Brief title
AARDVARC

Condition

- Metastases

Synonym
Progressive Metastatic Castrate-Resistant Prostate Cancer - Prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: AZD4635, Combination with Cabazitaxel and Durvalumab, Metastatic castrate-resistant prostate cancer, Phase II

Outcome measures

Primary outcome

The primary efficacy endpoint is 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 comes first.

Radiological progression-free survival (rPFS)

Progression-free survival is defined as the time interval from the first dose of AZD4635 until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the participant withdraws from treatment or receives another anti-cancer therapy prior to progression. Participants who have not progressed (defined as CR, PR or SD by RECIST v1.1 for soft tissue disease, or non-PD for bone disease) at the time of analysis will be censored at the time of the last evaluable RECIST v1.1 assessment or bone scan.

However, if the participant progresses or dies after 2 or more missed

radiologic visits the participant will be censored at the time of the last evaluable RECIST v1.1 or bone scan assessment prior to the 2 missed visits. If a participant has an assessment for soft tissue disease (MRI/CT) but not for bone disease (bone scan), or vice versa, then this will count as a missed assessment. If the participant has no evaluable post-baseline RECIST v1.1 or bone scan assessments they will be censored at Day 1 unless they die within 2 visits of baseline (in which case their date of death will be used). Progression-free survival will be derived based on scan/assessment dates not the scheduled visit dates. If RECIST v1.1 assessments/bone scans contributing toward a particular visit are performed on different dates then the date of progression will be determined based on the earliest of the dates of the component that triggered the progression. With regard to censoring, a participant will be censored at the latest of the dates contributing to a particular overall visit assessment. Summaries (number of events, medians, proportion and 95% CI for progression free at fixed time points using the Kaplan-Meier estimate) and Kaplan-Meier plots will be provided. A 2-sided 95 % CI for the median PFS will be produced in addition to the 25th and 75th percentiles.

Secondary outcome

Secondary endpoints include: safety, OS, ORR, DoR, PSA50 response, time to pain progression, and PK. The analysis will be descriptive and summaries will be presented for each arm. Relevant efficacy endpoints will also be summarised for biomarker high and low subgroups.

Secondary endpoints

* 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.
* 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.
* Confirmed ORR, defined as the percentage of participants with a confirmed Investigator-assessed response of 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.
* 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.
* 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]).
* AZD4635, durvalumab and cabazitaxel plasma concentrations and derived PK parameters, where deemed appropriate.

* rPFS, defined as the time from first dose until 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.
* 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.
* Confirmed objective response rate (ORR), defined as the percentage of participants with a confirmed Investigator-assessed response of 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. Duration of response (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.
* 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]).
* Time to pain progression based on Brief Pain Inventory (Short Form) (BPI SF) Item 3 *pain at its worst in the last 24 hours*.
* rPFS, defined as the time from first dose until 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.

* 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.

* Confirmed objective response rate (ORR), defined as the percentage of participants with a confirmed Investigator-assessed response of 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.

* Duration of response (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.

* 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]).

* Time to pain progression based on BPI SF Item 3 *pain at its worst in the last 24 hours*.

* 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, 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.

Exploratory

* iRECIST.

The results of this exploratory biomarker research will not form part of the CSR.

* Exploratory endpoints will include but are not limited to genomic status, including gene expression, whole blood and serum analytes, and biopsies where possible. This may include collection of genomic status including gene expression, whole blood and serum analytes from previous samples, if available. Their association with efficacy endpoints will be explored. Features of immune status such as T cell receptor repertoire, expression of immune-related genes, tumour mutational burden and microsatellite instability (MSI) status will be explored.

The results of this exploratory biomarker research will not form part of the CSR.

* Correlation of polymorphisms with variations in safety or response parameters to study interventions.

The results of this exploratory biomarker research will not form part of the CSR.

* Collection of plasma samples to include, but not be limited to extraction of ctDNA for investigation of blood-borne cancer biomarkers. Correlate ctDNA

longitudinal kinetics with patterns of response and relapse.

The results of this exploratory biomarker research will not form part of the

CSR.

* Collection of samples to include but, not be limited to, whole blood, plasma,

and tissue samples (tumour, bone, or lymph node biopsies). Measured methods

including, but not be limited to gene and protein expression, DNA

amplification, and enzymatic activity.

The results of this exploratory biomarker research will not form part of the

CSR.

Study description

Background summary

Prostate cancer is the second most common cancer in men. In 2018, over 1.2 million new cases of prostate cancer were diagnosed worldwide and there were 350,000 deaths due to the disease (Bray et al. 2018). For men requiring systemic therapy, hormonal therapy has been the mainstay. Once the disease becomes resistant to hormonal therapy, the disease is known as castration-resistant prostate cancer (CRPC). Treatment for both metastatic and non-metastatic prostate cancer has evolved over the past 15 years. In 2004, the development of a docetaxel regimen for the treatment of CRPC was the first chemotherapy to show a survival benefit and subsequently became the standard-of-care chemotherapy for CRPC. A regimen of docetaxel given Q3W had a median OS of 18.9 months (95% CI 1417.0-21.2), which was greater than the survival of 16.5 months (95% CI 14.4 * 18.6 months) for a mitoxantrone control arm. The hazard ratio (HR) for death was 0.76 (95% CI 0.62-0.94, p=0.009) for docetaxel compared to mitoxantrone (Tannock et al. 2014). However, many of the treatments for prostate cancer, including docetaxel and cabazitaxel for mCRPC, are not suitable for all patients and many patients are refractory to these treatments so alternative treatment options are needed.
New hormonal agents have become standard of care for mCRPC and include enzalutamide and abiraterone plus prednisone. Enzalutamide, a targeted androgen-receptor inhibitor that blocks the binding of androgen to the androgen receptor, translocation to the nucleus, and DNA binding (Tran et al. 2009), was approved for the first-line treatment of patients with mCRPC. Abiraterone, a

selective inhibitor of 17 *-hydroxylase/C17,20-lyase (CYP17), was also approved in combination with prednisone for the treatment of mCRPC in the first-line setting (Ryan et al. 2013a, Ryan et al. 2013b).

AZD4635 is being developed as monotherapy and as an immuno-oncology agent in combination with durvalumab (anti-PD-L1) and durvalumab plus oleclumab (cluster of differentiation 73 [CD73] monoclonal antibody), exploiting complementary immune-related mechanisms to broaden and deepen clinical responses. AZD4635 has shown activity in a variety of tumour types, with encouraging data being seen for the combination AZD4635 and durvalumab in the Phase I study. As stated previously, this Phase II study will evaluate the efficacy, safety and tolerability of the combination of AZD4635 and durvalumab and the combination of AZD4635 with durvalumab and cabazitaxel. In addition, the study will explore the combination of AZD4635 plus durvalumab in a selected participant population using a biomarker-derived signature shown to correlate with participant outcomes (Sidders et al., recently accepted by Clinical Cancer Research.)

Durvalumab (IMFINZI®) is FDA-approved in patients with bladder urothelial carcinoma who have disease progression during or following platinum containing chemotherapy and in patients who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy. Durvalumab is also approved in patients with NSCLC whose disease has not progressed following concurrent platinum based chemotherapy and radiation therapy. Durvalumab, in combination with etoposide and either carboplatin or cisplatin, is also approved for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) (IMFINZI® US Prescribing Information).

Durvalumab is approved by the European Medicines Agency (EMA) as monotherapy for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on *1% of tumour cells and whose disease has not progressed following platinum-based chemo-radiation therapy (IMFINZI®, EU SmPC). Although NHAs have changed the landscape of treatment for mCRPC, for patients who have progressed on NHAs and docetaxel, there remain limited therapeutic options. While immunotherapy has led to impressive responses in a subset of patients with immunologically *activated* tumours, this approach has shown little progress in mCRPC. The addition of AZD4635 to anti-PD/PDL1 therapy or the combination of anti-PDL1 plus cabazitaxel may lead to an improvement in rPFS in these patients.

Study objective

Objectives

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.

Secondary
* To evaluate the safety and tolerability of each treatment regimen in participants with mCRPC.
* 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.
* To determine the efficacy of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel, by assessment of ORR in participants with mCRPC.
* To determine the efficacy of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel by assessment of DoR in participants with mCRPC.
* To determine the efficacy of AZD4635 plus durvalumab and separately of AZD4635 plus durvalumab plus cabazitaxel, by assessment of PSA response in participants with mCRPC.
* Investigate the PK of AZD4635 when given in combination with durvalumab, and when given in combination with durvalumab plus cabazitaxel.
* To determine the efficacy of AZD4635 plus durvalumab and AZD4635 plus durvalumab plus cabazitaxel in participants with mCRPC, by adenosine (ADO) signalling gene expression in high and low subgroups in each arm separately.
* To determine the efficacy of AZD4635 plus durvalumab and AZD4635 plus durvalumab plus cabazitaxel in participants with mCRPC, by adenosine deaminase (ADA) gene expression in high and low subgroups in each arm separately.
* To determine the effects of AZD4635 on pain and other prostate cancer related symptoms.

Exploratory
* Evaluate response using a modified RECIST criteria for immunotherapy (iRECIST)
* Investigate the impact of genomic status on the participant response to the treatment combinations.
* DNA for future exploratory research into genes/genetic variations that may influence response (i.e., distribution, safety, tolerability, and efficacy) to AZD4635 treatment.
* To investigate baseline circulating tumour DNA (ctDNA), as well as changes in ctDNA levels with treatment for correlation with tumour burden.
* Evaluation of prostatic acid phosphate (PAP) levels and activity.
* To explore the relationship between PK parameters and selected endpoints (which may include PD/biomarker, efficacy, and/or safety), where deemed appropriate.

Study design

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

durvalumab plus cabazitaxel (Arm B) (see Figure 1 in the protocol).
Participants in each arm will be stratified by the presence of measurable soft tissue metastasis (per RECIST v1.1, Appendix F of the protocol) or bone-only metastasis (per PCWG3 criteria, Appendix H of the protocol). There will be no formal comparisons between treatment arms. Secondary endpoints include; safety, OS, confirmed ORR, DoR, confirmed PSA50 response, time to pain progression, and PK.

AZD4635 plus durvalumab plus cabazitaxel (Arm B) will consist of 80 participants mCRPC previously treated with docetaxel and one prior NHA (either abiraterone acetate or enzalutamide but not both; prior apalutamide is not permitted in Arm B).
Eligible participants must have histologically diagnosed mCRPC with no evidence of small cell histology, have had progression of disease * 6 months prior to study entry either by RECIST v1.1 or bone lesions per PWCG3 and have ongoing androgen deprivation with serum testosterone < 50 ng/mL.

Participants will be allocated to one of the following treatment arms:
Arm A: AZD4635 (75 mg PO daily) plus durvalumab (1500 mg IV Q4W) (n = 80)
or
Arm B: AZD4635 (75 mg PO daily) plus durvalumab (1500 mg IV Q3W) plus cabazitaxel (20 or 25 mg/m2 IV Q3W as per local prescribing guidelines) (n = 80).
Participants in Arm B will receive cabazitaxel chemotherapy as per the local label. This will start approximately 1 hour (or up to a maximum of 2 hours) after the end of the durvalumab infusion. Cabazitaxel will be administered as per the local prescribing guidelines for a maximum of 10 cycles. After cycle 10 durvalumab + AZD4635 will be administered Q4W to harmonise with the Arm A treatment cycle length.

Treatment in group A is only proposed to patients already enrolled in this study group, because enrollment in group A is closed.

Arm B participants must receive premedication to manage cabazitaxel-associated reactions (hypersensitivity or other):
* Prednisone (10 mg daily continuously [or equivalent steroid]) for the duration of cabazitaxel administration
* Primary G-CSF prophylaxis (G-CSF should be administered according to the product label and institutional standards).
An archival tumour sample is required or the participant must be willing to undergo a baseline tumour biopsy (see Section 8.6.1.3 of the protocol). The collection of paired tumour biopsies will be requested during the study; however, this is optional (see Section 8.6.2.1 of the protocol).

Participants in Arm A (AZD4635 plus durvalumab) will have disease assessments/imaging at baseline and every 8 weeks (± 7 days) from the start of dosing for the first 24 weeks and then every 12 weeks (± 7 days) thereafter.

During the study, tests for active COVID-19 infection may be prescribed, if required, and in accordance with local guidelines.

If a participant is symptomatic for active COVID-19 infection during a site visit, he may be prescribed a COVID-19 test. Dosing may continue while results are awaited, per the Investigator*s discretion and local guidelines, and the Medical Monitor/AstraZeneca Study Physician should be consulted. For participants who test positive (for COVID-19) the study drugs may be temporarily interrupted and later resumed, per the Investigator*s discretion and local guidelines, and this should be discussed with the Medical Monitor/AstraZeneca Study Physician. Where applicable, home or remote visits may be conducted for study assessments and study drug administration (see Appendix L of the protocol).

Participants in Arm B (AZD4635 plus durvalumab and cabazitaxel) will have disease assessments/imaging at baseline and every 9 weeks (± 7 days) from the start of dosing for the first 27 weeks and then every 12 weeks (± 7 days) thereafter. A safety assessment to determine the safety and tolerability of this combination will be completed by the SRC after the first 6 participants have completed a safety assessment period of at least 1 cycle (see Section 4.1.1 of the protocol).

The participant reported outcome (PRO) instruments, a BPI-SF (see Appendix J) and FACT P (see Appendix K) will be administered to all participants. These two instruments will be used to assess pain and quality of life in study participants. These will be measured as shown in Table 1*1 and Table 1*2 of the protocol

The two arms will enrol and assign to study treatment approximately 160 participants (80 per arm) with metastatic disease documented by either bone lesions on bone scan or with soft tissue disease that is evaluable for assessment. At least 40 participants with RECIST v1.1 measurable disease (Section 5.1 of the protocol) at baseline will be enrolled and assigned to study treatment in each arm, and the remainder of participants in the arm (n=40 per arm) may have bone-only disease or measurable disease. The primary analysis, rPFS, will be assessed, and is defined as the time from first dose to radiographic progression as determined by the Investigator per RECIST v1.1 for soft tissue disease or PCWG3 for bone disease or death from any cause, whichever occurs first. Overall survival, ORR, DoR, PSA50 response, and time to pain progression will also be evaluated for efficacy.

Intervention

Study intervention in this study refers to AZD4635, durvalumab and cabazitaxel. In this protocol AZD4635, durvalumab and cabazitaxel are also referred to as either study drugs, study interventions, IPs, or investigational medicinal products * and these terms are used interchangeably.

Arm A: AZD4635 capsules will be taken by mouth once daily.
Durvalumab will be given via an IV at the study site once every 4 weeks (every cycle).

If the patient's previous treatment included docetaxel and one NHA (e.g., abiraterone acetate or enzalutamide but not both), you will be treated according to Arm B (AZD4635, durvalumab and cabazitaxel).

Arm B:
AZD4635 capsules will be taken by mouth once daily.
Durvalumab will be given via an IV at the study site once every 3 weeks (every cycle).
Treatment with AZD4635 and durvalumab will continue after Cycle 10, with durvalumab given once every 4 weeks thereafter.
Cabazitaxel will be given via an IV at the study site once every 3 weeks (every cycle).

Treatment in group A is only proposed to patients already enrolled in this study group, because enrollment in group A is closed.

Prednisone will be taken by mouth once daily, for as long as you are receiving cabazitaxel, to lessen side effects associated with cabazitaxel.
Cabazitaxel will be administered as per standard treatment, for a maximum duration of 10 cycles (approximately 7.5 months). Treatment with AZD4635 and durvalumab will continue, but treatment with durvalumab will be adjusted to every 4 weeks, instead of every 3 weeks.

Granulocyte-colony stimulating factor (G-CSF) will be given during the cycles in which cabazitaxel is given. G-CSF is given to lessen the chance of infection caused by cabazitaxel chemotherapy. G-CSF will be monitored and administered by the study doctor.

Study burden and risks

Data from treatment with AZD4635 alone in 141 subjects as of 02 December 2019 showed.

AZD4635 side effect(s)
Very common (seen in more than 1 in 10 people)
Nausea
Fatigue/Tiredness
Vomiting
Decreased appetite
Dizziness
Diarrhoea

Common (seen between 1 in 20 and 1 in 10 people)

Altered sense of taste

Risks associated with the combination of AZD4635 and durvalumab
The combination of AZD4635 and durvalumab is being evaluated in ongoing studies. It is possible that the combination may lead to side effects related to immune reactions, which are known to occur with durvalumab. In an ongoing study, two patients developed type 1 diabetes when AZD4635 was taken in combination with durvalumab.

Overlapping side effects to date include nausea, fatigue, vomiting, constipation, diarrhea, decreased appetite, stomach pain, dehydration, muscle aches, and depression. The side effects can be worse or different than if the patient takes either drug by itself. Patients will be closely monitored during therapy.

Potential risk associated with the combination of AZD4635, durvalumab and cabazitaxel
It is possible that the combination of study drugs used in this study may lead to increased severity and incidence of side effects related to febrile neutropenia - a condition marked by fever and a lower-than-normal number of neutrophils in the blood. A neutrophil is a type of white blood cell that helps fight infection and having too few neutrophils can increase the risk of infection.

Durvalumab
Most of the possible side effects listed below are mild to moderate. However, some side effects can be very serious and life-threatening and may even result in death. Some side effects do not need treatment, while others generally get better with treatment. The patient may need to delay doses of durvalumab to allow the side effects to get better. Management of these side effects may also require the administration of drugs such as steroids or other agents that can affect the patient's immune system and reduce inflammation.

Durvalumab side effect(s)
Very common (seen in more than 1 in 10 people)
Diarrhea
Rash/Dry itchy skin
Abdominal pain
Upper respiratory tract infections
Cough
Fever
Underacitve thyroid gland that causes tiredness or weight gain (hypothyroidsm)

Durvalumab side effect(s)
Common (seen in more than 1 in 100 people)
Inflammation in the lungs (pneumonitis)
Overactive thyroid gland that can cause fast heart rate or weight loss

Changes in lab tests related to kidney and liver function
Infusion-related reactions
Pain in muscles and joints (myalgia)
Pneumonia
Influenza
Hoarse voice
Painful urination
Night sweats
Fungal infection in the mouth (oral candidiasis)
Dental and soft tissue infections
Accumulation of fluid causing swelling in the legs

Cabazitaxel
Cabazitaxel is an anti-cancer medication given with the medication prednisone. It is approved and licensed to treat men with prostate cancer that has worsened (progressed) after treatment with other anti-cancer medicines, including docetaxel. The side effects associated with cabazitaxel are recorded in the prescribing information.

Contacts

Public
Astra Zeneca

Cambridge CB21 -
Cambridge 6GH
GB
Scientific
Astra Zeneca

Cambridge CB21 -
Cambridge 6GH
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion Criteria

Age
1 Participant must be 18 years of age inclusive at the time of signing the informed consent.
Type of Participant and Disease Characteristics
2 Histologically confirmed adenocarcinoma of the prostate
* Disease must be metastatic and inoperable and for which there is no curative intervention available. Participants may have bone-only disease.
* Participants presenting with treatment-emergent neuroendocrine differentiation, but not primary small-cell features, are eligible.
3 Known castrate-resistant disease, defined as:
* Testosterone level in the castration range (levels < 50 ng/dl) because of a previous, and ongoing, androgen-deprivation with luteinizing hormone-releasing hormone (LHRH) agonists or antagonists or bilateral orchiectomy. Participants must have developed progression of metastases following surgical castration or during medical androgen ablation therapy. Participants receiving medical castration therapy with gonadotropin-releasing hormone (GnRH) analogues should continue this treatment during this study.
4 Evidence of disease progression * 6 months defined by one or more of the following:
* Progression as defined by RECIST v1.1 criteria for assessment of malignant soft tissue disease and lymph nodes
* Progression of bone lesions on bone scan from a previous or baseline assessment per PCWG3
* Rising PSA defined as at least two consecutive rises in PSA to be documented over a reference value (measure 1) taken at least 1 week apart. The first rising PSA (measure 2) should be taken at least 7 days after the reference value. A third confirmatory PSA measure is required (2nd and beyond the reference level) to be greater than the second measure and it must be obtained at least 7 days after the 2nd measure. If this is not the case, a fourth PSA measure is required to be taken and be greater than 2nd measure. The third (or the fourth) confirmatory PSA should be taken within 4 weeks prior to study entry.
5 Must have measurable disease:
* At least 1 documented lesion on either a bone scan or a computed tomography (CT)/magnetic resonance imaging (MRI) scan that can be followed for response is

suitable for repeated measurement
Or
* Non-measurable disease must have measurable PSA * 1.0 ng/mL as the minimum starting level for trial entry if the confirmed rise is the only indication of progression (excluding small cell carcinoma).

Weight
6 Body weight > 30 kg at screening.

Reproduction
7 Willingness to adhere to the study treatment-specific contraception requirements: Participants must be surgically sterile or using an acceptable method of contraception (defined as a male condom in conjunction with spermicides) for the duration of the study (from the time they sign ICF) and for 12 weeks (3 months) after the last dose of AZD4635 and/or durvalumab and for 24 weeks (6 months) after the last dose of cabazitaxel to prevent pregnancy in a female partner. Participants must not donate or bank sperm for 24 weeks after treatment. The reporting of any pregnancy in the female partner of a participant is described in Section 8.3.9.1 of the protocol.

Bone Marrow Reserve and Organ Function
8 Adequate bone marrow reserve and organ function as demonstrated by all of the following laboratory values:
* Absolute neutrophil count (ANC) * 1.5 × 109/L
* Platelet count * 100 × 109/L
* Haemoglobin * 9.0 g/dL (* 10.0 g/dL for Arm B)
* Creatinine * 1.5 × ULN concurrent with creatinine clearance > 50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is > 1.5 × ULN.

Additional Inclusion Criteria Specific for Arm A
9 Adequate organ function for Arm A as demonstrated by all of the following laboratory values:
* Alanine aminotransferase (ALT) * 2.5 × the upper limit of normal (ULN) if no demonstrable liver metastases or * 5 × ULN in the presence of liver metastases.
* Aspartate aminotransferase (AST) * 2.5 × ULN if no demonstrable liver metastases or * 5 × ULN in the presence of liver metastases
* Total bilirubin (TBL) * 1.5 × ULN
* TBL * 2.0 × ULN in the case of known Gilbert syndrome with normal direct bilirubin
10 Participants in Arm A must have received the following prior therapy:
* Maximum of 3 lines of therapy in the mCRPC setting
* Prior therapy with one or more NHAs (e.g., abiraterone acetate, enzalutamide, apalutamide, darolutamide) in either hormone-sensitive or hormone-refractory settings
* Prior therapy with one or more lines of taxanes (e.g., docetaxel and/or cabazitaxel)

* Alternatively, must be taxane-ineligible
* Prior therapy can be in either the hormone-sensitive or the hormone-refractory setting
* Patients who were eligible for both Arm A and Arm B will be preferentially allocated to Arm B, until enrollment of Arm B is completed.

Additional Inclusion Criteria Specific for Arm B
11 Adequate organ function for Arm B as demonstrated by all of the following laboratory values:
* AST and/or ALT * 1.5 × ULN
* TBL * ULN
* TBL * 2.0 × ULN in the case of known Gilbert syndrome with normal direct bilirubin
12 Participants in Arm B must have received the following prior therapy:
* Prior docetaxel (taxane) in either hormone-sensitive or hormone-refractory settings
* Received no prior cytotoxic chemotherapy other than docetaxel for prostate cancer except for estramustine and except adjuvant/neo-adjuvant treatment completed > 3 years ago.
* Prior therapy with only one NHAs (e.g., abiraterone acetate or enzalutamide; prior apalutamide is not permitted) for treatment of mCRPC in either hormone-sensitive or hormone-refractory settings.
* Be suitable to receive concomitant GCSF during all cycles of cabazitaxel.
* Participants who meet inclusion criteria for Arm B will be allocated preferentially to that arm until recruitment to that arm is completed.

Other Inclusion Criteria
13 World Health Organisation (WHO) performance status of 0-1 with no clinical deterioration over the previous 2 weeks prior to the 28-day screening period and likely able to complete at least 12 weeks of treatment.
14 Normotensive or well controlled blood pressure (BP) (systolic < 150 and diastolic < 90), with or without current antihypertensive treatment. If there is a diagnosis or history of hypertension, participant must have adequately controlled BP on antihypertensive medications.
15 Availability of an archival tumour sample. If an archival tumour sample is not available, then a tumour biopsy will be required to obtain a tumour sample.
16 Participants must be able to swallow and retain oral medications (e.g., AZD4635 and/or prednisone).

Informed Consent
1 Capable of giving signed informed consent as described in Appendix A and able to comply with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol
2 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative

Exclusion criteria

Exclusion Criteria
Participants are excluded from the study if any of the following criteria apply:

Medical Conditions
1 Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if treated and there is no evidence of progression for at least 8 weeks after treatment is completed and within 28 days prior to the first dose of study intervention.
2 There must be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone/equivalent) for at least 2 weeks prior to study enrollment. For current or prior use of immunosuppressive medication within 14 days before the first dose the following will be exceptions to this:
* Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection)
* Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
* Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
3 Participant with a history of pneumonitis.
4 History of a second malignancy that is progressing and/or received active treatment * 3 years before the first dose of study intervention.
5 As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, active infection including hepatitis B, hepatitis C, and human immunodeficiency virus, chronic gastrointestinal diseases (e.g., Crohn's disease, chronic colitis), ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, or active interstitial lung disease (ILD). Screening for chronic conditions is not required.
6 Creatinine clearance < 50 mL/min (calculated by Cockcroft-Gault equation).
7 Prior exposure to immune-mediated therapy including, but not limited to anti-CTLA-4, anti-PD-1, anti-PD-L1 and anti-PD-L2 antibodies, excluding therapeutic anti-cancer vaccines.
8 History of allogeneic organ transplantation.
9 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
* Participants with vitiligo or alopecia
* Participants with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
* Any chronic skin condition that does not require systemic therapy

* Participants without active disease in the last 5 years may be included but only after consultation with the Study Physician
* Participants with coeliac disease controlled by diet alone
10 History of active primary immunodeficiency.
11 Active infection including tuberculosis (clinical evaluation that may include clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice).
12 Receipt of live attenuated vaccine within 30 days prior to the first dose of study intervention.

Additional Exclusion Criteria Specific for Arm B: Medical Conditions
13 Participant with active grade * 2 peripheral neuropathy
14 Participant with active grade * 2 stomatitis

Prior/Concomitant Therapy
15 Any small-molecule, biologic, or hormonal agent from a previous treatment regimen or clinical study within 21 days or 5 half-lives (whichever is shorter) prior to the first dose of study intervention. At least 7 days must have elapsed between the last dose of such agent and the first dose of study intervention. Exception: androgen-deprivation therapy is permitted.
16 History of hypersensitivity to any of the study drugs or any of the study drug excipients including hypersensitivity to polysorbate-80 if allocated to cabazitaxel.
17 Nitrosourea or mitomycin C within 6 weeks of the first dose of study intervention.
18 Prescription or non-prescription drugs or other products known to be sensitive BCRP, OATP1B1/3, OAT1, OCT1, OCT2, MATE1 and P-gp substrates or to be strong inhibitors/inducers of CYP1A2 (see Appendix I), which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study, until 2 weeks after the last dose of study intervention.

19 Exclusion Criteria for Arm B: Concurrent or planned treatment with strong inhibitors or strong inducers of cytochrome P450 3A4/5 (CYP3A4/5) are excluded (a 2-week washout period is required for participants already on these treatments) (see Appendix I).
20 Herbal preparations/medications are not allowed throughout the study. These herbal medications include but are not limited to St. John*s wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Participants should stop using these herbal medications 7 days prior to the first dose of study intervention. Exceptions may be agreed, but the circumstances must be reviewed by the Medical Monitor/AstraZeneca Study Physician in advance.
21 Ongoing treatment with warfarin (Coumadin).
22 Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study intervention.
23 Radiotherapy with a wide field of radiation within 4 weeks or radiotherapy with a limited field of radiation for palliation within 2 weeks of the first

dose of study intervention.

Prior/Concurrent Clinical Study Experience
24 AZD4635 in the present study (i.e., dosing with AZD4635 previously initiated in a different arm in this study) or prior therapy with AZD4635 or any other A2AR antagonist or other CD73/CD39 antagonists.
25 History of allogeneic organ, or other transplant, such as bone marrow transplant.
26 With the exception of alopecia, any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 Grade 1 at the time of starting study treatment. Participant with chronic Grade 2 unresolved toxicities may be eligible following discussion with the Medical Monitor/AstraZeneca Study Physician.
27 Concurrent enrollment into another therapeutic clinical trial.
28 Concomitant treatment with another adenosine 1 receptor (A1R) antagonist that would increase risk of seizure (e.g., theophylline, aminophylline).

Diagnostic Assessments
29 Any of the following cardiac criteria:
* Mean resting corrected QT interval (QTcF) > 470 msec obtained from 3 ECGs
* Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECGs, e.g., complete left bundle branch block, third-degree heart block
* Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, or family history of long QT syndrome or unexplained sudden death under 40 years-of-age
* Ejection fraction < 55% or the lower limit of normal of the institutional standard, ascertained by an echocardiogram or multiple-gated acquisition (MUGA) that has been obtained in the 6 months prior to screening. If there has been a change in the participant*s cardiac status, or if there has not be an echocardiogram or MUGA within the 6 months prior to study enrollment, this should be performed as part of the screening assessments.

Other Exclusions
30 Judgment by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	AZD4635
Generic name:	AZD4635
Product type:	Medicine
Brand name:	Cabazitaxel
Generic name:	Cabazitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Durvalumab
Generic name:	Imfenzi
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-10-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-01-2021

Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-02-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-03-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-03-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-06-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-06-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-07-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-07-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-09-2021

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-09-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-000209-10-NL
ClinicalTrials.gov	NCT04495179
CCMO	NL75405.028.20