Enzalutamide (MDV3100) in combination with AZD5363 in patients with metastatic castration-resistant prostate cancer

Submission date	Recruitment status	[X] Prospectively registered
08/05/2014	No longer recruiting	☐ Protocol
Registration date	Overall study status	Statistical analysis plan
08/05/2014	Completed	[X] Results
Last Edited	Condition category	Individual participant data
20/06/2022	Cancer	

Plain English summary of protocol

http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-azd5363-and-enzalutamide-for-advanced-prostate-cancer

Contact information

Type(s)

Scientific

Contact name

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Additional identifiers

Clinical Trials Information System (CTIS)

2013-004091-34

ClinicalTrials.gov (NCT)

Protocol serial number

16580

Study information

Scientific Title

A randomised Phase II study of enzalutamide (MDV3100) in combination with AZD5363 in patients with metastatic castration-resistant prostate cancer

Acronym

RE-AKT

Study objectives

The primary aim is to determine the anti-tumour activity of enzalutamide (potent AR targeting drug) in combination with AZD5363 (AKT inhibitor) compared to enzaluatmide alone in patients with castration-resistant prostate cancer.

Ethics approval required

Old ethics approval format

Ethics approval(s)

NRES Committee London-Surrey Borders, 19/03/2014, ref. 14/LO/0259

Study design

Randomised; Interventional; Design type: Treatment

Primary study design

Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied

Topic: Cancer; Subtopic: Prostate Cancer; Disease: Prostate

Interventions

AZD5363: Phase I safety run-in: Enzalutamide and AZD5363 will be given in a combination of once daily enzalutamide (MDV3100) with twice daily AZD5363 administered four days on and three days off

Randomised Phase II: AZD5363 + enzalutamide versus placebo + enzalutamide Single-stage phase II expansion: AZD5363 + enzalutamide in patients who have previously progressed on enzalutamide alone; Enzalutamide, Phase I safety run-in: Enzalutamide and AZD5363 will be given in a combination of once daily enzalutamide (MDV3100) with twice daily AZD5363 administered four days on and three days off

Randomised Phase II: AZD5363 + enzalutamide versus placebo + enzalutamide Single stage phase II expansion: AZD5363 + enzalutamide in patients who have previously progressed on enzalutamide alone

Intervention Type

Drug

Phase

Phase II

Drug/device/biological/vaccine name(s)

Enzalutamide (MDV3100), AZD5363

Primary outcome(s)

Phase I - safety run in

1. Type, frequency, severity, seriousness and relatedness of adverse events - assessed at C0D1, C1D1, C1D4, C1D11, C2D1, C2D11, C3D1, C4D1 and D1 each subsequent cycle (28-day cycle), treatment discontinuation and safety follow-up visit (30 days after last dose)

2. Laboratory abnormalities. - Screening (C0D1-28 days), C0D1, C1D1, C1D11, C2D1, C2D11, C3D1, C4D1 and D1 each subsequent cycle (28-day cycle), treatment discontinuation and safety follow-up visit (30 days after last dose)

Randomised Phase II

1. Best overall tumour response by RECIST (v1.1) and PCWG2 criteria - RECIST: Screening (C0D1-28 days), C1D4 or C1D11), treatment discontinuation. PCWGC2: Screening, C1D1, C2D1, 12 weekly, safety follow-up visit

Single-stage phase II - expansion cohort

2. Best overall tumour response by RECIST (v1.1) and PCWG2 criteria. - RECIST: Screening (C0D1-28 days), C1D4 or C1D11), treatment discontinuation. PCWGC2: Screening, C1D1, C2D1, 12 weekly, safety follow-up visit

Key secondary outcome(s))

Phase I - safety run-in

- 1. PK assay analyses C0D1, C0D2, C0D3, C2D1, C2D2, C2D3, C2D4, C2D11
- 2. Antitumour activity of the combination every 12 weeks

Randomised Phase II and single-stage phase II - expansion cohort

- 1. Overall survival and radiographic progression-free survival OS: patients will be followed up 3 monthly for 12 months and then 6 monthly from 12 months. Radiographic PFS: RECIST and bone scan every 12 weeks
- 2. Maximum PSA decline and circulating tumour cell (CTC) fall Screening, C1D1, C4D1 and D1 each subsequent cycle (28-day cycle), safety follow-up visit
- 3. Pain palliation (using BPI-SF) (randomised phase II only) Screening, C1D1, C2D1, C3D1, C4D1 and D1 each subsequent cycle (28-day cycle), safety follow-up visit
- 4. Safety adverse events measured every visit
- 5. PK assay analyses C1D1, C2D1, C2D4, C2D11

Completion date

30/09/2019

Eligibility

Key inclusion criteria

- 1. Written informed consent
- 2. Histological diagnosis of adenocarcinoma of the prostate and with archival tumour tissue

- 3. Metastatic castration-resistant prostate cancer (mCRPC)
- 4. Progressed after one or two lines of taxane-based chemotherapy
- 5. Progressed after at least 12 weeks of abiraterone
- 6. Age 18 years or above.
- 7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 02
- 8. PSA greater than or equal to 10 ng/ml
- 9. Documented willingness to use an effective means of contraception while participating in the study and for 12 months post last dose of treatment
- 10. Documented ongoing castrate serum testosterone <50 ng/dL (<2.0 nM)
- 11. Received prior castration by orchiectomy and/or ongoing luteinizing hormone releasing hormone (LHRH) agonist treatment
- 12. Progression of disease by PSA utilizing PCWG2 criteria and at least another of the following criteria:
- 12.1. Dsease progression as defined by at least two new lesions on bone scan
- 12.2.Soft tissue disease progression defined by modified RECIST 1.1
- 12.3.Clinical progression (worsening pain and the need for palliative radiotherapy)

PHASE I SAFETY RUN IN and EXPANSION COHORT inclusion criteria:

13. Willing to have a biopsy to obtain tumour tissue for biomarker analyses prior to and after treatment

SINGLE STAGE PHASE II EXPANSION COHORT ONLY inclusion criteria:

- 14. Prior exposure to enzalutamide of at least 12 weeks is required with documented disease progression
- 15. Archival tumour tissue available for the analysis of PTEN loss by the central laboratory

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 years

Sex

Male

Key exclusion criteria

- 1. Prior treatment with enzalutamide (not applicable for the phase I safety run in or for the single stage phase II expansion cohort)
- 2. Prior treatment with PI3K, AKT, TOR kinase or mTOR inhibitors
- 3. Surgery, chemotherapy, or other anticancer therapy within 4 weeks prior to trial entry /randomisation into the study (6 weeks for bicalutamide). Any other therapies for prostate cancer, other than GnRH analogue therapy, such as progesterone, medroxyprogesterone, progestins (megesterol), or 5-alpha reductase inhibitors (e.g., finasteride or dutasteride), must be discontinued at least 2 weeks before the first dose of study drug
- 4. Participation in another clinical trial and any concurrent treatment with any investigational

drug within 4 weeks prior to trial entry/randomisation.

- 5. Prior limited field radiotherapy within 2 weeks or wide field radiotherapy within 4 weeks of trial entry/randomisation
- 6. History of seizure or any condition that may predispose to seizure including, but not limited to underlying brain injury, stroke, primary brain tumours, brain metastases, or alcoholism
- 7. History of loss of consciousness or transient ischemic attack within the previous 12 months of trial entry/randomisation
- 8. Known brain or leptomeningeal involvement
- 9. Use of potent inhibitors or inducers of CYP3A4, CYP2C9 and CYP2C19 within 2 weeks before trial entry/randomisation (3 weeks for St John's Wort) must be avoided
- 10. Clinically significant abnormalities of glucose metabolism as defined by any of the following:
- 10.1. Diagnosis of diabetes mellitus type I or II
- 10.2. Glycosylated haemoglobin (HbA1C) =8.0% at screening
- 10.3. Fasting plasma glucose =8.9mmol/L at screening
- 11. Inadequate organ and bone marrow function as evidenced by:
- 11.1. Haemoglobin <8.5 g/dL
- 11.2. Absolute neutrophil count <1.0 x 10^9/L
- 11.3. Platelet count $< 75 \times 10^9/L$
- 11.4. Albumin =25 g/dL.
- 11.5. AST/SGOT and/or ALT/SGPT = $2.5 \times ULN = 5 \times ULN =$
- 11.6. Total bilirubin = $1.5 \times ULN$ (except for patient with Gilbert's disease)
- 11.7. Serum creatinine > 1.5 x ULN
- 12. Inability or unwillingness to swallow oral medication
- 13. Malabsorption syndrome or other condition that would interfere with enteral absorption
- 14. Any of the following cardiac criteria:
- 14.1. Mean resting corrected QT interval (QTcF) >470 msec obtained triplicate ECGs
- 14.2. Clinically important abnormalities (rhythm/conduction/morphology) resting ECG
- 14.3. Factors that increase risk of QTc prolongation or risk of arrhythmic events
- 14.4. Experience of any of the following in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure NYHA = Grade 2
- 14.5. Uncontrolled hypotension
- 15. Clinically significant history of liver disease consistent with ChildPugh Class B or C, including viral or other hepatitis, current alcohol abuse, or cirrhosis
- 16. Any other finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patients at high risk from treatment complications
- 17. Need for chronic corticosteroid therapy of >10 mg of prednisolone or >0.5 mg of dexamethasone per day or an equivalent dose of other anti-inflammatory corticosteroid
- 18. Malignancies other than prostate cancer within 5 years prior to trial entry/randomisation, except for adequately treated basal or squamous cell skin cancer
- 19. Unresolved clinically significant toxicity from prior therapy except for alopecia and Grade 1 peripheral neuropathy
- 20. Inability to comply with study and follow-up procedures

Date of first enrolment

17/12/2014

Date of final enrolment

30/09/2019

Locations

Countries of recruitment

United Kingdom

England

Study participating centre Institute of Cancer Research Sutton United Kingdom SM2 5NG

Sponsor information

Organisation

Royal Marsden NHS Foundation Trust

ROR

https://ror.org/0008wzh48

Organisation

The Institute of Cancer Research (UK)

Funder(s)

Funder type

Industry

Funder Name

Astellas Pharma Europe

Alternative Name(s)

Astellas Pharma Europe Ltd

Funding Body Type

Private sector organisation

Funding Body Subtype

International organizations

Location

United Kingdom

Funder Name

AstraZeneca

Alternative Name(s)

AstraZeneca PLC, Pearl Therapeutics, AZ

Funding Body Type

Government organisation

Funding Body Subtype

For-profit companies (industry)

Location

United Kingdom

Funder Name

Cancer Research UK (UK)

Alternative Name(s)

CR UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type

Private sector organisation

Funding Body Subtype

Other non-profit organizations

Location

United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

Not provided at time of registration

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/05/2020	20/06/2022	Yes	No
HRA research summary			28/06/2023	No	No