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

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

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Additional identifiers

EudraCT/CTIS number
2013-004091-34

IRAS number

ClinicalTrials.gov number
NCT02525068

Secondary identifying numbers
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

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

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 measure
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

Secondary outcome measures
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

Overall study start date
01/12/2014

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

Age group
Adult

Lower age limit
18 Years

Sex

Male

Target number of participants
Planned Sample Size: 136; UK Sample Size: 136

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 x 10^9/L
11.4. Albumin =25 g/dL.
11.5. AST/SGOT and/or ALT/SGPT = 2.5 x ULN (=5 x ULN if liver metastases)
11.6. Total bilirubin = 1.5 x 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
England

United Kingdom

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

Sponsor information

Organisation
Royal Marsden NHS Foundation Trust

Sponsor details
Downs Road
Sutton
England
United Kingdom
SM2 5PT

Sponsor type
Hospital/treatment centre

Website
http://www.royalmarsden.nhs.uk/pages/home.aspx

ROR
https://ror.org/0008wzh48

Organisation
The Institute of Cancer Research (UK)

Sponsor details
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Sponsor type
Research organisation

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

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, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not provided at time of registration

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