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An open label phase I/randomised, double-blind phase II study in metastatic castration resistant Prostate Cancer of AZD5363 in combination with Docetaxel and prednisolone chemotherapy (ProCAID)

Submission date 25/02/2014	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 25/02/2014	**Overall study status** Completed	
Last Edited 09/07/2021	**Condition category** Cancer	

Plain English summary of protocol
http://www.cancerresearchuk.org/cancer-help/trials/a-trial-of-azd5363-with-docetaxel-and-prednisolone-for-prostate-cancer-that-has-spread-and-is-no-longer-responding-to-hormone-therapy-procaid

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2013-002391-41

IRAS number

ClinicalTrials.gov number
NCT02121639

Secondary identifying numbers
15888

Study information

Scientific Title
An open label phase I/randomised, double-blind phase II study in metastatic castration resistant Prostate Cancer of AZD5363 in combination with Docetaxel and prednisolone chemotherapy (ProCAID)

Acronym
ProCAID

Study objectives
Docetaxel and prednisolone chemotherapy (DP) is the only treatment proven to extend survival as first-line chemotherapy in metastatic castration-resistant prostate cancer (mCRPC). Clinical benefit from DP is modest however and DP resistance is a common problem raising a pressing clinical need to build on the benefits of DP.
One approach to this is to develop a rational combination of docetaxel with a drug with likely clinical synergy and complimentary toxicity profile that might circumvent DP resistance. AKT (Protein Kinase B) activation is common in prostate cancer reaching up to 100% in metastatic disease. This contributes to disease progression and DP resistance. AZD5363 is an orally available potent AKT inhibitor. The ProCAID trial will test the hypothesis that AZD5363 prolongs progression-free survival when combined with DP for mCRPC.

Ethics approval required
Old ethics approval format

Ethics approval(s)
13/LO/1691; First MREC approval date 13/11/2013

Study design
Interventional open label phase I/randomised, double-blind phase II; 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: National Cancer Research Network; Subtopic: Prostate Cancer; Disease: Prostate

Interventions
IMP, AZD5363

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
AZD5363

Primary outcome measure
Determination of a suitable dose of AZD5363; Timepoint(s): Phase I

Secondary outcome measures
1. AZD5363 pharmacokinetics in combination with DP; Timepoint(s): Phase I
2. Biochemical (PSA) response rates according to PCWG2 criteria; Timepoint(s): Phase II
3. Bone pain changes using the BPI Questionnaire; Timepoint(s): Phase II
4. Overall survival; Timepoint(s): Phase II
5. PFS excluding biochemical (PSA) alone progression; Timepoint(s): Phase II
6. Progression Free Survival from start of study treatment; Timepoint(s): Phase II - Primary outcome
7. Safety and tolerability profiles; Timepoint(s): Phase I and II

Overall study start date
29/01/2013

Completion date
30/04/2021

Eligibility

Key inclusion criteria
Current inclusion criteria as of 31/07/2019:
1. Histologically or cytologically proven mCRPC with documented metastases (measurable or evaluable disease is acceptable) now eligible for treatment with docetaxel chemotherapy
2. Disease progression since the last change in therapy defined by one or more of the following according to the Prostate Cancer Working Group (PCWG2) criteria (J Clin Oncol 2008¿26: 11481159):
2.1. PSA progression as defined by the prostate cancer working group 2 (PCWG2) criteria (Scher et al. 2008 J Clin Oncol. 26; 1148). This must be based on a series of at least 3 readings at least 7

days apart demonstrating rising PSA. The 3rd reading must be ≥ 2ng/ml If biochemical progression alone is to be used as the basis for determining disease progression (without radiographic or bone scan progression also). In the event where an intermediate reading is lower than a previous reading, then the patient will still be eligible (i.e. the 3 readings do not need to be consecutive). The first of the three readings must have been obtained after commencing the previous systemic therapy.
2.2. Radiographic progression of nodal or visceral metastases as defined by RECIST version 1.1 (See Appendix 6)
2.3. The appearance of two or more new bony metastases
3. Serum testosterone <1.7 nmol/L (ongoing LHRH analogue or antagonist therapy is permitted to maintain a castrate state)
4. Discontinuation of prior therapies for prostate cancer ≥ 2 weeks prior to commencing study treatment (with the exception of an LHRH agonist or antagonist where required for ongoing testosterone suppression)
5. No current anti-androgen withdrawal response from bicalutamide or flutamide. Consistent with PCWG2 guidelines, investigators should evaluate patients to exclude withdrawal response for 6 weeks after stopping bicalutamide or flutamide. Investigators need not wait to assess for withdrawal response in patients who did not respond, or who showed a PSA decline for ≤ 3 months, after bicalutamide or flutamide was administered as a second-line or later intervention
6. ECOG performance status 0 or 1
7. Hb ≥ 9g/dL¿ platelets ≥ 100 x 109/L¿ neutrophils ≥ 1.5 x109/L
8. Bilirubin ≤ ULN ¿ ALT and AST ≤ 1.5 x ULN
9. Sodium and potassium within the normal range for the site
10. Able to swallow study drugs (without crushing/opening in the case of AZD5363)
11. Life expectancy > 3 months
12. Aged 18 years or over
13. Provision of written informed consent

Previous inclusion criteria:
1. Histologically or cytologically proven mCRPC with documented metastases (measurable or evaluable disease is acceptable) now eligible for treatment with docetaxel chemotherapy
2. Disease progression since the last change in therapy defined by one or more of the following according to the Prostate Cancer Working Group (PCWG2) criteria (J Clin Oncol 2008¿26: 11481159):
2.1. PSA progression as defined by the prostate cancer working group (2) (PCWG2) criteria (Scher et al. 2008 J Clin Oncol. 26¿ 1148). This must be based on a series of at least 3 readings at least 7 days apart. The 3rd reading must be >= 2ng/ml. In the event where an intermediate reading is lower than a previous reading, then the patient will still be eligible (ie. the 3 readings do not need to be consecutive). The first of the three readings must have been obtained after commencing the previous systemic therapy, or, in the case of androgen receptor antagonists, after discontinuing.
2.2. Radiographic progression of nodal or visceral metastases as defined by RECIST version 1.1 (Eur J Cancer 2009¿45:228). See Appendix 5
2.3. The appearance of two or more new bony metastases
3. Serum testosterone <1.7 nmol/L (ongoing LHRH analogue or antagonist therapy is permitted to maintain a castrate state)
4. Discontinuation of prior therapies for prostate cancer ≥ 4 weeks prior to commencing study treatment (with the exception of an LHRH agonist or antagonist where required for ongoing testosterone suppression)
5. No antiandrogen withdrawal response. Withdrawal responses typically occur following combined androgen blockade (LHRH analogue/antagonist or orchidectomy combined with an antiandrogen) as initial therapy for a prolonged period, or in patients who respond to an

antiandrogen as second-line therapy. Consistent with PCWG2 guidelines, investigators should evaluate such patients for withdrawal response for 6 weeks and then confirm disease progression. Investigators need not wait to assess withdrawal response in patients who did not respond, or who showed a PSA decline for ≤ 3 months, after an antiandrogen was administered as a second-line or later intervention
6. ECOG performance status 0 or 1
7. Hb ≥ 9g/dL¿ platelets ≥ 100 x 109/L¿ neutrophils ≥ 1.5 x109/L
8. Bilirubin ≤ ULN ¿ ALT and AST ≤ 1.5 x ULN
9. Sodium and potassium within the normal range for the site
10. Able to swallow study drugs (without crushing/opening in the case of AZD5363)
11. Life expectancy > 3 months
12. Aged 18 years or over
13. Provision of written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Male

Target number of participants
Planned Sample Size: 150; UK Sample Size: 150; Description: England: Phase 1 up to 12, Phase II - 105N. Ireland: Phase II - 9Scotland: Phase 1 up to 6, Phase II - 9Wales: Phase II - 9

Total final enrolment
150

Key exclusion criteria
Current exclusion criteria as of 31/07/2019:
1. Previous treatment with cytotoxic chemotherapy for castrate resistant prostate cancer. Patients may have received previous docetaxel for up to 6 cycles given in the 'hormone sensitive setting' or ongoing bisphosphonates or denosumab. There are no restrictions on prior use of second generation hormonal therapies e.g. abiraterone, enzalutamide as long as they have been discontinued > 2 weeks prior to commencing study treatment.
2. Other prior malignancy with an estimated ≥ 30% chance of relapse within 2 years
3. Previously identified brain metastases, or spinal cord compression unless treated with full functional recovery
4. Prior radiotherapy to > 30% of bone marrow
5. Administration of an investigational agent within 30 days of first dose of study medication
6. Patients will be excluded with any of:
6.1. Diabetes mellitus type I
6.2. Fasting plasma glucose [fasting is defined as no calorific intake for at least 8 hours] of either ≥ 7.0mmol/L (126 mg/dL) for those patients without a pre-existing diagnosis of Type 2 diabetes mellitus or ≥ 9.3 mmol/L (167mg/dL) for those patients with a pre-existing diagnosis of Type 2 diabetes mellitus

6.3. Glycosylated haemoglobin (HbA1C) ≥8.0% (63.9 mmol/mol)
6.4. Requirement for insulin for routine diabetic management and control
6.5. Requirement for more than two oral hypoglycaemic medications for routine diabetic management and control
7. Malabsorption syndrome, previous gastrointestinal surgery, or other gastrointestinal condition that may affect drug absorption
8. Coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris or congestive heart
failure (NYHA ≥ grade 2) within the last 6 months
9. Abnormal echocardiogram (LVEF 10.Uncontrolled hypotension (systolic blood pressure <90 mmHg and/or diastolic blood pressure <50 mmHg)
10. Uncontrolled hypotension (systolic blood pressure
11. QTc interval of >480 msec at two or more time points within a 24 hour period
12. Proteinuria (either 3+ on dipstick analysis or >500 mg/24 hours) or creatinine >1.5 x ULN concurrent with creatinine clearance
13. Proteinuria (either 3+ on dipstick analysis or >500 mg/24 hours) or creatinine >1.5 x ULN concurrent with creatinine clearance <50 mL/min (assessed as per local practice e.g. by Cockcroft and Gault estimation)
14. Exposure to potent inhibitors or inducers of CYP3A4 or substrates of CYP3A4 and CYP2D6 within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort)
15. Unresolved toxicity ≥ grade 2 (except alopecia) from previous cancer therapy
16. Patients with a partner of child-bearing potential who are not using a highly effective method of contraception, who are unwilling to use condoms during the study and for 30 days after the last dose of study drug
17. Known hypersensitivity to AZD5363, its excipients, or drugs in its class
18. Previous exposure to agents with the following mechanisms of action:
18.1. Inhibition of AKT (e.g., MK2206, GDC0068, GSK2110183, GSK2141795) any inhibitor with PI3K pharmacology (e.g., GDC0941, XL147, BKM120, PX866, BYL719, AMG319, GDC0032, INK1117, INK119)
18.2. Any compound with mixed PI3K and mammalian target of rapamycin (mTOR) kinase pharmacology (e.g., BEZ235, GDC0980, PF04691502, PF05212384, GSK2126458, XL765)
18.3. Or any mTOR kinase inhibitor (e.g., AZD8055, AZD2014, OSI027, INK128)

Previous exclusion criteria:
1. Previous treatment with cytotoxic chemotherapy (patients may have received previous or ongoing bisphosphonates or denosumab). There are no restrictions on prior use of second-generation hormonal therapies e.g. abiraterone, enzalutamide
2. Prior malignancy with an estimated ≥ 30% chance of relapse within 2 years following curative treatment
3. Previously identified brain metastases, or spinal cord compression unless treated with full functional recovery
4. Prior radiotherapy to > 30% of bone marrow
5. Administration of an investigational agent within 30 days of first dose of study medication
6. Type I or II diabetes mellitus requiring either insulin or oral hypoglycaemics for routine management. Patients with type II diabetes mellitus that is well controlled by dietary measures alone are eligible to participate. Patients found to have a fasting glucose ≥7 mmol/L (≥126 mg /dL) or glycosylated haemoglobin >8% (64 mmol/mol) at screening should be assessed for appropriate management according to local policy. Those in whom dietary measures alone provide good diabetic control will be eligible for inclusion
7. Malabsorption syndrome, previous gastrointestinal surgery, or other gastrointestinal condition that may affect drug absorption
8. Coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina

pectoris or congestive heart
failure (NYHA ≥ grade 2) within the last 6 months
9. Abnormal echocardiogram (LVEF 10.Uncontrolled hypotension (systolic blood pressure <90 mmHg and/or diastolic blood pressure <50 mmHg)
11. QTc interval of >480 msec at two or more time points within a 24 hour period
12. Proteinuria (3+ on dipstick analysis or >500 mg/24 hours) or creatinine >1.5 x ULN concurrent with creatinine clearance <50 mL/min
13. Proteinuria (either 3+ on dipstick analysis or >500 mg/24 hours) or creatinine >1.5 x ULN concurrent with creatinine clearance <50 mL/min (assessed as per local practice e.g. by Cockcroft and Gault estimation)
14. Exposure to potent inhibitors or inducers of CYP3A4 or CYP2D6 or substrates of CYP3A4 within 2 weeks before the first dose of study treatment (3 weeks for St Johns Wort)
15. Unresolved toxicity ≥ grade 2 (except alopecia) from previous cancer therapy
16. Patients with a partner of childbearing potential who are not using a highly effective method of contraception, who are unwilling to use condoms during the study and for 30 days after the last dose of study drug
17. Known hypersensitivity to AZD5363, its excipients, or drugs in its class
18. Previous exposure to agents with the following mechanisms of action:
18.1. inhibition of AKT (e.g., MK2206, GDC0068, GSK2110183, GSK2141795)any inhibitor with PI3K pharmacology (e.g.,
GDC0941, XL147, BKM120, PX866, BYL719, AMG319, GDC0032, INK1117, INK119)
18.2. any compound with mixed PI3K and mammalian target of rapamycin (mTOR) kinase pharmacology (e.g., BEZ235,
GDC0980, PF04691502, PF05212384, GSK2126458, XL765)
18.3. or any mTOR kinase inhibitor (e.g., AZD8055, AZD2014, OSI027, INK128) Note: Do not exclude patients previously treated with a rapalogue (allosteric inhibitor of mTOR¿ mTORC1 complex inhibitor) including temisirolimus (Torisel¿Pfizer), everolimus (Affinitor¿ Novartis), ridoforolimus (Ariad).

Date of first enrolment
29/01/2013

Date of final enrolment
31/01/2019

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Clinical Trials Unit, MP 131, Tremona Road
Southampton
United Kingdom
SO16 6YD

Sponsor information

Organisation
University Hospital Southampton NHS Foundation Trust

Sponsor details
Tremona Road
Southampton
England
United Kingdom
SO16 6YD

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/0485axj58

Funder(s)

Funder type
Charity

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

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

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal - publish date expected December 2020.

Updated 31/07/2019:
Planned publication in a high-impact peer reviewed journal - publish date expected 28/02/2021.

Intention to publish date
30/04/2021

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	Phase I results	01/10/2017	31/07/2019	Yes	No
Results article	results	20/01/2021	21/01/2021	Yes	No
HRA research summary			28/06/2023	No	No