

# 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)

<b>Submission date</b> 25/02/2014	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 25/02/2014	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 09/07/2021	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data

## 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

### Contact name

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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  $\geq 2\text{ng/ml}$  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  $<1.7\text{ nmol/L}$  (ongoing LHRH analogue or antagonist therapy is permitted to maintain a castrate state)

4. Discontinuation of prior therapies for prostate cancer  $\geq 2$  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  $\leq 3$  months, after bicalutamide or flutamide was administered as a second-line or later intervention

6. ECOG performance status 0 or 1

7. Hb  $\geq 9\text{g/dL}$ ; platelets  $\geq 100 \times 10^9/\text{L}$ ; neutrophils  $\geq 1.5 \times 10^9/\text{L}$

8. Bilirubin  $\leq \text{ULN}$ ; ALT and AST  $\leq 1.5 \times \text{ULN}$

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;26:1148-1159):

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  $\geq 2\text{ng/ml}$ . 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  $<1.7\text{ nmol/L}$  (ongoing LHRH analogue or antagonist therapy is permitted to maintain a castrate state)

4. Discontinuation of prior therapies for prostate cancer  $\geq 4$  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  $\leq 3$  months, after an antiandrogen was administered as a second-line or later intervention

6. ECOG performance status 0 or 1

7. Hb  $\geq 9\text{g/dL}$ ; platelets  $\geq 100 \times 10^9/\text{L}$ ; neutrophils  $\geq 1.5 \times 10^9/\text{L}$

8. Bilirubin  $\leq \text{ULN}$ ; ALT and AST  $\leq 1.5 \times \text{ULN}$

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  $\geq 30\%$  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  $\geq 7.0\text{mmol/L}$  (126 mg/dL) for those patients without a pre-existing diagnosis of Type 2 diabetes mellitus or  $\geq 9.3 \text{ mmol/L}$  (167mg/dL) for those patients with a pre-existing diagnosis of Type 2 diabetes mellitus

- 6.3. Glycosylated haemoglobin (HbA1C)  $\geq 8.0\%$  (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  $\geq$  grade 2) within the last 6 months
9. Abnormal echocardiogram (LVEF  $< 50\%$ )
10. Uncontrolled hypotension (systolic blood pressure  $< 90$  mmHg and/or diastolic blood pressure  $< 50$  mmHg)
11. Uncontrolled hypotension (systolic blood pressure  $< 90$  mmHg)
12. QTc interval of  $> 480$  msec at two or more time points within a 24 hour period
13. Proteinuria (either 3+ on dipstick analysis or  $> 500$  mg/24 hours) or creatinine  $> 1.5 \times$  ULN concurrent with creatinine clearance  $< 50$  mL/min (assessed as per local practice e.g. by Cockcroft and Gault estimation)
14. Proteinuria (either 3+ on dipstick analysis or  $> 500$  mg/24 hours) or creatinine  $> 1.5 \times$  ULN concurrent with creatinine clearance  $< 50$  mL/min (assessed as per local practice e.g. by Cockcroft and Gault estimation)
15. 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)
16. Unresolved toxicity  $\geq$  grade 2 (except alopecia) from previous cancer therapy
17. 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
18. Known hypersensitivity to AZD5363, its excipients, or drugs in its class
19. Previous exposure to agents with the following mechanisms of action:
  - 19.1. 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)
  - 19.2. Any compound with mixed PI3K and mammalian target of rapamycin (mTOR) kinase pharmacology (e.g., BEZ235, GDC0980, PF04691502, PF05212384, GSK2126458, XL765)
  - 19.3. 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  $\geq 30\%$  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  $\geq 7$  mmol/L ( $\geq 126$  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  $\geq$  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  $>1.5 \times$  ULN concurrent with creatinine clearance  $<50$  mL/min

13. Proteinuria (either 3+ on dipstick analysis or  $>500$  mg/24 hours) or creatinine  $>1.5 \times$  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  $\geq$  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 temsirolimus (Torisel; Pfizer), everolimus (Affinitor; Novartis), ridofolelimus (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?
<a href="#">Results article</a>	Phase I results	01/10/2017	31/07/2019	Yes	No
<a href="#">Results article</a>	results	20/01/2021	21/01/2021	Yes	No
<a href="#">HRA research summary</a>			28/06/2023	No	No