ISRCTN13103155 https://doi.org/10.1186/ISRCTN13103155

# The study of pexidartinib and enzalutamide as a combined treatment in men with prostate cancer resistant to other treatments

| | | |
|---|---|---|
| **Submission date**<br>27/03/2017 | **Recruitment status**<br>Stopped | [X] Prospectively registered<br>[ ] Protocol<br>[ ] Statistical analysis plan<br>[ ] Results<br>[ ] Individual participant data<br>[ ] Record updated in last year |
| **Registration date**<br>28/03/2017 | **Overall study status**<br>Stopped | |
| **Last Edited**<br>21/06/2019 | **Condition category**<br>Cancer | |

**Plain English summary of protocol**
-

## Contact information

**Type(s)**
Public

**Contact name**
Mrs Denise Dunkley

**ORCID ID**
https://orcid.org/0000-0003-2220-3987

**Contact details**
Southampton Clinical Trials Unit
University of Southampton
MP131
Southampton,
United Kingdom
SO16 6YD

## Additional identifiers

**Clinical Trials Information System (CTIS)**
2016-003291-47

**Protocol serial number**
32858

# Study information

## Scientific Title
A phase Ib/IIa clinical trial to combine the CSF1 receptor inhibitor pexidartinib with the androgen receptor antagonist enzalutamide in metastatic castration resistant prostate cancer

## Acronym
POLERISE

## Study objectives
The dose escalation phase aims to establish the maximum tolerated dose for the study treatment pexidartinib when given to patients in combination with the already liscensed drug enzalutamide. Patients may be enzalutamide naïve or refractory. The aim is to determine a safe biologically effective dose (bed) and a recommended phase ii dose (rp2d).

The dose expansion phase will then use the rp2d of pexidartinib in combination with enzalutamide to determine the anti-tumour activity (composite response rate) in enzalutamide refractory patients and provide further information on the safety and toxicity of the combined treatment for patients with metastatic castration resistant prostate cancer.

## Ethics approval required
Old ethics approval format

## Ethics approval(s)
West Midlands - Coventry & Warwickshire Research Ethics Committee, 25/01/2017, ref: 16/WM /0480

## Study design
Non-randomised; Interventional; Design type: Treatment, Drug

## Primary study design
Interventional

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
Prostate cancer

## Interventions
Dose escalation phase:
All patients will receive enzalutamide (current standard of care treatment) in combination with pexidartinib. There are five potential cohorts to the escalation phase with a rolling 6 trial design which means a minimum of three evaluable patients and a maximum of six per cohort will receive a dose level. Escalation to the next dose will be dependent on the number of dose limiting toxicities (dlts) as assessed by a safety review committee. For cohorts 1 and 2, there will be a 2-week run-in period with single agent pexidartinib, followed by the combination therapy. Cohorst 3-5 begin treatment immediately on the combination therapy. Patients will receive up

to 5 cycles of treatment (28 days each cycle) and may continue beyond if positive response and will be followed up until progression. The primary endpoint will be assessed at 6-weeks of treatment.

Dose expansion phase:
Patients will receive combination therapy using the rp2d established during phase Ib (escalation phase) for up to 5 cycles of treatment (28 days each cycle) and may continue beyond if a positive response is determined. Patients will be followed up until progression. The primary endpoint will be assessed at 12-weeks of treatment. Patients who have prior evidence of PSA and/or radiological progression on enzalutamide, and where there has been a treatment break of greater than 8 weeks prior to restarting enzalutamide on this trial, will receive a 4-week run-in of enzalutamide, single treatment, prior to the combination therapy commencing. This is to exclude a PSA response.

## Intervention Type
Other

## Primary outcome(s)
Dose escalation phase:
1. Maximum tolerated dose (MTD) for pexidartinib is measured using treatment emergent adverse events data (dose limiting toxicity) measured according to CTCAEv4.03 at screening and at each study visit until end of treatment (EoT)
2. Biologically Effective Dose for pexidartinib is measured by plasma CSF-1 rise at 6 weeks (cycle 2 day 15) of combination therapy compared to baseline

Dose expansion phase:
Anti-tumour activity (composite response rate) for pexidartinib at the RP2D is measured by:
1. PSA reduction from baseline by > 50% (PSA measured at Day 1 of each cycle. Additionally, at run-in of days 1, 8, 15 and 22)
1. RECIST objective response (measured by disease progression at Cycle 4 Day 1 and at EoT /progression)
1. Circulating tumour cell (CTC) conversion: change from unfavourable (≥ 5 cells per 7.5 mL of blood) to favourable (≤ 4 cells per 7.5 mL) as measured at cycle 1 day 1, cycle 4 day 1 and at EoT /progression

## Key secondary outcome(s))
Dose escalation phase:
1. Pharmacokinetics of pexidartinib is measured from blood plasma testing at run-in, then on cycle 1 day 1, cycle 2 day 1 (pre-dose, 1,2,4,8 hours). Pre-dose PK on day 1 of all subsequent cycles and at EoT
2. Efficacy is measured from blood sampling to measure PSA reduction from baseline by > 50% (PSA measured at Day 1 of each cycle). Additionally, at run-in day 1 (cohort 1 and 2 only) and RECIST objective response (measured by disease progression at Cycle 4 Day 1 and at EoT /progression)

Dose expansion phase:
Safety and toxicity profile of pexidartinib at the RP2D measure by blood sampling of PSA and CTC:
1. PSA progression free survival and radiological progression-free survival by PCWG3 criteria (measured at run-in for single agent enzalutamide at day 1,8,15 and 22). Then cycle day 1 for all other cycles

2. CTC conversion: change from unfavourable (≥ 5 cells per 7.5 mL of blood) to favourable (≤ 4 cells per 7.5 mL) as measured at cycle 1 day 1, cycle 4 day 1 and at EoT/progression
3. Objective response rate by RECIST version 1.1 at 12 weeks and best response (measured by disease progression at Cycle 4 Day 1 and at EoT/progression)
4. PSA reduction from baseline by > 50% at 12 weeks and best response

### Completion date
31/12/2019

# Eligibility

### Key inclusion criteria
1. Histologically or cytologically proven castrate resistant prostate cancer
2. Metastatic disease. Measurable or evaluable disease is acceptable
3. Serum testosterone <1.7 nmol/L (< 50 ng/dL)
4. No other current therapies for prostate cancer. Allowable exceptions are:
4.1. Use of an LHRH agonist or antagonist where required for ongoing androgen deprivation
4.2. Ongoing enzalutamide for patients entering the Dose Expansion Phase
4.3. Denosumab or bisphosphonates such as zoledronate or pamidronate
5. ECOG performance status 0 to 2
6. Haemoglobin ≥ 8.5 g/dL; platelets ≥ 100 x 109/L; neutrophils ≥ 1.0 x109/L; INR ≤ 1.5
7. Bilirubin ≤ ULN; ALT and AST ≤ 1.5 x ULN
9. For patients entering the Dose Expansion Phase of the trial: PSA of ≥ 2 ng/mL
9. Able to swallow oral trial drugs without crushing
10. Able to safely provide both an archival formalin fixed paraffin embedded (FFPE) prostate cancer tissue sample and a prostate cancer fresh tissue sample from either the prostate or a metastatic site
11. Fertile men must agree to use a highly effective method of birth control while on study drug and up to 3 months after the last dose of study drug (see section 4.7)
12. Life expectancy > 3 months
13. Aged 16 years or over
14. Provision of written informed consent

Dose escalation phase:
Patients may be enzalutamide naive or refractory by either:
1. Commencing enzalutamide for the first time as a treatment for mCRPC as a result of entering this trial
1. Receiving retreatment with enzalutamide as a result of entering this trial providing a minimum of 12 weeks has elapsed since prior enzalutamide dosing. Prior enzalutamide in these circumstances may have been given for either hormone sensitive prostate cancer (for example within the STAMPEDE or ENZAMET clinical trials) or as a conventional treatment for mCRPC. There are no restrictions on other treatments used during this period. Such patients should have tolerated an enzalutamide dose of 160mg once daily.

Dose expansion phase:
Patients will be enzalutamide refractory by either:
1. Currently receiving enzalutamide (for a minimum of 12 weeks) and with evidence of PSA and /or radiological progression according to RECIST 1.1 and PCWG3 criteria as judged by the investigator. These patients should have tolerated an enzalutamide dose of 160mg once daily. These patients may continue enzalutamide through the screening period.
2. Have previously had evidence of PSA and/or radiological progression during a minimum of 12

weeks of enzalutamide treatment according to RECIST 1.1 and PCWG3 criteria as judged by the investigator. There are no restrictions on the time period since this prior use of enzalutamide or other treatments used during this period. These patients must have tolerated an enzalutamide dose of 160mg once daily. Where there has been a break of >8 weeks between prior enzalutamide and restarting it in this trial, patients will initially receive a four week run in period of single agent enzalutamide before commencing combination therapy to exclude a PSA response. Patients who exhibit a PSA decrease during the first four weeks will have the option to continue enzalutamide until the point of subsequent disease progression and could then enter the trial to commence combination therapy after discussion with the sponsor.

## Participant type(s)
Patient

## Healthy volunteers allowed
No

## Age group
Adult

## Sex
Male

## Key exclusion criteria
1. Patients with predominantly small cell or neuroendocrine differentiated prostate cancer
2. Administration of an investigational agent, chemotherapy or major surgery within 28 days of first dose of trial medication
3. Receiving a known CYP3A4 or CYP2C8 inducer or inhibitor (see appendix) within 2 weeks of starting trial treatment
4. Use of systemic corticosteroids within 2 weeks of starting trial treatment (topical and inhaled corticosteroids are acceptable)
5. Malabsorption syndrome, previous gastrointestinal surgery or other gastrointestinal condition that may affect drug absorption
6. Clinically significant cardiac arrhythmias including bradyarrhythmias and/or patients who require anti-arrhythmic therapy (excluding beta blockers or digoxin)
7. Congenital long QT syndrome or patients taking concomitant medications known to prolong the QT interval
8. Patients with a prolonged QTc interval > 480msec
9. History of clinically significant cardiac disease or congestive heart failure > New York Heart Association (NYHA) class 2. Patients must not have unstable angina (anginal symptoms at rest) or new-onset angina within the last 3 months or myocardial infarction within the past 6 months
10. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within the 6 months before start of study medication
11. Patients taking warfarin. (Use of low molecular weight heparin is acceptable as an alternative for anticoagulation.)
12. For patients entering the Dose Expansion Phase of the trial: Prior malignancy with an estimated > = 30% chance of relapse within 2 years in the view of the investigator with the exception of surgically treated basal or squamous cell carcinoma of the skin, melanoma in-situ or non-muscle invasive bladder cancer
13. History of seizures or any condition that may predispose to seizure including, but not limited to, underlying brain injury, stroke, primary brain tumours, brain metastases or alcoholism

14. History of loss of consciousness within the previous 12 months
15. Known brain or leptomeningeal involvement
16. Unresolved clinically significant toxicity from prior therapy (except alopecia and grade 1 peripheral neuropathy)
17. Inability to comply with trial and follow up procedures

### Date of first enrolment
31/12/2018

### Date of final enrolment
30/04/2019

## Locations

### Countries of recruitment
United Kingdom

England

Scotland

### Study participating centre
### The Royal Marsden Hospital
Royal Marsden NHS Foundation Trust
Downs Road
Sutton
United Kingdom
SM2 5PT

### Study participating centre
### Southampton General Hospital
University Hospital Southampton NHS Foundation Trust
Tremona Road
Southampton
United Kingdom
SO16 6YD

### Study participating centre
### Churchill Hospital
Oxford University Hospitals NHS Foundation Trust
Old Road
Headington
Oxford
United Kingdom
OX3 7LE

**Study participating centre**
**The Beatson Institute for Cancer Research**
Garscube Estate
Switchback Road
Bearsden
Glasgow
United Kingdom
G61 1BD

## Sponsor information

**Organisation**
University Hospital Southampton NHS Foundation Trust

**ROR**
https://ror.org/0485axj58

## Funder(s)

**Funder type**
Charity

**Funder Name**
Cancer Research 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

The current data sharing plans for the current study are unknown and will be made available at a later date.

## IPD sharing plan summary

Data sharing statement to be made available at a later date

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| HRA research summary | | | 28/06/2023 | No | No |
| Study website | Study website | 11/11/2025 | 11/11/2025 | No | Yes |