

# Phase II trial of olaparib in patients with advanced castration resistant prostate cancer

<b>Submission date</b> 19/07/2012	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 19/07/2012	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 31/03/2016	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

<http://cancerhelp.cancerresearchuk.org/trials/a-trial-of-olaparib-for-prostate-cancer-that-has-spread-and-got-worse-despite-hormone-therapy-and-chemotherapy-toparp>

## Contact information

### Type(s)

Scientific

### Contact name

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## Additional identifiers

### EudraCT/CTIS number

2011-000601-49

### IRAS number

### ClinicalTrials.gov number

NCT01682772

## Secondary identifying numbers

12313

# Study information

## Scientific Title

TOPARP: Phase II Trial of Olaparib in Patients with Advanced castration Resistant Prostate cancer: a non-randomised study

## Acronym

TOPARP

## Study objectives

Prostate cancer is the second commonest cause of male cancer death in the UK with a third of patients developing advanced disease. This initially responds to treatment called androgen deprivation, but invariably progresses to a terminal phase, called castration resistant. Docetaxel is the mainstay of treatment for patients with metastatic castration resistant prostate cancer (mCRPC) but only 40-45% of patients have a survival benefit from this treatment. Thus, effective therapeutic options that offer sustained responses and clinical benefit for mCRPC patients remain an important area of unmet medical need. Prostate cancer is a clinically and molecularly heterogeneous disease. Improved understanding of the biological and clinical significance of the molecular subclassification of this disease could positively impact treatment outcomes by allowing doctors to target the most appropriate therapy for patients.

We hypothesise that a proportion of mCRPC have defects in a form of DNA repair. The drug olaparib has shown activity in other cancer types that have this DNA repair deficit and we are testing whether mCRPC patients also will benefit from olaparib treatment. We also hope that predictive biomarkers can be identified to define this patient population.

The aims and objectives of this trial are therefore:

1. To evaluate the antitumour activity of olaparib in mCRPC.
2. To identify predictive biomarkers of HR repair deficiency for mCRPC. To do this, we have developed a novel trial designed to test the benefit of the drug while looking for molecular predictors of clinical response.

More details can be found at <http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=12313>

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

NRES Committee London - Surrey Borders, 29/12/2011, ref: 11/LO/2019

## Study design

Non-randomised; Interventional; Design type: Treatment

## Primary study design

Interventional

## Secondary study design

Non randomised study

**Study setting(s)**

Hospital

**Study type(s)**

Treatment

**Participant information sheet**

Not available in web format, please use the contact details below to request a patient information sheet

**Health condition(s) or problem(s) studied**

Topic: National Cancer Research Network; Subtopic: Prostate Cancer; Disease: Prostate

**Interventions**

All patients will receive single agent olaparib (AZD2281) at a dose of 400 mg twice daily, continuously on a 28-day cycle. Olaparib will be administered until objective disease progression or unacceptable toxicity or patient withdrawal for whatever reason.

**Intervention Type**

Drug

**Phase**

Phase II

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

Olaparib

**Primary outcome measure**

Response will be defined on the basis of the following outcomes, if any of these occur patients will be considered to have responded:

1. Objective response by modified Response Evaluation Criteria In Solid Tumors (RECIST)
2. Prostate-specific antigen (PSA) decline of  $\geq 50\%$  according to the Prostate Cancer Working Group 2 and
3. Conversion of circulating tumour cell count (CTC) from  $\geq 5$  cells/7.5ml blood at baseline to  $< 5$  cells/7.5ml blood confirmed by at least 2 readings 4 weeks apart

**Secondary outcome measures**

1. Radiological progression free survival
2. Time to radiological progression
3. Progression free survival
4. Overall survival
5. Time to PSA progression
6. Proportion of patients with conversion of circulating tumour cell count from  $\geq 5$  cells/7.5ml blood at baseline to  $< 5$ /7.5ml blood nadir
7. Duration of PSA response and objective response if applicable
8. Safety and tolerability of Olaparib

**Overall study start date**

04/07/2012

## Completion date

31/01/2014

## Eligibility

### Key inclusion criteria

1. The subject is capable of understanding and complying with the protocol requirements and has signed the informed consent document
2. Age  $\geq 18$  years
3. Histologically confirmed adenocarcinoma of the prostate with tumour tissue available for molecular analyses. If archival tissue for biomarker analysis is not available then the patient must be willing to have a further biopsy to obtain tumour tissue for histological diagnosis.
4. At least one but no more than two previous taxanebased chemotherapy regimens. If docetaxel chemotherapy is used more than once, this will be considered as one regime. Patients may have had prior exposure to cabazitaxel treatment.
5. At least 28 days since the completion of prior therapy, including major surgery, chemotherapy and other investigational agents. Additionally, clinically relevant sequelae should have resolved to grade 1 or less prior to recommencing treatment. For hormonal treatment and radiotherapy refer to the guidelines below:
  - 5.1. At least 28 days since the completion of prior flutamide treatment. Patients whose Prostate-specific antigen (PSA) did not decline in response to anti-androgens given as a second line or later intervention will only require a 14 days washout prior to Cycle 1, Day 1.
  - 5.2. At least 42 days since the completion of prior bicalutamide (Casodex) and nilutimide (Nilandron) treatment. Patients whose PSA did not decline for 3 or 4 months in response to antiandrogens given as second line or later intervention will require only a 14 day washout period prior to Cycle 1 Day1.
  - 5.3. At least 14 days from any radiotherapy with the exception of a single fraction of radiotherapy for the purposes of palliation (confined to one field) is permitted.
6. Documented prostate cancer progression as assessed by the investigator with one of the following:
  - 6.1. PSA progression defined by a minimum of three rising PSA levels with an interval of  $\geq 1$  week between each determination. The PSA value at the Screening visit should be  $\geq 2$   $\mu\text{g/L}$  (2 ng /ml); patients on systemic glucorticoids for control of symptoms must have documented PSA progression by PCWG22 while on systemic glucocorticoids prior to commencing Cycle1 Day1 of treatment.
  - 6.2. Radiographic progression of soft tissue disease by modified RECIST criteria or of bone metastasis with two or more documented new bone lesions on a bone scan with or without PSA progression.
7. Surgically or medically castrated, with testosterone levels of  $< 50$  ng/dL ( $< 2.0$  nM). If the patient is being treated with LHRH agonists (patient who have not undergone orchiectomy), this therapy must have been initiated at least 4 weeks prior to Cycle 1 Day 1 and must be continued throughout the study.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status of  $\leq 2$  (Karnofsky Performance Status = 50%)
9. Life expectancy  $> 12$  weeks
10. Patient must be able to swallow a whole tablet
11. Patient and the patients partner of childbearing potential, must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 3 months after the last dose of study drug.

12. Agreeable to have all the biomarker studies including the paired fresh tumour biopsies
13. Subjects must have a circulating tumour cell (CTC) count of  $\geq 5$  cells/7.5mls blood at screening
14. Subjects must have adequate bone marrow, hepatic and renal function documented within 7 days of registration, defined as:
- 14.1. Haemoglobin  $\geq 10$ g/dL independent of transfusions
- 14.2. White blood cells  $> 3 \times 10^9$ /L
- 14.3. Absolute neutrophil count  $\geq 1.5 \times 10^9$ /L
- 14.4. Platelets  $\geq 100 \times 10^9$ /L
- 14.5. Total bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN) except for patients with known Gilberts syndrome.
- 14.6. Aspartate transaminase (AST) (SGOT) and alanine transaminase (ALT) (SGPT)  $\leq 2.5 \times$  ULN or  $\leq 5 \times$  ULN in the presence of liver metastases
- 14.7. Serum creatinine  $\leq 1.5 \times$  ULN or a calculated creatinine clearance  $> 40$  mL/min for patients with creatinine levels above institutional normal. For GFR estimation, the Cockcroft and Gault equation should be used:  $GFR = CrCl (ml/min) = (140 \text{ age}) \times wt (kg) / (\text{serum creatinine} \times 72)$
- 14.8. Albumin  $> 30$  g/dl

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Male

**Target number of participants**

Planned Sample Size: 89; UK Sample Size: 89

**Key exclusion criteria**

1. Surgery, or local prostatic intervention (excluding a prostatic biopsy) less than 28 days of Cycle 1 Day 1
2. Less than 28 days from any active anticancer therapy or investigational agents. For hormonal treatment and radiotherapy refer to the guidelines outlined in the inclusion criteria
3. Prior treatment with a PARP inhibitor, platinum, cyclophosphamide or mitoxantrone chemotherapy
4. Uncontrolled intercurrent illness including, but not limited to, active infection, symptomatic congestive heart failure (New York Heart Association Class III or IV heart disease), unstable angina pectoris, cardiac arrhythmia, uncontrolled hypertension or psychiatric illness/social situations that would limit compliance with study requirements
5. Any acute toxicities due to prior chemotherapy and / or radiotherapy that have not resolved to a National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.02 grade 1 with the exception of chemotherapy induced alopecia and grade 2 peripheral neuropathy.
6. Malignancy within the previous 2 years with a  $> 30\%$  probability of recurrence within 12 months with the exception of non-melanoma skin cancer, in-situ or superficial bladder cancer
7. Patients with myelodysplastic syndrome/acute myeloid leukaemia

8. Patients with known symptomatic brain metastasis are not suitable for enrolment. Patients with asymptomatic, stable, treated brain metastases are eligible for study entry
9. Patients with symptomatic or impending cord compression unless appropriately treated beforehand and clinically stable and asymptomatic
10. Patients who experience a seizures within 6 months of study treatment or who are currently being treated with cytochrome P450 enzyme inducing antiepileptic drugs for seizures (use of antiepileptic drugs to control pain is allowed in patients not suffering from seizures unless drug is excluded due to CYP3A4 induction phenytoin, carbamazepine, phenobarbital
11. Patients receiving any of the following classes of inhibitors of CYP3A4; -Azole antifungals - Macrolide antibiotics -Protease inhibitors
12. Patients with gastrointestinal disorders likely to interfere with absorption of the study medication
13. Initiating bisphosphonate therapy or adjusting bisphosphonate dose/regimen within 30 days prior to Cycle 1 Day 1. Patients on a stable bisphosphonate regimen are eligible and may continue.
14. Presence of a condition or situation, which, in the investigators opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with patients participation in the study
15. The subject is unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee

**Date of first enrolment**

04/07/2012

**Date of final enrolment**

31/01/2014

## Locations

**Countries of recruitment**

England

United Kingdom

**Study participating centre**

ICR Clinical Trials & Statistics Unit (ICR-CTSU)

Sutton

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## Sponsor information

**Organisation**

The Institute for Cancer Research (UK)

**Sponsor details**

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**Sponsor type**

Research organisation

**Organisation**

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**Sponsor details**

Department of Medicine  
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Sutton  
England  
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SM2 5PT

**Sponsor type**

Hospital/treatment centre

**Organisation**

Institute of Cancer Research

**Sponsor details**

**Sponsor type**

Not defined

**Website**

<http://www.icr.ac.uk/>

**ROR**

<https://ror.org/043jzw605>

**Funder(s)**

**Funder type**

Industry

**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****IPD sharing plan summary**

Not provided at time of registration

**Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Results article</a>	results	29/10/2015		Yes	No



