ISRCTN15124653 https://doi.org/10.1186/ISRCTN15124653

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

Submission date	Recruitment status	[_] Prospectively registered
19/07/2012	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
19/07/2012	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
31/03/2016	Cancer	

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
Ms Claire Paulding

Contact details
ICR Clinical Trials & Statistics Unit (ICR-CTSU)
Section of Clinical Trials,
Sir Richard Doll Building
15 Cotswold Road
Sutton
United Kingdom
SM2 5NG
-
Toparp-icrctsu@icr.ac.uk

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 ≥50% according to the Prostate Cancer Working Group 2 and
3. Conversion of circulating tumour cell count (CTC) from ≥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 ≥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 >= 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 >= 1 week between each determination. The PSA value at the Screening visit should be >= 2 µg/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 <= 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 >= 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 >=10g/dL independent of transfusions
14.2. White blood cells >3x109/L
14.3. Absolute neutrophil count >=1.5x109/L
14.4. Platelets >=100 x109/L
14.5. Total bilirubin <= 1.5 x upper limit of normal (ULN) except for patients with known Gilberts syndrome.
14.6. Aspartate transaminase (AST) (SGOT) and alanine transaminase (ALT) (SGPT) <=2.5 x ULN or <=5 x ULN in the presence of liver metastases
14.7. Serum creatinine <=1.5 x ULN or a calculated creatinine clearance >40mL/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 age) × wt (kg)/(serum creatinine × 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
United Kingdom
SM2 5NG

Sponsor information

Organisation
The Institute for Cancer Research (UK)

Sponsor details

ICR Clinical Trials & Statistics Unit (ICR-CTSU)
Section of Clinical Trials
Sir Richard Doll Building
15 Cotswold Road
Sutton
United Kingdom
SM2 5NG

Sponsor type
Research organisation

Organisation
Royal Marsden Hospital NHS Foundation Trust (UK)

Sponsor details
Department of Medicine
Downs Road
Sutton
England
United Kingdom
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?
Results article	results	29/10/2015		Yes	No

HRA research summary	28/06/2023	No	No